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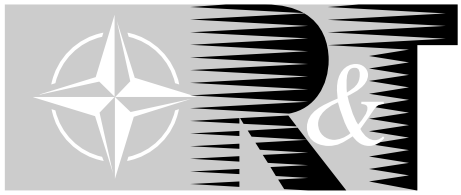

RESEARCH AND TECHNOLOGY ORGANIZATION

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RTO TECHNICAL REPORT 14

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(les Médicaments pour les équipages militaires : Consommation actuelle, questions et stratégies pour des options élargies)

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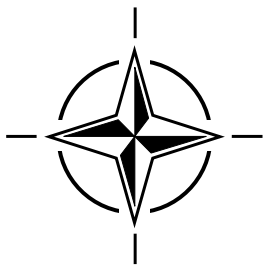

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Medication for Military Aircrew: Current Use, Issues, and Strategies for Expanded Options

(les Médicaments pour les équipages militaires : Consommation actuelle, questions et stratégies pour des options élargies)

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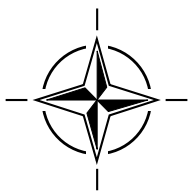
Report of the Human Factors and Medicine Panel (HFM) Working Group 26.



The Research and Technology Organization (RTO) of NATO

RTO is the single focus in NATO for Defence Research and Technology activities. Its mission is to conduct and promote cooperative research and information exchange. The objective is to support the development and effective use of national defence research and technology and to meet the military needs of the Alliance, to maintain a technological lead, and to provide advice to NATO and national decision makers. The RTO performs its mission with the support of an extensive network of national experts. It also ensures effective coordination with other NATO bodies involved in R&T activities.

RTO reports both to the Military Committee of NATO and to the Conference of National Armament Directors. It comprises a Research and Technology Board (RTB) as the highest level of national representation and the Research and Technology Agency (RTA), a dedicated staff with its headquarters in Neuilly, near Paris, France. In order to facilitate contacts with the military users and other NATO activities, a small part of the RTA staff is located in NATO Headquarters in Brussels. The Brussels staff also coordinates RTO's cooperation with nations in Middle and Eastern Europe, to which RTO attaches particular importance especially as working together in the field of research is one of the more promising areas of initial cooperation.

The total spectrum of R&T activities is covered by the following 7 bodies:

- AVT Applied Vehicle Technology Panel
- HFM Human Factors and Medicine Panel
- IST Information Systems Technology Panel
- NMSG NATO Modelling and Simulation Group
- SAS Studies, Analysis and Simulation Panel
- SCI Systems Concepts and Integration Panel
- SET Sensors and Electronics Technology Panel

These bodies are made up of national representatives as well as generally recognised 'world class' scientists. They also provide a communication link to military users and other NATO bodies. RTO's scientific and technological work is carried out by Technical Teams, created for specific activities and with a specific duration. Such Technical Teams can organise workshops, symposia, field trials, lecture series and training courses. An important function of these Technical Teams is to ensure the continuity of the expert networks.

RTO builds upon earlier cooperation in defence research and technology as set-up under the Advisory Group for Aerospace Research and Development (AGARD) and the Defence Research Group (DRG). AGARD and the DRG share common roots in that they were both established at the initiative of Dr Theodore von Kármán, a leading aerospace scientist, who early on recognised the importance of scientific support for the Allied Armed Forces. RTO is capitalising on these common roots in order to provide the Alliance and the NATO nations with a strong scientific and technological basis that will guarantee a solid base for the future.

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Medication for Military Aircrew: Current Use, Issues, and Strategies for Expanded Options

(RTO TR-014 / HFM-014)

Executive Summary

Working Group 26 was originally chartered by the AGARD Aerospace Medicine Panel to study issues relating to use of medications in military aircrew. The group began its work in April, 1997 and was charged to continue its work by the newly created NATO Research and Technology Organization in 1998 following the dissolution of AGARD. Working Group 26 has completed its work under the auspices of the Human Factors and Medicine Panel.

Working Group 26 was formed to seek out the means for cooperatively expanding our pharmacologic options in supporting military aircrew. Over the past decade the limited aeromedical drug armamentarium has become too restrictive for flight surgeons and their aircrew. There has been growing frustration with the difficulties in gaining knowledge of aeromedically significant effects of medication.

Flight surgeons and the military aircrew they support currently share heightened interest in expanding the list of medications known to be suitable for use in the military flying mission. Flight surgeons have traditionally taken a conservative approach to use of medications in military. This conservatism, while enhancing mission safety, has led to relatively few options for treating military aircrew for medical conditions or for enhancing their performance.

Working Group 26 surveyed NATO air forces regarding their current employment of medication in aircrew. Patterns emerge from this data in medication use for asthma, allergic rhinitis, gastroesophageal reflux/dyspepsia, hypertension, malaria prevention, and lipid disorders. Use of medications for operational indications primarily pertained to support of sustained operations with stimulants and hypnotics. The data also reveals trends in prohibition of certain medication use in military aircrew.

Several areas of particular need for expanded medication options for aircrew emerged from the data and from the working group's reviews of existing aeromedical issues. Areas of particular need include treatment of mild to moderate hypertension, prevention of malaria, treatment of depression/anxiety disorders, performance enhancement during prolonged sleepless periods, and aids for short periods of sleep during periods of sustained operations. Particular drugs are identified in review papers as candidates for these indications and aeromedical issues in need of further study before using these drugs in military aircrew are presented. Several drugs are identified by the working group as candidates for immediate study for the benefit of NATO military aircrew and their air forces.

The working group proposes that the data on aeromedical medication usage will be of significant utility to NATO flight surgeons. We propose that this data be kept current with regular updates, perhaps as an official NATO publication. This data is of particular value to smaller air forces depending significantly on the research and experience of larger air forces when establishing aeromedical policy regarding medication use.

The working group also finds the difficulty NATO air forces are encountering in evaluating the large number of new drugs on the market for aeromedical suitability could be addressed through cooperative research. Most air forces have some areas of aeromedical research capability but none have a completely comprehensive capability. Cooperative research on aeromedical issues for a particular drug would provide the needed knowledge about aeromedical effects without any single nation having to fund a comprehensive research protocol.

The working group encourages prototype studies to demonstrate the feasibility of a cooperative approach. We encourage such prototype studies on one or more of the following drugs as candidates for immediate study: losartan (for hypertension), mefloquine (for malaria prevention), serotonin/norepinephrine reuptake inhibitors (for depression and anxiety), pemoline (for sustained operations), modafanil (for sustained operations), and ultra short-acting hypnotics (for brief rest periods during sustained operations).

les Médicaments pour les équipages militaires : Consommation actuelle, questions et stratégies pour des options élargies

(RTO TR-014 / HFM-014)

Synthèse

Le groupe de travail 26 a reçu pour mandat initial du Panel AGARD de médecine aérospatiale (AMP) d'étudier les problèmes liés à la délivrance de médicaments aux équipages militaires. Le groupe a commencé ses travaux en avril 1997 et a été autorisé à poursuivre ses activités par la nouvelle Organisation pour la recherche et la technologie de l'OTAN (RTO) qui a succédé à l'AGARD en 1998. Le groupe de travail 26 a achevé ses travaux sous l'égide de la commission RTO sur les facteurs humains et la médecine (HFM).

Le groupe de travail 26 a été créé dans le but d'identifier les moyens qui permettraient d'accroître en coopération les options pharmacologiques pour le soutien des équipages. Au cours de la dernière décennie l'arsenal de médicaments aéromédicaux est devenu trop restrictif pour les besoins des médecins du personnel navigant et des équipages. Parallèlement, de plus en plus de frustrations ont été exprimées face aux difficultés à obtenir des informations concernant les effets des médicaments délivrés aux équipages.

Les médecins du personnel navigant et les équipages militaires qu'ils soignent, sont donc vivement intéressés par l'augmentation de la liste des médicaments reconnus adaptés aux missions aéronautiques militaires. En effet, traditionnellement, les médecins du personnel navigant adoptent une approche conservatrice lorsqu'il s'agit de délivrer des médicaments aux équipages militaires. Ce conservatisme, bien que susceptible d'améliorer la sécurité des vols, a du coup pour effet de réduire les options de traitement des équipages, ainsi que les possibilités d'amélioration de leurs performances.

Le groupe de travail 26 a réalisé une étude sur la consommation actuelle de médicaments par les équipages des armées de l'air de l'OTAN. Les profils de consommation extrapolés de ces données montrent la récurrence de l'asthme, de la rhinite allergique, du reflux gastro-oesophagien, de la dyspepsie, du paludisme et de troubles associés aux lipides. La délivrance de médicaments pour le traitement de troubles liés aux opérations concerne principalement les missions longues et soutenues effectuées à l'aide de stimulants et d'hypnotiques. Les données montrent aussi une certaine tendance à prohiber certains médicaments pour les équipages militaires.

Il est ressorti des données et des études des problèmes actuels en médecine aéronautique qu'il existe un besoin d'étendre la gamme de médicaments délivrables aux équipages. Les domaines prioritaires comprennent le traitement de l'hypertension légère et moyenne, la prévention du paludisme, le traitement des troubles anxieux et dépressifs, l'amélioration des performances pendant les périodes d'éveil prolongées, et les somnifères légers permettant de dormir pendant des courtes périodes au cours des opérations soutenues. Des études présentent certains médicaments recommandés pour le traitement de ces symptômes, ainsi que les questions aéromédicales qui seraient à étudier de façon plus approfondie avant de délivrer ces médicaments aux équipages militaires. Un certain nombre de médicaments sont identifiés par le groupe de travail comme méritant une étude rapide au profit des armées de l'air de l'OTAN et des équipages militaires.

Le groupe de travail pense que les données recueillies sur l'utilisation aéromédicale des médicaments seront d'une grande utilité pour les médecins du personnel navigant de l'OTAN. Il propose que ces données soient mises à jour régulièrement, peut-être dans le cadre d'une publication officielle de l'OTAN. Ces données sont d'un intérêt particulier pour les armées de l'air de moyenne envergure qui dépendent dans une large mesure de l'expérience des armées de l'air plus importantes pour l'établissement de leurs politiques aéromédicales en matière de médicaments.

Le groupe trouve également que les difficultés rencontrées par les armées de l'air de l'OTAN en ce qui concerne l'évaluation du grand nombre de médicaments existant sur le marché en vue de leurs applications aéromédicales pourraient être abordées par le biais de la recherche en coopération. La majorité des armées de l'air ont un certain nombre de capacités de recherche aéromédicale mais aucune ne possède un éventail exhaustif. La recherche en coopération sur les aspects aéromédicaux d'un médicament spécifique permettrait de disposer des connaissances recherchées concernant ses effets aéromédicaux sans obliger les pays en question à financer de larges protocoles de recherche.

Le groupe de travail recommande la réalisation d'études de prédéveloppement afin de démontrer la faisabilité de l'approche coopérative. Il est préconisé de réaliser le plus vite possible de telles études sur l'un au moins des médicaments suivants : le losortan (pour l'hypertension), la méfloquine (pour la prévention du paludisme), la sérotonine et la noradrénaline (inhibiteurs de recaptage pour la dépression et les états anxieux), la pémoline (pour les opérations soutenues), le modafanil (pour les opérations soutenues), et les hypnotiques de durée ultra-courte (pour les brèves périodes de repos lors des opérations soutenues).

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Section I: Introduction

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Working Group 26 was originally chartered by the AGARD Aerospace Medicine Panel to study issues relating to use of medications in military aircrew. The group began its work in April, 1997 and was charged to continue its work by the newly created NATO Research and Technology Organization in 1998 following the dissolution of AGARD. Working Group 26 has completed its work under the auspices of the Human Factors and Medicine Panel.

Members

Table 1 shows the members of Working Group 26 as nominated by NATO member nations and appointed by the Aerospace Medicine Panel in 1997.

Table 1

Working Group 26 Members	
Col Mark Ediger - Chairman	United States
Air Cdre Anthony Nicholson	United Kingdom
Col Erich Rödig	Germany
Col Jeb Pickard	United States
Col Ronald Davidson	Canada
Dr. Gary Gray	Canada
Lt Col Daniele Danese	Italy
Lt Col Berry Lam	Netherlands
Lt Col Themis Eliopoulos	Greece
Med des Armees Philippe Doireau	France
Med en Chef Jean Francois Paris	France
Dr. Paul Kuklinski	Germany
Mrs. Barbara Stone	United Kingdom
Med Cdt Stephan van den Bemden	Belgium

The Issues

Flight surgeons and the military aircrew they support currently share heightened interest in expanding the list of medications known to be suitable for use in the military flying mission. Flight surgeons have traditionally taken a conservative approach to use of medications in military aircrew because of 1) the complexity, and lethality, of the weapons systems, 2) the physiologic demands of military aviation, and 3) incomplete information about side effects pertinent to the aviation environment. This conservatism has led to relatively few options for treating military aircrew for medical conditions. Available medications are generally limited to medications that have been in clinical use for a sufficient length of time for flight surgeons to be comfortable with their safety, or newer medications that research has shown to be safe in the aviation environment.

Over the past few years the limited aeromedical drug armamentarium has become too restrictive for flight surgeons and their aircrew. There has been growing frustration with the difficulties in gaining knowledge of aeromedically significant effects of medication. Working Group 26 was formed to seek out the means for cooperatively expanding our pharmacologic options in supporting military aircrew.

The following are the factors driving requirements in this area:

- Rapid expansion of the number of new drugs available for clinical indications, offering enhanced disease management
- Diminished funding for research making it difficult for any single nation to completely evaluate aeromedical issues for one or more drugs
- Sustained round-the-clock operations and rapid deployment across multiple time zones

- Increased emphasis on mitigating the risk of chronic disease development, through early intervention and reduction of risk factors
- Focus on population-based medicine leading to the understanding that consistently sound disease management, often involving newer pharmacologic agents, will maintain higher qualification rates in the aviation force
- Emphasis on force protection and emerging infectious disease threats, increasing demand for effective pharmacologic prophylaxis
- Absence of information on aeromedically significant effects of drugs from initial research required for licensure.

The Group's Working Process

Table 2 shows the goals and objectives established by the members of Working Group 26 in accordance with their taskings from the Aerospace Medicine Panel and the Human Factors and Medicine Panel.

The group was supported in its work by the member nations who provided the services of the members, whose expertise in aerospace medicine, pharmacology and clinical medicine enabled the group to attain its goals.

Information gathered by the working group was obtained in two ways: 1) via surveys of aerospace medicine leaders in NATO member nations, and 2) via literature research performed by members of the working group.

For the purposes of this report we define military aircrew as personnel with defined duties on board military aircraft. This definition is not limited to pilots, although the working group recognizes that aeromedical issues differ between crew positions.

Content of This Report

Information in this report concerns current use of medication in NATO aircrew, and the expansion of therapeutic and operational pharmacologic options. The first part of the report takes the form of literature reviews on the present state of the art in the pharmacologic treatment of disorders commonly encountered in the practice of military aviation medicine.

Information on current medication use is contained in the results of a survey sent to NATO member nations. We believe this data will be of considerable value to flight surgeons because it gives an overview of NATO nation policy and experience that is not available from any other source. Unfortunately, we were unable to obtain data from four NATO countries, but we believe the data remains very useful, and that this sort of data has great potential if we can keep it current.

Table 2

Working Group 26 Goals and Objectives		
Goal 1	**Create a database for medications in use by military aviators of NATO member nations**	
	Obj 1	Define categories for medications in the data tables
	Obj 2	Establish what information will be contained in the database
	Obj 3	Gather data from member nations
	Obj 4	Establish means of access to the database for member nations
Goal 2	**Define the approach to determining the suitability of medications for use by military aviators and identify opportunities for collaboration between member nations in conducting aeromedical research on medications**	
	Obj 1	Define the approach for therapeutic medications
	Obj 2	Define the approach for operational medications
	Obj 3	Describe the categories of aeromedical concern when evaluating drugs
	Obj 4	Describe the best means ("Gold Standard") for studying each category of aeromedical concern for medications
	Obj 5	Determine the capabilities of each member nation for conducting aeromedical research on medications, intramural and extramural
	Obj 6	Determine which drugs are candidates for immediate study
Goal 3	**Establish mechanisms for keeping the database current and for future determination of the suitability of drugs for use by military aviators**	
	Obj 1	Identify a recommended means of updating and maintaining the database after the term of Working Group 26 has expired
	Obj 2	Develop a recommended mechanism for future collaboration in aeromedical research on medications
Goal 4	**Produce a report of the work products and recommendations of Working Group 26**	

Information about expanding our therapeutic and operational options is contained in the final section, which discusses potential approaches to evaluating new medications. This is followed by recommended testing methods to evaluate specific aeromedical concerns in military aircrew, which we refer to as "gold standards." We believe that future sharing between NATO nations of aeromedical research on medication must include some commonly accepted measures ("gold standards") for evaluating specific aeromedical issues. The section concludes with a sample review of a candidate medication, in this case losartan potassium, with a possible approach to evaluation.

We consider this report to be an initial step towards cooperative evaluation of medications between NATO nations and sharing of experience with medications between NATO flight surgeons. The goal we should be able to achieve is an expanded knowledge of the aeromedical effects of medications and an expanded range of medication available for use in military aircrew.

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Section II: Reviews

Antihypertensive Drugs In Aircrew

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Chronic diseases are relatively rare in the military aviator population, but essential hypertension is a distinct exception. Estimates of prevalence vary considerably, in part due to the typical lability of early hypertension in the young to middle-aged, predominantly Caucasian population characteristic of NATO air forces. Suffice it to say that, for most services, antihypertensive drugs represent some of the most common, if not the commonest, waivers for chronic medication use in aviation personnel.

OVERVIEW

After a century of research into the mechanisms of essential hypertension, understanding the pathogenesis of this disorder seems as elusive as ever. Undoubtedly, much of the reason for this is that even primary hypertension is a warning manifestation of one of a number of underlying disorders, none of which is well understood.[1] While there is no doubt that treatment of hypertension is associated with improved morbidity and mortality, we are nonetheless treating a complication of another disorder. Furthermore, the heterogeneity of the underlying disorders probably explains much of the variability in response to drug therapy.

With the caution that our understanding of the pathogenetic mechanisms of hypertension is rudimentary at best, two major "types" of essential hypertension are generally recognized. One is characterized by suppressed renin activity and a sensitivity to dietary sodium, the other by high renin activity and a lack of response to sodium intake. Generally, most hypertensives of African descent, and the majority of elderly hypertensives, appear to fit into the "salt-sensitive" category, whereas young to middle-aged Caucasian hypertensives are more often "salt-resistant," with high circulating renin levels. In salt-sensitive hypertension, the defect appears to be an inability to excrete the daily intake of sodium, until mean arterial pressure rises to a level that forces a pressure natriuresis.[2] The relative deficiency in natriuresis may be due to a renal defect in handling sodium, as data from transplant studies would suggest; [3,4] alternatively, it may be due to subtle abnormalities in the sympathetic nervous system or renin-angiotensin system. Salt-resistant hypertension has been postulated to be neurogenic in origin. Evidence in animals for sympathetic activation eventually inducing chronic blood pressure elevation is fairly clear; evidence is less conclusive in humans, but direct recording of sympathetic nerve traffic in the peroneal and brachial nerves has documented increased activity in borderline hypertensive subjects, and even greater activity in moderate and severe hypertensives.[5] While it must be stressed that such a classification is almost certainly simplistic, it does serve to provide some theoretical basis for observed differences in response to drug therapy.

It is beyond the scope of this discussion to delve into secondary hypertension. Even when workups for underlying renal or endocrine diseases are limited to those hypertensives who present with severe blood pressure elevations of recent onset, the yield of such workups is low. However, one diagnosis that should be considered is obstructive sleep apnea,[6] because it is significantly more common than other causes of secondary hypertension, and because sleep apnea is associated with its own aeromedical risks. Fortunately, this disorder can usually be ruled out rather easily, by questioning the bed partner about snoring and observed apneic episodes.

The major goal of antihypertensive therapy is to lessen the increased morbidity and mortality associated with hypertension, while avoiding

deleterious side effects. Such side effects are usually annoying, and occasionally morbid, in the civilian population, but could lead directly to early mortality in the aviation environment. It is important to note that any drug which reduces blood pressure is usually presumed to reduce the morbidity and mortality of hypertension, but for most classes of drugs this has yet to be shown.[7] Of the two cardiovascular events most likely to result from uncontrolled hypertension, a meta-analysis of primary prevention trials has shown that the increased risk of stroke could be negated by control of the blood pressure, while the increased risk of myocardial infarction was reduced by approximately half.[8]

The initial period of treatment with antihypertensive medication is marked by compensatory physiologic changes, such as resetting of baroreceptor reflexes and cerebral autoregulation. The clinical corollary, common to all antihypertensive drugs, is the fatigue that is often seen after the patient begins treatment. Because of these physiologic alterations, it is particularly important that the aviator starting an antihypertensive drug undergo an adequate ground trial before resuming aviation duties.

ANTIHYPERTENSIVE MEDICATIONS

Agents useful in the chronic treatment of hypertension may be classified into one of nine categories.[9] They are in no particular order: 1) diuretics, 2) beta-blockers, 3) angiotensin-converting enzyme inhibitors, 4) angiotensin receptor antagonists, 5) calcium channel blockers, 6) alpha-adrenergic blockers, 7) central alpha-adrenergic agonists, 8) direct vasodilators, and 9) peripheral adrenergic neuron antagonists.

Diuretics

Although over 40 years have elapsed since the synthesis of chlorothiazide, diuretics continue to be one of the more useful drugs for hypertension and, with the exception of beta-blockers, are the only class of drugs that have been proven to reduce hypertensive mortality. There have been scattered data suggesting a vasodilatory effect of thiazide diuretics, perhaps mediated through increased nitric oxide production or decreased sympathetic outflow.[10] However, such evidence is weak, and most research suggests that the hypertensive effect of diuretics is due, directly or indirectly, to natriuresis.[11] The initial response to thiazide diuretics is a 10-15% reduction in plasma volume, accompanied by a fall in cardiac output and a rise in peripheral vascular resistance. With chronic administration, however, blood volume and cardiac output return nearly to pretreatment levels, while total peripheral resistance declines.[12] This correlates well with the purported mechanism of salt-sensitive hypertension; when the relative defect in sodium clearance has been overcome by a drug-induced natriuresis, pressure natriuresis is no longer required, and cardiovascular homeostasis reverts to a more normal milieu.

Such a mechanism of action is obviously attractive in an aviation environment, since cardiac function and vascular reflexes are preserved, and indeed diuretics are an excellent therapeutic choice in the aviator – when they work. Although diuretic efficacy is not entirely limited to the low-renin hypertensive, these drugs tend to be most efficacious as monotherapy in those of African descent, and in the elderly. Since the typical military aviator in NATO is likely to be a Caucasian in the third to fifth decade of life, diuretics alone frequently prove to be insufficient to reduce blood pressure. On the other hand, they are highly effective drugs for combination therapy, particularly in conjunction with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and beta-blockers.

Adverse effects of diuretics include impotence, with an incidence perhaps as high as 31%.[13] Data on psychomotor performance is limited, but on the whole there appears to be no performance decrement.[14] The adverse effects from diuretics that have received the most attention have been metabolic derangements. Thiazides commonly cause potassium loss, usually reducing total body potassium by 5%.[15] They also induce a mild resistance to insulin, which in one study resulted in glucose intolerance in 3% of subjects.[16] Much recent attention has been given to the lipid effects of diuretics, as a possible explanation for the less-than-expected reduction in coronary events seen in primary hypertension trials. LDL levels typically increase by 5-15% in the first 12 weeks of diuretic therapy, with a return to baseline by one year. However, in the corresponding placebo groups, LDL fell by one year, with values 2-3% lower than the treatment group, and in the active treatment group cessation of diuretic therapy resulted in a further fall in lipid levels.[17] While this effect on lipids may contribute to the relative

lack of efficacy in preventing coronary events, it is unlikely to be a sufficient explanation. Since atherogenesis is a multifactorial disease, and hypertension is inextricably linked with other conditions, such as hyperlipidemia and diabetes, which also predispose to atherogenesis, it is probably naive to expect blood pressure reduction alone to abolish the associated risk of coronary disease. The metabolic effects of diuretics, with the possible exception of lipid derangements, are dose-related[17,18]; on the other hand, antihypertensive efficacy appears to be equivalent between higher and lower doses of diuretics. Three of four recent trials using low dose diuretics (e.g., 12.5-25 mg/day of hydrochlorothiazide), along with potassium sparing agents, showed much more significant reduction in deaths in the treatment group when compared with earlier high-dose trials.[19,20,21,22] Since these trials involved elderly patients, there was more opportunity to reduce mortality, and furthermore a given dose of drug was likely to be equivalent to a somewhat higher dose in young patients, given the slower drug clearance typical of the elderly. Nonetheless, it appears that optimal therapy of hypertension with diuretics consists of lower doses than have been used in the past. If the aviator fails to respond to 25 mg, or at most 50 mg, of hydrochlorothiazide, or an equivalent dosage of other diuretics, there is little point in using a higher dose.

Beta-blockers

This is a complex class of drugs, differing in selectivity, partial agonism, and the presence or absence of associated alpha-adrenergic blockade. Propranolol, timolol, and nadolol are nonselective beta-blockers, while metoprolol, atenolol, betaxolol, and bisoprolol are more selective for cardiac ($beta_1$) adrenergic receptors, at least in low doses. Pindolol, penbutolol, carteolol, and acebutolol have partial agonist activity, also known as intrinsic sympathomimetic activity (ISA); the first three are nonselective for beta receptors, while acebutolol displays $beta_1$ selectivity at low doses. Labetalol is a nonselective beta-blocker with ISA, but also blocks alpha-adrenergic receptors. Carvedilol is a nonselective beta-blocker which also blocks alpha receptors, although it displays no ISA; it has been promoted more for treatment of congestive heart failure than for hypertension. These drugs also differ in relative solubility, with propranolol, metoprolol, and timolol being more lipophilic, and atenolol, nadolol, and bisoprolol more hydrophilic.

The mechanism of blood pressure lowering from beta-blockade is not well understood, but has been attributed to negative inotropic and chronotropic effects resulting in a decreased cardiac output, as well as to inhibition of renin release. These agents work relatively well in hypertensives with high renin levels, particularly young, non-obese Caucasians. Beta-blockers are the only class of drugs besides diuretics demonstrated to decrease the morbidity of hypertension, on a level probably comparable with diuretics.[7]

Adverse effects due to beta-blockers are highly significant, and while some, such as precipitation or worsening of diabetes, heart failure, and claudication, are unlikely in the aviator population, other side effects are common in this age group. Much of the rationale for developing $beta_1$-selective agents, and beta-blockers with ISA, had been to avoid some of the distressing side effects associated with this class of drugs, but results have been mixed. $Beta_1$-selective blockers do improve the side effect profile, but precipitation of bronchospasm is a persistent concern even with low doses of these agents. Fatigue and diminished exercise tolerance are common complaints, which do not appear to be improved by agents displaying partial agonism.[23] Indeed, with the exception of metabolic profile, beta-blockers with ISA have yet to show any convincing advantage.[24] Central nervous system effects from beta-blockers are common, and include sleep disturbance and diminished concentration. Hydrophilic beta-blockers such as atenolol appear to have a lower risk of CNS effects, but results of objective testing have been contradictory.[14] Curiously, in primary and secondary prevention trials, lipophilic beta-blockers (propranolol, metoprolol, and timolol) have resulted in reduced complications, while hydrophilic beta-blockers (atenolol, sotalol) have not.[25] However, it seems premature to make any generalization at this point. Metabolic effects of most beta-blockers include lipid disturbance, with an increase in triglycerides and a decrease in HDL, although agents with significant ISA are lipid-neutral.[18] All beta-blockers, except the newer vasodilating agents such as carvedilol, worsen insulin resistance.[26] Impotence is a common complaint with this class of drugs.

Beta-blockers work well in combination with diuretics and with calcium channel blockers, although negative inotropy may be additive with the latter class of drugs. The combination of beta-blockers with ACE inhibitors or with angiotensin receptor antagonists has not proven to be particularly effective.[27]

Angiotensin-Converting Enzyme Inhibitors

The renin-angiotensin system is tightly linked to blood pressure control and volume status. Reduced sodium delivery or decreased perfusion to the kidney, as well as sympathetic activation, all stimulate renin secretion from the juxtaglomerular apparatus. Renin cleaves the inactive decapeptide angiotensin I from angiotensinogen. Angiotensin-converting enzyme (ACE) then cleaves the C-terminal dipeptide from angiotensin I, to form the vasoactive angiotensin II. ACE serves another role as the enzyme responsible for degrading bradykinin, hence its alternative name of kininase II. Angiotensin II, in addition to being a potent direct vasoconstrictor, also promotes aldosterone secretion and thus sodium retention, stimulates the sympathetic nervous system, and promotes cellular migration, proliferation, and hypertrophy, an effect documented in both vascular smooth muscle and in myocardium.[28]

Angiotensin II levels are nearly always within a range that exerts a direct effect on arterial pressure, both in normotensives and hypertensives, such that infusion of an ACE inhibitor causes an immediate reduction in blood pressure proportional to the prior level of angiotensin II.[29] However, with chronic administration of the drug a further fall in blood pressure often occurs, and peak hypotensive effects don't correspond well to peak serum concentration or to peak ACE inhibition.[30] Also, patients with normal or even low renin levels may respond to ACE inhibitors. As a rule, however, younger Caucasians usually respond well to ACE inhibitors, while black or elderly patients respond less well, at least to monotherapy. On the other hand, converting a low-renin to a high-renin hypertensive by diuresis or salt restriction often renders ACE inhibitors very effective in treating otherwise resistant individuals.

ACE inhibitors are divided into three groups based on the ligand interacting with the enzyme, either a sulfhydryl moiety in the case of captopril, a phosphinyl moiety in the case of fosinopril, or a carboxyl moiety in most of the remaining agents. Of the commonly available drugs, captopril and lisinopril are active drugs, while the remainder are administered as esterified prodrugs to enhance gastrointestinal absorption. With the exception of the sulfhydryl moiety, which may be responsible for the neutropenia and certain other side effects seen with high doses of captopril, the ACE inhibitors are more similar than different.

With the exception of cough, adverse effects are uncommon, explaining why ACE inhibitor therapy typically scores well on quality of life studies. Cough is the most common adverse effect, occurring in up to 20% overall; the risk is higher in women than in men, and in nonsmokers than in smokers. Probably because of its unusual nature as a drug side effect, cough was not even described in initial clinical trials. Presumed to be due to elevated levels of bradykinin, cough is most often seen within the first month, and is usually cross-reactive with other drugs in the class.[31] Angioedema, a potentially life-threatening effect, occurs in 0.1-0.2% of cases overall, with a higher risk in those of African descent. Although it usually appears within the first week of therapy, in some cases it has occurred after several years.[32] While originally assumed to also be due to bradykinin elevation, no conclusive evidence for this has been found, and at least two cases have occurred with angiotensin receptor antagonists, agents which do not cause elevated bradykinin levels. Neutropenia, an uncommon manifestation, was largely confined to early trials using high doses of captopril. Fetal toxicity is well described both in animals and humans. It is distinctive in that the period of known risk is the second and third trimesters; ACE inhibitors do not appear to be teratogenic in the first trimester.[33] Nonetheless, the female aviator desiring to become pregnant should, if at all possible, change to another antihypertensive drug prior to conception. Metabolically, ACE inhibitors are lipid-neutral, and may even improve insulin sensitivity.[18]

In normal volunteers, ACE inhibitors have either shown no change or an improvement in psycho-motor testing. In hypertensive subjects, results of cognitive testing are limited. Captopril appeared to result in better cognitive scores than did methyldopa or propranolol, but in another study cilazapril, atenolol, and nifedipine appeared to be equivalent.[14] The acceleration effects of captopril have been measured in normal volunteers, with a

decrease in G-tolerance of 0.35 +Gz during gradual onset run.[34] However, G-tolerance was measured after only four days of captopril treatment in normotensive patients, so the significance of this observation is uncertain.

Angiotensin Receptor Antagonists

In addition to angiotensin converting enzyme inhibition, the renin-angiotensin axis may also be pharmacologically altered by blocking the angiotensin II receptor. Angiotensin receptor antagonists show efficacy which is comparable to ACE inhibitors, but avoid some of the side effects such as cough.[35] Except for uricosuria with losartan, they appear to have neutral metabolic effects as well.[36] These may well prove to be excellent antihypertensive agents for aviation purposes, but the available information is incomplete at this time.

Calcium Channel Blockers

Also known as calcium antagonists, this is a diverse group of drugs, originally represented by verapamil, a phenylalkylamine, diltiazem, a benzothiazepine, and nifedipine, a dihydropyridine. Nearly all the agents developed since then, such as nicardipine, nimodipine, nitrendipine, nisoldipine, amlodipine, felodipine, and isradipine, are dihydropyridine derivatives. A fourth class, benzimidazolyl tetralines, was introduced in the form of mibefradil, but this drug was recently withdrawn in all countries because significant inhibition of the cytochrome P-450 system resulted in rhabdomyolysis and *torsades de pointes* when mibefradil was taken in conjunction with a number of other drugs.[37]

Given the lack of structural homology between different classes of calcium channel blockers, the similarities between the classes are perhaps more surprising than the differences. All these agents act through inhibiting the movement of calcium into cells, by blocking voltage-dependent channels. All but mibefradil, a transient (T) channel blocker, inhibit the long-lasting (L) channels. Calcium is normally maintained in the extracellular space, with an extra- to intracellular gradient of over 10,000:1. Many cellular functions, notably smooth muscle contraction and hormone secretion, are regulated by small releases of calcium into the cytosol. Calcium channel blockers both reduce basal vascular tone, and blunt the usual response to pressor agonists like angiotensin II and vasopressin.[38]

As one might expect from a mode of action that involves a "final common pathway," calcium antagonists effectively reduce blood pressure in nearly all hypertensives regardless of race or age; they also reduce blood pressure in normotensives, albeit to a lesser extent. They are quite effective in combination with ACE inhibitors, but the combination of calcium channel blockers and diuretics seems relatively ineffective, perhaps due to the type of natriuresis induced by calcium antagonists.[38]

Although their effects on the peripheral vasculature are similar, the different classes of calcium channel blockers affect the heart differently, at least in vivo. Verapamil and diltiazem, as well as mibefradil, all decrease heart rate under rest and exercise conditions. They slow both the sinoatrial and atrioventricular nodes, an effect which is additive to that of beta-blockers. The dihydropyridines have no clinically evident effect on the cardiac conduction system, at least directly. However, the vasodilation induced by short-acting dihydropyridines results in sympathetic activation and tachycardia. This effect has been shown to be dependent on the rate of increase in plasma concentration of the drug.[39] All classes of calcium channel blockers vasodilate the coronary arteries, and all have negative inotropic effects, with verapamil reducing systolic function the most, and dihydropyridines the least.

The introduction of calcium channel blockers was greeted with considerable enthusiasm, since the combined effects of reduced myocardial oxygen demand and coronary vasodilation were considered to be ideal for reducing coronary mortality. However, with the exception of a single trial using verapamil, the results of approximately two dozen trials have been uniformly disappointing.[40] Whether the same will be true of hypertensive morbidity and mortality is unknown. The Shanghai Trial of Nifedipine in the Elderly showed a significant reduction in endpoints with the use of slow release nifedipine compared with a placebo, but it was neither blinded nor randomized.[41]

Adverse effects of calcium antagonists are limited, and rarely cause discontinuation. Ankle edema, a fairly common finding, is due to a direct effect on the microcirculation rather than fluid retention.[42] Data regarding cognitive effects has been limited to nifedipine. In a study of that drug in relatively young normotensive volunteers, no

effect was seen using a range of tests.[43] Two studies using nifedipine in elderly hypertensives have shown disparate results. In the first, memory recall and digit symbol substitution deteriorated when nifedipine was instituted, while atenolol showed no significant change.[44] In the second study, improvements were seen on several portions of a psychomotor test battery when either nifedipine or captopril was used.[45]

The purported adverse effect of greatest concern is the potential for increased coronary mortality with the use of calcium antagonists, a subject of hot debate in recent years. Beginning in 1995, three studies, two retrospective and one prospective, suggested an increased mortality associated with the use of short-acting calcium channel blockers.[46,47,48] Subsequent studies of patients receiving longer-acting calcium antagonists have not shown a similar increase in risk, although one of these studies did demonstrate an increased risk in those using short-acting calcium antagonists, when those were compared with beta-blockers.[49] As noted earlier, there is a physiologic rationale for these observations, since rapidly rising levels of nifedipine cause marked sympathetic activation, an effect not seen when levels are raised slowly. While this controversy has yet to be fully resolved, most authorities recommend that short-acting calcium antagonists be avoided for the treatment of hypertension, a recommendation that also makes sense with respect to patient compliance.

Given the direct relaxation of vascular tone induced by this class of drugs, there is certainly theoretic concern about the effect in G tolerance, but at the present time no data exist.

Alpha-adrenergic Blockers

This class of drugs, represented initially by prazosin, and more recently by doxazosin and terazosin, blocks alpha-$_1$ receptors in both arterioles and veins, reducing blood pressure acutely by about 15%.[50] They are additive to beta blockers, diuretics, and ACE inhibitors, but are not useful in combination with central alpha-adrenergic agonists. They display little reflex stimulation of cardiac output, probably because presynaptic alpha$_2$ receptors continue to inhibit norepinephrine release. Uniquely, they improve lipid levels, with a 10% decrease in the cholesterol/HDL ratio, and improve insulin sensitivity.[51] The tachyphylaxis seen with prazosin treatment of chronic heart failure does not appear to occur when the same drug is used to treat hypertension.

Unfortunately, the advantages of these drugs are largely outweighed by adverse effects. Because of the venodilatory action, these agents induce a greater reduction in standing than in supine blood pressure.[52] The postural syncope that proved to be such a problem with prazosin is less common with the newer agents, but it still occurs in nearly 2% of patients treated with doxazosin or terazosin. Approximately 20% of patients complain of orthostatic dizziness. Sedation has been reported in a variable but significant percentage of patients on prazosin. Such a profile of adverse effects makes these agents poor choices to treat the hypertensive aviator.

Central Alpha-adrenergic Agonists

Also known as alpha$_2$-adrenoceptor agonists, this is a fairly diverse class of drugs, represented by methyldopa, clonidine, guanabenz acetate, and guanfacine. The primary mode of action seems to be alpha$_2$ receptor stimulation in the brain stem, which leads to decreased sympathetic outflow. As drug dosage is raised, the antihypertensive effect is often reversed, perhaps due to peripheral alpha$_2$ stimulation.[53]

These agents show consistent efficacy regardless of race or age, and may be combined effectively with diuretics, and probably with ACE inhibitors and calcium channel blockers. They cause little or no change in cardiac output and, with the exception of methyldopa, they are neutral with respect to lipids and glucose. Unfortunately, disadvantages are highly significant, and include sedation, drowsiness, depression, and a readily measurable degradation of psychomotor performance.[14] Dry mouth is a common complaint. Withdrawal of the drug, especially in the case of clonidine, risks a rebound phenomenon characterized by elevated blood pressure, anxiety, and tachycardia. This syndrome is more severe with concomitant beta-blocker usage.[53] Like alpha blockers, these drugs appear to be poor choices to treat the hypertensive flyer.

Direct Vasodilators

Although in theory vasodilators should correct the underlying abnormality common to hypertension, they cause reflex activation of the sympathetic nervous system and the renin-angiotensin axis, rendering them nearly useless as monotherapy. Concomitant treatment with diuretics and even

beta-blockers is typically required. These agents act by entering the smooth muscle cell and causing direct vasodilation, and see their greatest utility in treating hypertensive emergencies. Only hydralazine and minoxidil are suitable for outpatient use. In addition to tachycardia and volume retention, hydralazine causes a lupus-like syndrome, the frequency of occurrence depending on dose and duration.[54] Minoxidil causes severe volume retention and hypertrichosis, and is generally reserved for severe refractory hypertension. These agents are not suitable for military aviation, and hypertension severe enough to require these drugs is probably incompatible with military aviation.

Peripheral Adrenergic Neuron Antagonists

Reserpine, guanethidine, and guanadrel are older drugs which are rarely used now in clinical practice. Reserpine causes significant sedation, while depression is common with higher doses. Guanethidine and guanadrel cause orthostatic and exertional hypotension, which is aggravated in a hot environment.[9] None of these drugs is compatible with the military aviation environment.

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Lipid Lowering Agents
Aeromedical Concerns

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The Problem of Hyperlipidemia in Military Aviators

Hyperlipidemia is one of the major risk factors for coronary heart disease, a disease which, after a long asymptomatic period, may without warning cause sudden incapacitation due to angina, myocardial infarction or death. Hyperlipidemia is fairly common in military aviators, ranging from 30-68.5% in NATO countries.[1] In a survey among Greek fighter pilots, 10% had cholesterol levels over 300 mg/dl.[2]

Lipoprotein Levels

Cholesterol measurement is best performed in hospital chemical pathology departments after a fasting state (12-14 hour overnight fast) to allow concomitant measurement of triglyceride levels. Provided triglyceride levels are < 400 mg/dl (4.5 mmol /L), LDL is calculated according to the Friedewald formula.[3]

LDL= Total Cholesterol - HDL- TG/5

The current definitions of cholesterol and lipo-protein levels are listed in Table 1.

Risk Factors for Cardiovascular disease

The major risk factors for cardiovascular disease are:

a. age (male >45yr, female >55yr or premature menopause
b. family history of premature CHD (first degree male relative <55, first degree female relative < 65)
c. current cigarette smoking
d. hypertension (BP>140/90 mm Hg, or taking antihypertensive medication)
e. low HDL cholesterol (<35 mg/dl)
f. diabetes mellitus

Dietary and Drug Therapy

Dietary and drug therapy can lower cholesterol and prevent coronary heart disease. In particular, LDL cholesterol is strongly associated with atherogenesis and is the usual target for intervention. The indications for initiating dietary and drug therapy, and the suggested target levels, are listed in Tables 2 and 3.[3] However, it must be emphasized that correction of weight, aerobic exercise, and cessation of smoking should be considered part of the overall strategy.

Dietary measures should be pursued for at least 3-6 months before contemplating lipid lowering drugs. On average, around 5% reduction in LDL cholesterol is achievable with dietary therapy.[9] Drug therapy should be reserved for those military aviators at high risk for CHD, in the second and third priorities, where diet and healthy lifestyle measures have failed to achieve target levels.

Major Classes of Lipid Lowering Drugs

The major classes of lipid lowering drugs are:

a. Bile acid sequestrants (cholestyramine, colestipol)
b. Fibric acid derivatives (gemfibrozil, fenofibrate, etc.)
c. HMG-CoA reductase inhibitors, commonly referred to as “statins” (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin)
d. Others (nicotinic acid, probucol)

Bile acid sequestrants: The bile acid sequestrants currently available include cholestyramine and colestipol. Cholestyramine is dispensed in packets or scoops containing 4g of the active agent. The usual dosage ranges from 16 to 32g daily, taken with fluids in divided doses. Colestipol is dispensed in 5g packets. The usual dosage ranges from 15 to 30g daily in divided doses. These agents

are not absorbed. The major side effects are constipation and difficulty in ingesting the agents because of their bulk. Oddly enough, constipation tends to be a problem at lower dosages, and to decrease as the dosage is increased. Occasionally, cholestyramine can increase plasma triglyceride levels. Bile acid sequestrants have been used for years as the drug of choice for military aviators, and their long-term safety is well established. Compliance has usually been the major problem, even in clinical trials, as resins are not only inconvenient to take but also produce gastro-intestinal side effects. Because of the difficulty with compliance, resins may not be the optimal agent for use by aircrew.

Fibric acid derivatives: The most commonly used is gemfibrozil, which has been shown to decrease coronary mortality. Gemfibrozil can be used as first-line therapy in persons with concomitant high triglyceride and low HDL levels. Dosage is 600mg twice a day. Fenofibrate, ciprofibrate and bezafibrate are also used. They can reduce LDL by 20-30%, increase HDL by 10-15%, and reduce triglycerides by 40-60%. The most common side effect is gastrointestinal intolerance; myalgia is a rare complication. Gemfibrozil has also been associated with increased lithogenicity.

HMG-CoA Reductase Inhibitors: The statins are the most potent drugs available for reducing plasma concentration of LDL cholesterol. Statins reduce plasma LDL cholesterol by 30-40%, decrease plasma triglyceride by 10-30%, and increase HDL cholesterol by 2 - 15%. Many statins (pravastatin, atorvastatin, fluvastatin, lovastatin, and simvastatin) have been developed for clinical use and are now available in Europe and the United States.

Simvastatin and lovastatin are administered as lactones, and conversion to the active open acid occurs in the liver. In contrast, pravastatin is administered as a sodium salt of the open acid. Simvastatin is fat soluble, while pravastatin is water soluble and does not appear to cross the blood-brain barrier. Pravastatin has been shown to be minimally detectable in the cerebrospinal fluid of healthy volunteers, whereas lovastatin was present at concentrations that could have a pharmacologic effect.[6] The inability of pravastatin to penetrate into cerebrospinal fluid has been attributed to its hydrophilicity and low affinity for the transport mechanism of the blood-brain barrier.[7] The CNS penetration of lipophilic HMG-CoA reductase inhibitors may have clinical implications that are particularly relevant to military aviators.

The lipid lowering effect of statins is achieved by competitive and reversible inhibition of HMG-CoA reductase in hepatocytes, which induces a reduction in intracellular stores of cholesterol. As a consequence of the decline in cholesterol levels, there is up-regulation of LDL receptors on hepatocyte membranes, resulting in enhanced receptor-mediated catabolism and clearance of atherogenic LDL-cholesterol. Thus the liver is the primary site of action of statins. Administration of statins in the evening is associated with a greater lipid-lowering effect than that seen with morning administration.[5] This is almost certainly due to the increased nocturnal biosynthesis of cholesterol that occurs in humans. Clinically, the most important adverse events associated with HMG-CoA reductase inhibitors are myopathy and increases in hepatic transaminase levels. Myopathy, defined as muscular aching and weakness accompanied by a >10-fold elevation in CPK, is uncommon, occurring in <0.1% of patients in clinical trials of pravastatin.[8] If not recognized, however, myopathy can proceed to rhabdomyolysis and acute renal failure. It is generally recommended that HMG-CoA reductase inhibitor therapy be discontinued in patients developing markedly elevated CPK levels, or in those with symptoms suspicious for myopathy.

In common with other HMG-CoA reductase inhibitors, as well as other lipid-lowering drugs, biochemical abnormalities of liver function may occur with pravastatin therapy. Such increases in serum liver enzyme levels associated with pravastatin therapy routinely resolve on drug discontinuation, and are usually asymptomatic. In the WOSCOPS study, elevated SGOT and SGPT levels (> 3 times upper limit of normal) were present in 0.78% and 0.48% of 3302 pravastatin and 3293 placebo-treated patients, respectively.[8]

Clinical Experience in Primary Prevention of CAD with Lipid Lowering Agents

Five randomized, placebo-controlled trials have examined pharmacologic lipid-lowering therapy for primary prevention. The three early trials (World Health Organization study with clofibrate, LRC-CPPT with cholestyramine, and Helsinki Heart Study with gemfibrozil) showed a significant reduction in the risk of developing coronary events.[10,11]

The two latest trials, WOSCOPS, using pravastatin, and AFCAPS/TexCAPS, using lovastatin, clearly demonstrated reduction (31% and 37%, respectively) in the risk of cardiac death and nonfatal myocardial infarction with statin therapy for primary prevention.[8,12] These data show that lipid-lowering therapy, particularly with statins, can be effective in preventing cardiac events in patients without a previous diagnosis of coronary heart disease. To answer the question of cost-effectiveness for primary prevention we must compare the number of patients needed to treat in order to prevent one CHD death or nonfatal MI. Among patients enrolled in the primary prevention trial AFCAPS/TexCAPS, 83 patients required treatment to prevent one cardiac event. In the primary prevention trial WOSCOPS, treatment of 40 patients prevented one cardiac event. As the risk profile becomes more ominous, the cost-effectiveness increases.

Cholesterol Lowering Therapy and the Central Nervous System

Cholesterol is an important constituent of the central nervous system, which contains about 20% of the non-exchangeable pool of cholesterol in the body. Thus it is pertinent to consider whether lipid lowering therapy that decreases cholesterol synthesis might also adversely affect CNS functions, including emotional, intellectual and organic functions. This aspect of lipid lowering therapy is particularly relevant to military aviators.

Simvastatin and lovastatin, being lipophilic agents, have been shown to cross the blood brain barrier, in contrast to the hydrophilic agent pravastatin. This CNS penetration of HMG-CoA reductase inhibitors may also have clinical implications. Lovastatin and simvastatin, but not pravastatin, have been reported to be associated with sleep disturbance. Also, a recent study[13] suggested that lovastatin significantly affected daytime performance, with divided attention and vigilance worsening, effects that were not observed in the pravastatin group. Neither pravastatin nor lovastatin significantly affected nocturnal sleep or daytime sleepiness. Similar results were reported in later studies.[14,15] However, in a subsequent comparative study of lovastatin and pravastatin there was no significant effect by either drug on sleep or CNS function, including visual reaction time, auditory reaction time, verbal learning, embedded figures tests, verbal fluency test, trail making test, or visual memory test.[16] There are unpublished data about atorvastatin and pravastatin, in which both showed an increase in wakefulness during the latter part of the night, but neither drug appeared to affect subjective sleep assessment or performance.[17]

Conclusion

The basis for the usual therapy of hyperlipidemias, apart from severe and hereditary types, is strict dietary modification. Careful attention to all other coronary risk factors is essential. It is clear from epidemiologic studies that, even in the "normal" range of cholesterol, lower values are associated with fewer cardiovascular events, emphasizing the virtues of dietary advice for aircrew. Drug therapy can be used when dietary management fails or is inappropriate. No ideal lipid-lowering drug has yet been found. Statins are the most effective lipid-lowering agents, and seem to be safe according to large trials. Among the statins, the hydrophilic pravastatin has been preferred for use in aircrew, since both in theory and in studies it does not appear to affect the central nervous system. Whether the minor disturbances in sleep observed with some of the statins is of significance to aircrew involved in intensive operations is unclear at this time.

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TABLE 1: Lipoprotein Levels

Total Cholesterol	
Desirable	<200mg/dl (5.2mmol/L)
Borderline	200-250 mg/dl (5.2-6.5mmol/L)
High	>250mg/dl (6.5mmol/L)
LDL Cholesterol	
Desirable	<130mg/dl (3.4mmol/L)
Borderline	130-160mg/dl (3.5-4.1mmol/L)
High risk	>160mg/dl (5mmol/L)
HDL Cholesterol	
Low	<35mg/dl (0.9mmol/L)

TABLE 2: Indications for Initiating Dietary Therapy, and the Suggested Target Levels

		Total Cholesterol (mg/dl)		**LDL Cholesterol (mg/dl)**	
Priority	**Subject Category**	**Initiation Level**	**Target Level**	**Initiation Level**	**Target Level**
First	CHD	>200	<200	>100	<100
Second	**Without CHD, and with 2 or more risk** factors, or genetically determined hyperlipidemia	**>250**	**<200**	**>130**	**<130**
Third	Without CHD and with fewer than 2 risk factors	>300	<200	>160	<160

TABLE 3: Indications for Initiating Drug Therapy, and the Suggested Target Levels (mg/dl)

		Total Cholesterol (mg/dl)		LDL Cholesterol	
Priority	**Subject Category**	**Initiation Level**	**Target Level**	**Initiation Level**	**Target Level**
First	CHD	>200	<200	>130	<100
Second	Without CHD, and with 2 or more risk factors, or genetically determined hyperlipidemia	>250	<200	>160	<130
Third	Without CHD and with fewer than 2 risk factors	>300	<200	>190	<160

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Pharmacologic Agents for the Management of Asthma in Aircrew

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INTRODUCTION

Asthma is an inflammatory condition of the airways, producing variable bronchoconstriction. First line therapy is directed at controlling the inflammatory process with agents such as inhaled steroids, nedocromil, and the newer leukotriene inhibitor drugs. In severe cases, systemic steroids or other immunosuppressive therapies may be required for suppression of inflammation.

Other agents provide symptomatic relief of bronchospasm. Short-acting beta-agonists are the mainstay for providing relief of acute episodes. Anticholinergic inhaled agents have a minor role in acute episodes. Long-acting beta-agonists are used to smoothe long-term symptom control and help reduce the frequency of acute episodes when combined with inhaled steroids. Theophylline has bronchodilator properties and may have anti-inflammatory properties, but has a narrow therapeutic window.

Other newer agents are currently being developed, including anti-immunoglobulin E, antitryptase and anti-CD4 agents. These newer agents may expand the options for control of asthma over the next decade.[13]

The prevalence of asthma has been increasing in recent years, and occurs not uncommonly in an aviator population. Evaluation of aircrew requires a comprehensive respiratory assessment, including a detailed history of symptoms, triggering factors, and past treatment requirements, and a pulmonary function assessment with evaluation of bronchial reactivity. The challenge for the flight surgeon is to define as clearly as possible the severity of the disease, and to control the condition with agents acceptable for continuing aircrew duties. Good control of the inflammatory process with inhaled steroids alone, while minimizing or eliminating the need for bronchodilators, may allow continuing aircrew duties. The purpose of this monograph is to provide an overview of the agents currently available for the control of asthma from an aeromedical perspective. Reference (17) is a website providing excellent background information for both patients and physicians on asthma. Reference (10) provides a more comprehensive overview of the assessment and treatment of asthma in aircrew. In fast-jet aircrew, any degree of asthma is generally unacceptable because varying degrees of small-airway dysfunction may predispose to airway collapse with +Gz, thus contributing to both acceleration atelectasis and aggravation of the ventilation/perfusion mismatch induced by G. In non fast-jet aircrew, stability of bronchial reactivity and full control of asthmatic symptoms with acceptable medications is the prime objective. Aircrew whose airway reactivity is normalized and well-controlled on acceptable medications may be considered for continuing duties.

PHARMACOLOGIC AGENTS

Inhalation Delivery Devices

Most asthma medications are delivered through inhalation delivery devices. For decades, the standard delivery device has been the pressurized metered dose inhaler (MDI). For many patients, drug delivery with MDIs is improved significantly by the use of a spacer device. Chlorofluorocarbons (CFCs) have been the primary propellants for MDIs since their introduction over three decades ago. However, due to environmental concerns, CFCs are being phased out as MDI propellants, and are being replaced generally by hydrofluoroalkanes (HFAs). Environmental concerns aside, HFAs have several therapeutic advantages over CFCs. MDIs with HFAs demonstrate an improved consistency in delivered dose per actuation, and administer a warmer spray with reduced jetting velocity. HFAs also have a smaller particle size, resulting in better delivery of medication farther into the lungs.[14] Inhaled agents may also be delivered by dry powder

inhalers (DPIs). These devices deliver medication from either capsules, a bulk reservoir, or as multi-dose units. DPIs may be battery-powered or patient-driven. The latter are dependent on the patient's inspiratory effort for proper deposition. These are activated by inspiration itself, and may be easier to use for patients with difficulty with hand-breath co-ordination.[8]

The type of device, the drug formulation, and patient technique are all variables that determine the dose of inhaled drug that reaches the lungs – variables that must be kept in mind when assessing patient response and potential medication side-effects. In particular, both flunisolide and beclo-methasone are soluble in HFAs, but insoluble in CFCs; thus, HFA MDIs result in much greater delivery of these drugs to the lungs. This greater deposition results in an approximately 2.6 fold increased dose. Several studies with the newer MDIs support equal efficacy using half the apparent dose of the older CFC powered inhalers.[14] With the gradual phase-out of CFCs in favor of HFAs, flight surgeons must be aware of and assess the change in relative potency of the various preparations of inhaled steroids in particular.

BETA-AGONISTS

$Beta_2$ agonists are sympathomimetic amines which, despite variable degrees of beta-selectivity, display similar effects, such as cardiac excitation, CNS stimulation, and vasoconstriction, and similar side-effects, such as tremor, nervousness, headache, sweating, and increased heart rate and blood pressure. The requirement for beta-agonists indicates that the underlying inflammatory process is not fully controlled, and beta-agonists are required to provide either acute symptom control, in the case of short-acting agonists, or longer-term control of bronchoconstriction with long-acting agents.

Short-acting Agents

Short-acting beta-adrenergic stimulants provide rapid relief from acute bronchospasm. Non-selective agents such as isoproterenol have been superseded by relatively selective $beta_2$ agonists including terbutaline, isoetharine, and albuterol (salbutamol). Administered by MDI, these agents have a rapid onset (~15 minutes), and a relatively short duration of action (3-4 hours). Even with inhalation, there is some systemic absorption of these drugs, with side-effects including tachycardia, palpitations, headache, sweating, nervousness, and tremors. Oral preparations are also available, but have a slower onset of action (~1 hour), longer action (5-7 hours), and more side-effects, and thus are not suitable for use in aircrew. Short acting agents may be all that is required for very mild asthmatics with very infrequent or very specific trigger factors (step 1 therapy).

Aeromedical Recommendations: **Because of the side effect profile, the use of short-acting inhaled beta-agonists in aircrew is not advised within six hours of duty. The requirement for these agents for symptomatic control of bronchospasm is generally an indication that the asthma is inadequately controlled for aircrew duties. An exception might be pure exercise-induced asthma, where inhaled ß-agonists may provide excellent control of exercise-induced bronchoconstriction, and may be suitable for "as required" use up to six hours pre-flight, except in fast-jet aircrew, where the heavy exertion of anti-G straining maneuvers could precipitate bronchospasm and the sympathomimetic effect may aggravate G-related arrhythmias.**

Long-acting Agents

In the past decade, long-acting inhaled $beta_2$ agonists such as salbuterol and formoterol have been introduced to provide a more sustained action for control of bronchoconstriction. They are not intended for acute symptomatic relief of broncho-spasm. A common current clinical approach is to combine a long-acting inhaled agent with an inhaled steroid if adequate control is not achieved with the steroid alone. A recent study, dispelling earlier concerns that regular beta-agonist treatment might cause a worsening of asthma, demonstrated better control of asthma when inhaled cortico-steroids were combined with formoterol than with short-acting albuterol.[9]

Although cardiovascular and other non-pulmonary side-effects, largely related to direct cardiac stimulation, reflex activation of adrenergic mechanisms, and hypokalemia, are a concern with all beta-adrenergic agonists, the inhaled $beta_2$-agonists have proven in several clinical trials to be remarkably free from cardiovascular side effects in patients followed with ECGs and Holter monitoring.[6,15] In a group of patients with mild asthma, low (12 μg) doses of formoterol showed no cardiovascular side effects compared with placebo, although at higher doses (up to 96 μg), heart rate and blood pressure were increased, QT interval increased, blood glucose increased, and serum potassium decreased compared with placebo.[3] In

COPD patients with co-existing hypoxia, formoterol in a 24 μg dose was shown to significantly reduce serum potassium level, and increase ventricular and supraventricular ectopic activity.[5]

Aeromedical recommendations: **These long-acting highly selective beta-agonists have added a significant bullet to the pharmacologic armamentarium for maintenance control of asthma. Further assessment is required before these agents can be recommended for use in aircrew, especially in pilots. Based on the presently available clinical information, they might be considered for non-pilot aircrew in non-fast jet operations, in lower doses only, e.g., 50 μg of salmeterol or 12 μg of formoterol. The sustained beta-adrenergic stimulation induced by these agents may predispose to arrhythmias and other undesirable side effects in high-G operations, and their use in fast-jet aircrew cannot be recommended pending aeromedical evaluation.**

ANTI-INFLAMMATORY AGENTS

Steroids

Inhaled Steroids

Inhaled steroids form the mainstay for the treatment of asthma of all but very mild degree, where occasional use of inhaled short-acting beta-agonists may suffice. Inhaled steroids vary in potency but all act by suppressing airway inflammation, which is recognized as the primary mechanism in asthma. Apart from local upper airway irritation and infrequent oral candidiasis, inhaled steroids are generally free from side effects. Treatment is initiated at a low dosage, e.g., 400-800 μg daily of beclomethasone or equivalent, and the dosage titered upwards if symptoms and airway reactivity are not adequately controlled. In high dosages, inhaled steroids may suppress the adrenocortical axis, a potentially significant aeromedical concern, exposing aircrew to the risk of adrenal crisis at times of high stress. Decreased bone density, cataract formation, dermal thinning and glaucoma have also been reported.[8]

Doses of beclomethasone or budenoside of 1500 μg per day or higher have been shown to suppress hypothalamo-pituitary-adrenal axis (HPA) function,[1] although there is wide inter-individual variation,[2] with some individuals maintaining normal HPA function with dosages as high as 5 mg (5000μg) daily. However, in aircrew, dosages exceeding 1200 μg of beclomethasone or equivalent are not recommended; if additional maintenance medication is required, a long-acting beta-agonist (see above), or leukotriene inhibitor (see below) may be considered. (Note: The studies quoted were based on the use of CFC MDIs, and as noted earlier the possibility exists of altered absorption of inhaled steroids with HFA MDIs).

Aeromedical recommendations: **In moderate dosages, i.e., up to 1200 μg per day of CFC MDI beclomethasone or equivalent, inhaled steroids appear to be safe for use in all aircrew, including pilots. These drugs should form the first line Step 2 treatment for asthma in aircrew requiring more than very infrequent short-acting beta-agonists for control (Step 1 Rx). Good control of airway inflammation with inhaled steroids may well result in stabilization and normalization of airway function, including airway reactivity, and may allow aircrew including pilots to return to flying duties in other than fast-jet operations. This should be confirmed by a full pulmonary function assessment as part of the aeromedical disposition work-up; such testing should be carried out with the aircrew member taking his usual maintenance dose of inhaled steroid.**

Systemic Steroids

Although high-dose rapidly tapering oral steroids may be useful in the short-term suppression of an acute asthmatic episode, the requirement for systemic steroid therapy for maintenance control of asthma reflects a degree of asthma incompatible with all aircrew duties. Systemic steroids have side effects generally incompatible with aircrew duties, including psychotropic effects, hypertension, GI side effects including ulcers, bone mineral loss, and significant HPA suppression.

Aeromedical recommendations: **Aircrew should not be returned to flying duties while taking systemic steroids. The requirement for systemic steroids for control of an acute asthmatic episode should prompt a thorough aeromedical review with re-assessment of pulmonary function, including airway reactivity, before considering a return to flying duties.**

Nedocromil

Nedocromil is a non-steroidal pyranoquinolone anti-inflammatory agent which acts by stabilizing inflammatory cells, thus preventing the local release of inflammatory mediators and inhibiting

chemotaxis. It is administered by MDI at a dose of 4mg four times a day, or before exposure to precipitants such as exercise. Nedocromil is not as effective as inhaled steroids in reducing airway inflammation, but aside from bad taste, occasional headache, and GI upset, it is generally free from systemic side effects.

Aeromedical recommendation: Nedocromil may be helpful in some aircrew with mild asthma who require an anti-inflammatory inhaled medication to control airway reactivity, but better control is generally achieved with inhaled systemic steroids, and at less frequent dosing.

Disodium Cromoglycate

Disodium cromoglycate (DSCG) is an inhibitor of mast cell degranulation that can help decrease airway responsiveness. It has no bronchodilating activity and is useful only for prophylaxis. DSCG should not be added to an established regimen of inhaled glucocorticoids – it can neither augment nor sustain the improvement in airway responsiveness already achieved by inhaled glucocorticoids.[4] It has no systemic toxicity, and so is potentially a good drug for aircrew with mild asthma. Bad taste is virtually the only side-effect. Although it is not as effective as a beta-agonist, it may be helpful for preventing exercise-induced bronchospasm. For maintenance prophylaxis, the minimum effective dose is considered to be 10 mg 3-4 times daily. MDI formulations of DSCG contain only 1 mg per actuation, so effective adult dosages can really only be accomplished with a DPI capsule formulation, or a nebulizer.

Aeromedical recommendation: **DSCG is worth a trial for prophylaxis in aircrew with mild asthma symptoms because of its freedom from systemic side-effects.**

Theophylline

Theophylline has been a useful treatment for asthma for over 50 years, and although traditionally classified as a bronchodilator, has recently been shown to have immunomodulatory, anti-inflammatory and other non-bronchodilator properties that contribute to its efficacy as an anti-asthmatic medication.[16]

Aeromedical recommendation: Because of its markedly narrow therapeutic window, and significant side effects including cardiac arrhythmias, tremor, neuromuscular irritability and seizures, theophylline is not recommended for use in aircrew.

Leukotriene Inhibitors

Leukotrienes, along with prostaglandins and thromboxanes, belong to a group of biologically active fatty acids called eicosanoids. They are not stored in cells but are generated by lipoxidation of arachidonic acid. Leukotriene B_4, produced by neutrophils and monocytes, is chemotactic for neutrophils and causes leukocyte activation. Activated eosinophils and monocytes preferentially make cysteinyl leukotrienes, which are extremely potent bronchoconstrictive compounds. In addition, leukotrienes also increase vascular permeability, stimulate mucus release, and slow ciliary activity and mucus transport. Leukotrienes are thus central in the pathogenetic mechanism for the asthmatic response, and major efforts have been made to inhibit the synthesis of, or block the effects of, leukotrienes. This has led to the development of anti-leukotrienes, an entirely new and potentially extremely useful group of drugs in the anti-asthma armamentarium, which target specific sites in the inflammation cascade. Three of the currently available drugs are specific leukotriene D4 receptor (LTD4) antagonists, and the other is a 5-lipoxyenase inhibitor (see table below). Anti-leukotrienes are the subject of several recent major reviews.[7,11,12]

The anti-leukotrienes currently clinically available are in Table 1 (adapted from 12).

In antigen challenge studies, LTD4 antagonists inhibit 81% of the early airway response, and up to 57% of the late airway response. They can decrease airway responsiveness to methacholine, antigens, cold air, exercise, and aspirin in sensitive patients. A particular advantage is that they may also be effective for allergic rhinitis as well as asthma. Few studies have compared the effectiveness of these agents with other anti-asthmatic medications. The clinical effectiveness of LTD4 antagonists in asthma appears to be similar to low-dose inhaled steroids, nedocromil or cromoglycate

The established effects of the anti-leukotrienes are shown in Table 2 (adapted from reference 12).

Advantages/Disadvantages/Side-effects

- LTD4 antagonists have a rapid onset of therapeutic action (within 2 weeks), compared

with inhaled steroids, which may take up to six weeks to achieve full therapeutic benefit.

- Once or twice daily dosage may improve compliance.
- Oral delivery may produce more consistent therapeutic responses.
- They may be effective for allergic rhinitis as well as asthma.
- Side-effects have been minimal in initial clinical trials (2 years experience now).
  - Occasional headaches, nausea, diarrhea (incidence not different from placebo), with occasional mild elevation of liver enzymes, have been described.
  - Zafirlukast and pranlukast, but not montelukast, inhibit cytochrome p450 and may produce drug interaction effects.
  - A few cases of a Churg-Strauss-like syndrome have been reported in patients during initiation of zafirlukast, during tapering of systemic steroid dosages.

This new class of anti-asthmatic medications may be helpful in control, but not acute treatment, of asthma in mild or moderate cases, either as initial step 2 treatment or combined with inhaled steroids. They may also be used to achieve control with a lower steroid dosage in moderate to severe asthmatics. Improvement can be expected in approximately 50% of patients.

Aeromedical recommendation: Early clinical experience suggests these drugs are safe and moderately efficacious. There have been no trials published on possible effects on psychomotor or cognitive performance or vigilance, nor on other factors of aeromedical concern such as vision, special senses, or environmental effects. Until further clinical experience becomes available, the use of these agents cannot be recommended in pilot aircrew. In other aircrew, particularly in non-flight safety sensitive positions, consideration might be given to a trial of an LTD4 agent in step 2 control (requiring daily preventive medication).

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TABLE 1

Drug	Action	Status	Dosage	Cost (USD/month)
Montelukast (Singulair)	Leukotriene D4 receptor antagonist	Licensed worldwide	10 mg/day	75.80
Zafirlukast (Accolate)	Leukotriene D4 receptor antagonist	Licensed worldwide	20 mg BID	52.50
Pranlukast (Ultair)	Leukotriene D4 receptor antagonist	Launched in Japan	300-450 mg QD or BID	ND
Zileuton (Zyflo)	5-lipoxygenase inhibitor – inhibits leukotriene synthesis	Launched in US	600 mg QID	75.00

TABLE 2

	Montelukast	Pranlukast	Zafirlukast	Zileuton
Early response	Effective	Effective	Effective	Effective
Late response	Effective	Effective	Effective	Not effective
Bronchial hyper-responsiveness	ND	Effective (methacholine)	Effective (allergens)	Effective (cold air)
Exercise-induced asthma	Effective	Effective	Effective	Effective
Allergic rhinitis	ND	ND	Effective	Effective
ASA sensitivity	Effective	Effective	ND	Effective
Chronic asthma	Effective	Effective	Effective	Effective
Eosinophil level	Effective	Effective	Effective	Effective
Comparisons				
Inhaled steroids	Similar	Similar	Similar	ND
Nedocromil or cromoglycate	ND	Similar	Similar	ND
Theophylline	ND	ND	ND	Similar

ND = Not Demonstrated

H_1-Antihistamines and Aircrew

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For many years it was accepted that antihistamines were among the safest medications in the world, and this reputation was enhanced by the development of the so-called second generation compounds, which were largely free of adverse effects on vigilance and performance. It was against this background that there was wide agreement that they could be used safely by aircrew. However, cardiotoxicity has now become an issue with these antihistamines,[1] and the confidence which was once placed in their use for aircrew requires re-examination.

With certain antihistamines, plasma concentrations of the parent compound, caused by overdosage, inhibition of metabolism, or hepatic insufficiency, may lead to prolongation of the QT_c interval, and thus to ventricular dysrhythmias similar to those seen with quinidine. Such dysrhythmias are likely due to blockade of the rapidly activating component (I_{Kr}) of the delayed rectifier potassium channel, since inhibition of this channel is common to virtually all drugs that prolong the QT interval.[2] There is no evidence of any correlation between I_{Kr} inhibition and antihistamine potency or H_1 receptor blockade.

Inhibition of metabolism is a particularly important issue and some individuals may even be poor metabolisers. Antihistamines such as terfenadine and astemizole are metabolised by the P400 enzyme CYP3A4 to compounds which have little or negligible cardiac effects. The enzyme may be inhibited by anti-fungals such as ketoconazole, itraconazole and terbinafine, the macrolide antibiotics erythromycin, clarithromycin and troleandomycin, the azalide antibiotic azithromycin, 6,7-dihydroxybergamottin (an active principle of the flavonoids of grapefruit juice), and ethinylestradiol. Cimetidine and ranitidine are H_2-antihistamines which also inhibit CYP3A4. Caution must be exercised with any coadministered drug which inhibits the enzyme, and thus may raise the plasma concentration of the parent antihistamine or its metabolite.

Caution must also be exercised with the use of antihistamines in individuals with congenital prolongation of the QT_c interval, bradycardia, ischemic heart disease, congestive cardiac failure, electrolyte changes (especially hypokalemia) and drugs that prolong the QT_c interval such as quinidine. All potential H_1-antihistamines must be screened for cardiac toxicity, as some individuals may be susceptible to plasma concentrations near the therapeutic range.

At the time of writing, there are two antihistamines which may be considered for use by aircrew. These are fexofenadine, the metabolite of terfenadine, and loratadine. The metabolite of loratadine, desloratadine, is under clinical development. Fexofenadine and loratadine have been shown to be clinically effective, are believed to be free of central effects, and have low, if any, cardiotoxic effects.

Cetirizine has sedative activity, and is therefore not suitable for use by aircrew.[3]

LORATADINE

Loratadine is rapidly and completely absorbed, reaching peak plasma levels within 1 to 2 hours after ingestion. The elimination half-lives of loratadine and its metabolite (descarboethoxy-loratadine) are 8 to 14 hours and 17 to 24 hours respectively.[4,5] This elimination rate allows loratadine to remain active over 24 hours, enabling once daily dosing.

Performance studies have shown that loratadine (10mg) is free of effects on performance and sedation and so is suitable for those involved in skilled work or driving.[6,7] Loratadine has no effect on a wide variety of psychomotor skills including reaction time, vigilance, visuomotor coordination, visual acuity or digit symbol substitution. Studies using subjective and objective (daytime sleep latencies) measures of sleepiness have also shown no sedative effect. Further, the lack of any sedative effect of loratadine has also been shown in driving tests.[8]

In contrast with terfenadine and astemizole, loratadine is believed to be free of adverse cardiac effects in humans. However, there are reports which suggest it may be associated with atrial arrhythmias,[9,10] and studies have shown that loratadine in therapeutic concentrations[4] can modulate potassium currents in isolated human atrial myocytes.[11] The analysis of Lindquist & Edwards,[9] however, has been questioned.[12,13] The study by Crumb[11] evaluated the effect of loratadine on different potassium channels; studies using isolated ventricular myocytes have shown only a 10-15% suppression of the I_{Kr} channel at a loratadine concentration of 2.5 µM, a level which is probably clinically unachievable.[14] There is little, if any, firm evidence from clinical studies to support an increased risk of arrhythmias from loratadine. Co-administration of agents known to inhibit the metabolism of loratadine with high plasma concentrations have not led to changes in the QTc interval. Further, exposure to four times the recommended daily dose of loratadine, i.e., 40mg once daily, for 13 weeks has failed to show changes from baseline in any electrocardiographic parameter, and there was no evidence in any individual of prolongation of the QTc interval.[15]

FEXOFENADINE

Fexofenadine is a racemic mixture of two pharmacologically active isomers. It is the active metabolite of terfenadine, and is a highly specific H_1-receptor antagonist free of anticholinergic and antiadrenergic activity. It is rapidly absorbed by the oral route, reaching peak plasma levels within 1 to 3 hours. It is excreted unchanged by the biliary and renal routes and has an elimination half life of 11 to 15 hours.

In a study carried out at the UK Defence Evaluation and Research Agency Centre for Human Sciences, digit symbol substitution, tracking and vigilance tasks, as well as objective (daytime sleep latencies) and subjective measures of sleepiness, were studied in healthy volunteers from one hour to eight hours post-ingestion using 120, 180 and 240mg. There were no changes in performance or sleepiness with any dose of fexofenadine at any time compared with placebo.[16]

The effects of fexofenadine in doses up to 240mg daily have also been studied on driving and on psychomotor performance.[17] Volunteers were treated for five days with each of four different doses of fexofenadine (60mg twice daily, 120mg twice daily, 120mg once daily, 240mg once daily). On days one, four, and five of each treatment period the subjects underwent a highway driving test and a battery of psychomotor performance tests. The results for all fexofenadine doses were not significantly different from placebo.

In view of the clear cut cardiotoxic effects of terfenadine, careful attention has been given to the possibility that its metabolite, fexofenadine, might also modulate cardiac conduction. However, animal studies and human studies specifically designed to examine the effect of repeated doses of fexofenadine on the electrocardiogram have failed to show any changes of significance in the QT_c interval.

In a letter to the Lancet,[18] Pinto et al raised the possibility of QT lengthening from fexofenadine in a cardiac patient, which in turn led to correspondence with the manufacturer, Hoechst-Marion-Roussel. Giraud[19] pointed out that the patient reported by Pinto *et al* had several risk factors for ischemic heart disease, with evidence of progressive coronary artery disease and a

possible inferior infarction. Of even greater significance, there was evidence of QTc prolongation before the initiation of therapy with fexofenadine, and the first documented episode of ventricular tachycardia occurred during a drug-free interval, four days after discontinuing fexofenadine. Pinto *et al*[20] disputed the importance of the coronary disease, noting that the coronary lesion documented at follow-up angiography would not likely have been of hemodynamic significance; however, they did not dispute the other two points. Review of the original report by Pinto *et al*[18] also shows that the subject had pre-existing left ventricular hypertrophy, likely due to hypertension. Furthermore, the reported fluctuations in the measured QTc interval fell within the range of expected variability. Pratt *et al*[21] found, when comparing single tracings before and after exposure to a drug, that an increase in QTc of at least 60 msec was necessary before one could reasonably ascribe the difference to the medication. In essence, then, this was a report of questionable cardiotoxicity from fexofenadine, in one individual with numerous confounding factors, against a background of preclinical and clinical evidence that fexofenadine has no significant QT lengthening effect.

CONCLUSION

At the time of writing there would appear to be two antihistamines which could be used by aircrew. Both loratadine (10mg daily) and fexofenadine (120-180mg daily) are free of adverse effects on vigilance and performance. Though it is not possible in all circumstances to exclude an adverse effect on cardiac conduction, the considered evidence is that both loratadine and fexofenadine are acceptable for aircrew, and that it is not possible to state a preference for one drug over the other.

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Endocrine Drugs in Aircrew

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INTRODUCTION

Hormones are molecules that are synthesized and secreted by groups of cells clustered in specific tissues, usually known as glands, and are released into the blood, exerting biochemical effects on target cells at a distance from their site of origin. Hormones are chemical messengers, endogenous compounds that are involved in both intracellular and extracellular communication. The site of action is determined by the presence of specific hormone receptors on or in target cells.

Hormones have diverse molecular structures, as summarized in Table 1.

Historical interest in hormonal effects is ancient;[1,3] the physiological and morphological effects of accidental or intentional castration of man or domestic animals were known to be correlated with the loss of testes. Later, transplanted testes were demonstrated to prevent development of capon characteristics in the castrated rooster, and later still it was shown that testicular extracts, and finally testosterone itself, corrected the deficit. Similar discoveries were made concerning the ovary, the adrenal, and the thyroid, through the classic experiments of surgical extirpation and replacement.

In the beginning, hormonal therapy was developed by using *natural substances* extracted from animal or human organs, but now these have been almost entirely supplanted by *synthetic hormones*.

Worldwide prevalence of endocrine disorders varies significantly. Certain endocrine conditions are among the most prevalent diseases in general medicine, particularly diabetes mellitus, obesity, and thyroid disorders.[4]

In clinical endocrinology practice, the most common endocrine diseases are diabetes mellitus, thyrotoxicosis, hypothyroidism, nodular goiter, diseases of the pituitary gland and diseases of the adrenal gland.

Hormonal therapy is, usually, a substitutive treatment for endocrine disease resulting from inadequate hormone production, faulty transduction of a hormonal message, or, finally and rarely, resistance to hormonal action. Hormones are also widely administered in general and specialty medicine because of desired systemic effects of hormonal compounds, such as the anti-inflammatory action of corticosteroids, the contraceptive action of gonadal steroids, or the antineoplastic action of hormonal antagonists. Indeed, some synthetic hormones are only used for this purpose, since they are not suitable for hormonal replacement.

Aeromedical concerns with the therapeutic use of hormones should be addressed by evaluating the mode of action and side effects of hormonal agents when administered to flying personnel, with the goals of recovery and allowing return to qualification. These issues should be addressed whether a hormone is used for replacement, or for its pharmacologic effect. Aeromedical interest tends to focus on those endocrine disorders that arise in adulthood, since those with endocrine problems at an earlier age are usually screened out of flying training.

This monograph will focus mainly on three hormonal therapeutic agents: adrenal hormones, insulin and thyroid hormones. Hypothalamic and pituitary hormones will not be considered, since they are used primarily in diagnostic procedures, and only very rarely for medical treatment.

ADRENAL HORMONES

Adrenal hormones act in a variety of ways to maintain homeostasis and to aid survival in the face of fight-or-flight situations, fasting, injuries, shock, and other stresses.

The human adrenal consists of an outer cortex, which secretes steroid hormones, and an inner adrenal medulla, an extension of the sympathetic

nervous system, which secretes catecholamines.[5] The adrenal cortex produces three types of steroid hormones: glucocorticoids, influencing glucose metabolism; mineralocorticoids, which regulate Na^+ and K^+ balance; and androgens. The adult adrenal cortex is composed of three zones. The outer *zona glomerulosa*, which expresses the enzyme 18-oxidase, produces aldosterone and is regulated primarily by the renin-angiotensin system rather than by adrenocorticotropic hormone (ACTH) from the pituitary gland. The middle *zona reticularis* and the compact innermost *zona fasciculata* express the enzyme 17α-hydroxylase and produce cortisol and androgens; they are regulated by ACTH, via the hypothalamic-pituitary-adrenal axis.

Biologic Effects of Adrenal Hormones

Cortisol is a glucocorticoid hormone. It promotes gluconeogenesis (conversion of amino acids to glucose) in the liver, and increases protein catabolism to obtain the amino acids needed for gluconeogenesis.[6,7] Cortisol inhibits glucose uptake by muscle and fat, causing insulin resistance, promotes hepatic glycogen synthesis, and increases the blood glucose concentration.[8] In adipose tissue cortisol stimulates lipolysis and release of free fatty acids.[9]

An abnormally increased cortisol level, whether as a result of stress, adrenal hyperproduction, or pharmacologic administration, has many side effects. It stimulates appetite, with increased caloric intake and weight gain, and suppresses inflammation and the immune system.[10] Cortisol inhibits bone formation, and exerts catabolic effects on bone, connective tissue and muscle, causing loss of bone and muscle mass, and thus weakness.[11,12] An excess of cortisol causes altered mood, behavior and cognition, resulting in euphoria, insomnia and even psychosis. Cortisol excess increases blood pressure[13] due to its mineralocorticoid effects in increasing salt and retaining water.

Aldosterone is the principal adrenal mineralocorticoid hormone. It increases Na^+ retention, and urinary K^+ and hydrogen ion (H^+) excretion, by the distal renal tubules and collecting ducts; it also acts on other secretory glands, such as sweat glands, salivary glands, and glands in the intestinal tract.[14,15]

Dehydroepiandrosterone (DHEA) is a weak androgen. It is important in the maintenance of female axillary and pubic hair. Adrenal androgens can cause hirsutism and masculinization of females and prepubertal males.

The important differences among the systemically used corticosteroid compounds primarily relate to duration of action, relative glucocorticoid potency, and relative mineralocorticoid potency. Corticosteroids are classified as short-acting, intermediate-acting, and long-acting on the basis of the duration of ACTH suppression after a single dose equivalent to 50 mg of prednisone. The relative potencies of the corticosteroids correlate with their affinities for the intracellular specific receptors. The observed potency of a corticosteroid is determined not only by the intrinsic biologic potency, but also by the duration of action (Table 2).

Therapeutic Use of Adrenal Hormones

Systemic glucocorticoid therapy is usually employed for its anti-inflammatory and immunosuppressive action;[16] in fact, glucocorticoids inhibit the production or action of many mediators of immunity and inflammation, including interleukin-1, lymphokines, prostaglandins, collagenase, leukotrienes, thromboxanes, serotonin, bradykinin, histamine, and plasminogen activator.[16] The more severe the immune or inflammatory disorder, the more readily can glucocorticoid therapy be justified. Thus, corticosteroids are commonly used in patients with severe forms of systemic lupus erythematosus, sarcoidosis, active vasculitis, asthma, chronic active hepatitis, transplantation rejection, pemphigus, and immune hematologic diseases such as thrombocytopenia, hemolytic anemia, and medullary hypoplasia.[17]

The use of high-dose glucocorticoids for one or two weeks, in absence of a contraindication to therapy, is unlikely to be associated with serious side effects (Table 3).[18,19] A severe, but fortunately rare, exception is a corticosteroid-induced psychosis. Although this complication may occur after only a few days of therapy in patients with no previous history of psychiatric disease, the risk is generally related to the dose and duration of therapy; thus, the smallest possible dose should be prescribed for the shortest possible period.[20]

The side effects of glucocorticoids include the diverse manifestations of Cushing syndrome and hypothalamic-pituitary axis suppression. The latter may occur after withdrawal from treatment with the equivalent of 20 to 30 mg/day of prednisone for as little as five days, and carries a high risk of acute

adrenal insufficiency. For this reason glucocorticoids should be withdrawn gradually, over an interval of weeks to months, with frequent assessment of patients.[21,22]

Glucocorticoids are commonly administered to replace the missing hormones in adrenal insufficiency, acute and chronic (Addison's disease), and in adrenogenital syndromes (Table 4). The adequacy of glucocorticoid and mineralocorticoid replacement is currently best evaluated by the clinical response to therapy.[23] Adequate treatment results in the disappearance of weakness, malaise and fatigue. Anorexia and other gastrointestinal symptoms resolve, and weight returns to normal.[24,25]

Secondary adrenal insufficiency has an excellent prognosis with life-long therapy with glucocorticoids and mineralocorticoids, though there is the ever present risk that adrenal crisis may occur during superimposed physiologic stress.[26]

Aeromedical Considerations

There are no currently available biochemical procedures for assessing the response to treatment of adrenocortical insufficiency. Measurement of plasma cortisol or ACTH levels is of no particular value because of the wide variability of each, while measurement of urine free cortisol levels is likewise of little help. The clinical response is the best measure of the adequacy of replacement therapy. Most patients, appropriately treated, may lead normal lives without significant disability, although the risk of development of acute adrenal insufficiency persists. This complication is almost entirely preventable in previously diagnosed and treated patients, but is higher in patients exposed to relevant and frequent physical or psychological stressors.[27]

Aviation, military or civilian, is a high-performance and high-risk occupation, in which operational or conventional flying activity exposes pilots to stressful events that could represent a real risk, even in a subject with appropriately treated adrenocortical insufficiency. In our opinion adrenocortical insufficiency should be considered not suitable for operational flying, because of the serious risk of complications such as acute adrenal crisis. In aviators who will not be exposed to combat flying, those who receive replacement therapy with adrenocortical hormones may be cleared to return to flying duties. This should follow a grounding period to allow complete resolution of the clinical features of Addison's disease. Even then, it seems wisest to restrict such individuals to dual-piloted aircraft.

INSULIN AND DIABETES MELLITUS

Diabetes mellitus is the most common endocrine problem, with a worldwide prevalence of approximately 5%.[28] Recent advances in understanding the pathogenesis of the various types of diabetes and the mechanisms by which complications occur have allowed more effective methods of prevention and treatment.[29] Despite advances, however, the treatment of diabetes with insulin or oral hypoglycemic agents is still accompanied by the risk of hypoglycemia and of the micro- and macrovascular complications of the disease itself, features of great aeromedical concern when considering the possibility of returning a diabetic pilot to flying status.

Blood glucose concentration is maintained within normal range by the action of hormones from the pancreatic islets, which are dispersed throughout the exocrine pancreas and produce four different hormones, insulin, glucagon, somatostatin and pancreatic polypeptide. Insulin and glucagon, both polypeptides, oppose each other in regulating glucose metabolism. Insulin acts to move glucose into insulin-sensitive tissues, such as liver, muscle and fat, and to enhance the storage of fuels. Its major biochemical effect is anabolic, both by promoting anabolism and inhibiting catabolism.[30] Insulin promotes storage of glucose as glycogen, by increasing the rate of glycogen formation and decreasing the rate of glycogenolysis in both the liver and skeletal muscle.[31] By means of its inhibitory effects on both lipolysis and proteolysis, insulin also promotes the storage of fats and proteins. Glucagon, on the other hand, acts by opposing these actions of insulin. Somatostatin inhibits the secretion of both insulin and glucagon, and thus reduces the effects of both these hormones. In addition to insulin and glucagon, several other hormones contribute to the modulation of carbohydrate metabolism. Most are insulin antagonists, including growth hormone, glucocorticoids, epinephrine and thyroxine.

Insulin is continuously secreted by the pancreatic β cell, at a basal rate in the post-absorptive state (6-12 hours after a meal), at a suppressed rate during prolonged fasting, and in large quantities upon

ingestion of nutrients.[32] The action of both insulin and glucagon are mediated by cell surface specific receptors that bind to each hormone.[33] To maintain normal glucose tolerance, insulin secretion and sensitivity to insulin must be normal; absolute insulin deficiency and/or abnormalities in sensitivity to insulin may lead to diabetes. Primary diabetes is classified as Type 1 or Type 2.

Type 1 diabetes was formerly known as juvenile onset diabetes, or insulin-dependent diabetes mellitus. It is caused by an absolute deficiency of insulin and typically occurs because of autoimmune destruction of the pancreatic β cells in genetically susceptible individuals who are exposed to certain environmental factors. The rate at which this destruction occurs is variable, but if the disease occurs in childhood, the destructive process is rapid. Between 50%-85% of children with type 1 diabetes have antibodies to islet cells (ICA) present in their serum at the time of diagnosis, and some also have insulin antibodies, generated in response to destruction of β cells.[34] The worldwide prevalence of type 1 diabetes varies significantly. The highest prevalence is in Finland, which has a rate two to three times that of the USA. The peak age of onset of type 1 diabetes occurs between the ages of 10 and 16, with a second peak of onset occurring in the 40s.[26] Presenting symptoms typically include the classic triad of polyuria, polydipsia, and polyphagia, attributable to the wasting of glucose in the urine, which also results in weight loss.

Type 2 diabetes was formerly known as adult onset diabetes, or non-insulin-dependent diabetes. Type 2 usually occurs because of abnormalities in both insulin secretion and insulin action. The result is that glucose production from the liver increases, and glucose uptake into tissues decreases. The hyperglycemia that ensues exacerbates the problem by leading to further impairment of β cell function and insulin action.[35] Type 2 diabetes has a strong genetic component,[26] but its development is profoundly influenced by environmental factors such as obesity and lack of exercise, which increase insulin resistance. Prevalence of type 2 diabetes varies from 6% to 10%.[36]

Treatment of Diabetes

The aims of diabetes therapy are twofold: firstly to correct the symptoms of diabetes, and secondly to normalize plasma glucose concentration as much as possible to prevent the long-term complications of diabetes.[37]

Patients with type 1 diabetes have an absolute insulin deficiency, and therapy is designed to replace insulin in as physiologic a manner as possible. Insulin must be present throughout the day at a level sufficient to maintain normal plasma glucose concentrations under a variety of circumstances. The insulin preparations commonly used for treatment of diabetes are listed in Table 5. They have different times of peak effect and duration of action, and may be used alone or in combination. Patients with type 1 diabetes are totally dependent on exogenous insulin, with a significantly increased risk of serious ketoacidosis and hypoglycemic reactions.

In type 2 diabetics, diet and exercise are generally employed as the first line of therapy, unless patients are very symptomatic or significantly hyperglycemic. If the patient is obese, as is frequently the case, the primary goal of diet therapy is simply caloric reduction to achieve weight loss, which decreases insulin resistance. If adequate glycemic control cannot be obtained, pharmacologic therapy is added. Oral hypoglycemic agents are administered first (Table 6). Since the disease typically worsens over the course of time, most patients eventually find oral medication to no longer be sufficient; at that point, oral medications can be combined, or insulin can be added.

Management

The ideal management of an individual with diabetes would result in no symptoms attributable to diabetes; prevention of acute complications; prevention of microvascular and neuropathic disease; and, a life expectancy equal to nondiabetic individuals. Unfortunately ideal management is currently not attainable; the best that can be done is to strive for minimal morbidity and mortality.

Diabetes mellitus is associated with both acute and chronic complications. Acute complications include marked hyperglycemia, ketoacidosis, hyperosmolar nonketotic coma, and infections, to name a few. Chronic complications include microvascular, macrovascular and neuropathic manifestations, which usually require a number of years to become clinically evident.[38]

Glycemic control that maintains plasma glucose values at <200 mg/dl will generally eliminate the symptoms of polydipsia, polyuria, polyphagia, weight loss and increased fatigue. Plasma glucose levels at 150-165 mg/dl are usually associated with a sense of well-being and good health. Preventing

chronic microvascular and neuropathic complications, on the other hand, probably requires normoglycemic or near-normoglycemic regulation. Minimizing macrovascular disease also requires addressing other risk factors, including smoking, hypertension, plasma triglycerides and low/high-density lipoprotein cholesterol, in addition to glucose control. The maintenance of plasma glucose at near-physiologic levels using intensive insulin regimens will prevent the long-term complications of diabetes,[39] but will simultaneously expose patients to a greater risk of hypoglycemia, which in extreme cases can have a mortality rate as high as 10%,[40] and invariably has profound implications regarding cognitive function.

Aeromedical Concerns

Symptomatic diabetes is not suitable for flying duties. Symptoms as nausea, polyuria, polydipsia, fatigue, and blurred vision are usually disabling, and at a minimum alter the aviator's capabilities. Furthermore, the condition is acutely unstable. Untreated diabetic aviators are not fit to fly.

The most relevant problem in aircrew on diabetic therapy is the difficulty of maintaining control of blood glucose, a problem which may be increased by stressful events, due to the action of stress hormones.[40] Intensive treatments reduce diabetes complication, but expose the patient to three times greater risk of developing hypoglycemia than control groups receiving standard treatment. Symptoms of hypoglycemia[41] usually begin when the plasma glucose concentration falls to 45-50 mg/dL (normal: 70-110 mg/dL) and can be divided into two categories:

- Adrenergic symptoms, due to excessive secretion of epinephrine in response to hypoglycemia, which consist of sweating, tremor, tachycardia, anxiety and hunger.
- Neuroglycopenic symptoms, caused by dysfunction of the central nervous system due to hypoglycemia, which include dizziness, headache, clouding of vision, blunted mental activity, loss of fine motor skill, confusion, abnormal behavior, convulsions and loss of consciousness.

Hypoglycemia is the major concern in the care of diabetes treated with insulin, and is a more profound concern in the diabetic aviator. Some authors have proposed allowing continued flying for diabetics at low risk for hypoglycemia with regular blood monitoring during a limited duty period, and assigning such aviators to flight duties with geographic and operational flying limitations.[42] While such efforts to decrease losses of trained aviation personnel are readily understandable, diabetic aviators are subjects at risk, who require tight medical monitoring by their flight surgeon and an endocrinologist, repetitive ophthalmologic evaluation, and regular screening for cardiovascular and renal complications. In our opinion, type 1 diabetics should be considered not suitable for flying duties because of the serious risk of acute complications which in the aviation environment are particularly likely to be lethal.

The case of type 2 diabetics is different, particularly those controlled by diet and exercise, where no flying restrictions are usually imposed. As compared with insulin, oral agents result in more stable control, and, particularly in the case of biguanides are associated with a low risk of acute complications.[43] In selected cases, non-combat pilots could be returned fit to fly with some limitations; waiver authorities must individually determine the level of risk acceptable for continued flying duties, and which waiver restrictions should be applied.

THYROID HORMONES

The thyroid gland synthesizes two hormones, thyroxine (T_4) and triiodothyronine (T_3), which are iodinated amino acids. Although T_3 is the physiologically active hormone, most of the thyroid hormone secreted from the normal thyroid is T_4; less than 20% of total T_3 is produced in the gland, while the remaining 80-90% is derived from the deiodination, by desiodase enzymes, of T_4 in peripheral tissues such as liver, kidney and muscle.[44] Administration of T_4 or T_3, or the disease induced or iatrogenic absence of these hormones, produces general effects on metabolism, and has particular effects on specific organ systems.

Thyroid Hormone Action

Thyroid hormone action at the cellular level is initiated by the binding of thyroid hormone to a specific nuclear receptor.[45] Thyroid hormones exert major effects on growth and development. In all tissues except the brain, spleen and testis, they elevate O_2 consumption, resulting in increased heat production. They have marked chronotropic and inotropic effects on the heart, with low cardiac output, bradycardia, and slow myocardial contraction and relaxation being characteristic of hypothyroidism. Many actions of thyroid hormones, particularly on the cardiovascular system, are similar to those induced by catechol-

amines, which may be at least partially explained by the finding that thyroid hormones increase the number of catecholamine receptors in heart muscle cells.[46] Thyroid hormones are necessary for normal function of respiratory centers; hypoventilation with hypoxia is a consequence of hypothyroidism.

Thyroid hormones affect the metabolism and clearance of various hormones and pharmacologic agents.[47] Steroid hormone clearance is increased. Serum prolactin levels are increased in about 40% of patients with primary hypothyroidism. Insulin requirements in diabetics are frequently increased in hyperthyroidism. Thyroid hormones are necessary for normal LH and FSH secretion. In hypothyroidism, anovulation and menstrual disturbances may occur. Parathyroid hormone action may be diminished in hypothyroidism.

Clinical Syndromes

Since hyperthyroidism is an unstable clinical condition which requires definitive treatment, its management in the aviator differs little from the clinical patient, and it will not be considered further.

Hypothyroidism is a clinical, biochemical and metabolic syndrome resulting from inadequate thyroid hormone production with sub-normal thyroid hormone concentration, or from faulty transduction of the thyroid hormone message, which is characterized by a generalized slowing down of metabolic processes.[46] In adulthood, the disease is largely limited to this metabolic slowing, and the symptoms are usually reversible with therapy. Common features of hypothyroidism include easy fatigability, coldness, weight gain, constipation, menstrual irregularities and muscle cramps. Physical findings include a cool, dry skin, puffy face and hands, hoarse, husky voice, and slow reflexes. Hypothyroidism causes impairment of the cardiovascular system, with bradycardia and cardiac enlargement; of pulmonary function, characterized by shallow, slow respirations and defective ventilatory responses to hypercapnia; of intestinal peristalsis, resulting in chronic constipation; and of renal function, with decreased glomerular filtration rate and impaired ability to excrete a water load.[48] Many patients complain of symptoms referable to the neuromuscular system, such as severe muscle cramps, paresthesias and muscle weakness. Central nervous system symptoms may include chronic fatigue, lethargy and inability to concentrate.

Hypothyroidism, as well as other thyroid diseases, is more frequent in women, with a female/male ratio of 5/1. It may occur as a transient complication of the late phase of subacute thyroiditis, or more commonly as a permanent result of chronic thyroiditis (Hashimoto's thyroiditis). Hypothyroidism commonly occurs after ablative therapy, such as administration of radioactive iodine or subtotal thyroidectomy in Graves' disease, and occasionally after surgical treatment of nodular goiter or thyroid carcinoma.

Treatment of Hypothyroidism

Hypothyroidism is treated with synthetic thyroid hormones levothyroxine ($L\text{-}T_4$) and triiodothyronine (T_3) (Table 7), both available in pure and stable form. Desiccated thyroid, typically of porcine origin, is unsatisfactory because of its variable hormone content and frequent side effects. $L\text{-}T_4$ is converted in the body in part to T_3, so that both hormones become available even though only one is administered. T_3 therapy is unsatisfactory because of its rapid absorption and rapid disappearance from the bloodstream. The half-life of $L\text{-}T_4$ is about 8 days, so it need be given only once daily. Replacement doses of $L\text{-}T_4$ in the average adult average about 1.6 mcg/kg/d, with the goals of resolution of the features of hypothyroidism, and normalizing plasma TSH and thyroid hormone levels. Generally, only two thirds of the oral dose of the preparation is absorbed, but blood levels are easily monitored by following the free thyroxine and TSH levels.[49]

Aeromedical Concerns

The impact that hypothyroidism has on an aviator depends to some extent on the clinical stage and the treatment that is being used. Although clinical evidence of hypothyroidism varies considerably, physical and laboratory assessment of thyroid function usually allows the patient to be categorized as having either "overt" or "subclinical" hypothyroidism.[48] In the former, patients present with signs and symptoms indicating abnormal function of one or more organ systems, whereas in the latter, patients appear clinically normal, but display elevated serum TSH concentration, typically with normal or only slightly depressed levels of thyroid hormone.

The management of overt hypothyroidism is relatively straightforward; patients must be treated with replacement thyroxine therapy. Subclinical hypo-thyroidism, on the other hand, should not be viewed as a benign laboratory aberration despite the

absence of findings. In approximately 8% of these patients, the disease progresses to overt hypothyroidism.[50] Moreover, subclinical hypothyroidism may have significant effects on some peripheral target organs at an early stage; in particular, it appears to be a risk factor for atherosclerotic coronary heart disease. Of additional concern in aviators, it may also cause marked impairment of some cognitive functions such as memory and behavioral changes.[51-53]

Thyroid hormone metabolism may be altered in strenuous and extended flight.[27] Probably due to relative hypoxia, symptoms of subclinical hypothyroidism are more likely to evince themselves in the aviation environment. In view of the effect of thyroid hormone on oxygen consumption, this is not surprising. For instance, in such situations the latency of visual evoked potentials has been shown to be prolonged, and electroencephalography has shown a decreased amplitude and loss of alpha rhythm. Furthermore, there has been demonstrated impairment in memory and behavior in subclinical hypothyroidism, reinforcing that patients with subclinical hypothyroidism should be treated with adequate doses of L-T_4.[54]

After beginning replacement therapy with L-T_4, patients will be normo-metabolic in two or three weeks. Blood level evaluation of thyroid hormones and TSH, and perhaps dynamic testing with TRH, should be required to confirm euthyroidism before returning the aviator as fit to fly.

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Table 1. Categorization of Hormones by Molecular Structure

Peptides and Proteins			
Glycoprotein	**Polypeptides**	**Steroids**	**Amines**
Follicle-stimulating hormone (FSH) Human chorionic gonadotropin (hCG) Luteinizing hormone (LH) Thyroid-stimulating hormone (TSH)	Adrenocorticotropic hormone (ACTH) Angiotensin Calcitonin Cholecystokinin Erythropoietin Gastrin Glucagon Growth hormone Insulin Insulinlike growth peptides Melanocyte-stimulating hormone (MSH) Nerve growth factor Oxytocin Parathyroid hormone Prolactin Relaxin Secretin Somatostatin Vasopressin (ADH)	Aldosterone Cortisol Estradiol Progesterone Testosterone Vitamin D	Epinephrine Norepinephrine Thyroxine (T_4) Triiodothyronine (T_3)

Table 2. Biological Characteristics of Selected Corticosteroids

Duration of Action	**Glucocorticoid Potency**	**Equivalent Glucocorticoid Dose (mg)**	**Mineralocorticoid Activity**
Short-Acting			
Cortisol	1	20	Yes
Cortisone	0.8	25	Yes
Prednisone	4	5	No
Prednisolone	4	5	No
Methylprednisolone	5	4	No
Intermediate-Acting			
Triamcinolone	5	4	No
Long-Acting			
Betamethasone	25	0.60	No
Dexamethasone	30	0.75	No

Table 3. Complications and Side Effects of Corticosteroids

Cardiovascular
- Hypertension
- Congestive heart failure

Gastrointestinal
- Peptic ulcer disease
- Pancreatitis

Endocrine-Metabolic
- Iatrogenic Cushing
- Acne, hirsutism, menstrual irregularities
- Suppression of growth
- Diabetes mellitus
- Sodium retention, hypokalemia
- Secondary adrenal insufficiency

Ophthalmic
- Posterior subcapsular cataracts
- Glaucoma

Musculoskeletal
- Osteoporosis
- Myopathy

Neuropsychiatric
- Psychosis
- Pseudotumor cerebri

Immune, Infectious
- Decreased inflammatory responses
- Susceptibility to infections

Table 4. Adrenal Insufficiency Replacement Therapy

- CORTISOL, 15-20 mg in AM and 10 mg at 4-5 PM
- FLUDROCOTRISONE, 0.05-0.1 mg orally in AM
- CLINICAL FOLLOW-UP
- PATIENT EDUCATION TO INCREASING CORTISOL DOSAGE DURING “STRESS”

Table 5. Characteristics of Insulin Preparations

INSULIN	ONSET OF ACTION (hr)	PEAK OF ACTION (hr)	AVERAGE DURATION OF ACTION (hr)	MAXIMUM DURATION (hr)
Regular	0.5 – 1	2 – 3	3 – 6	4 – 8
Lispro	immediate	1 – 2	2 – 4	4
Neutral Protamine Hagedorn	2 – 4	4 – 10	10 – 16	14 – 18
Lente	3 – 4	4 – 12	12 – 18	16 – 20
Ultralente	6 – 10	none	18 – 20	18 - 24

Table 6. Oral Hypoglycemic Agents

DRUGS	SITE OF ACTION	ACTIONS	SIDE EFFECTS
Sulfonylureas: Glyburide Glipizide Glimepiride Tolazamide	Pancreas	Increase insulin secretion	Hypoglycemia, weight gain
Biguanides: Metformin Fenformin	Liver	Decrease hepatic glucose production	Anorexia, diarrhea and lactic acidosis
Inhibitors of Starch digestion: Acarbose Miglitol	Intestine	Delay starch and sucrose digestion, delay glucose absorption	Flatulence, diarrhea, abdominal pain
Thiazolidenediones: Troglitazone	Muscle and liver	Increase muscle glucose uptake, decrease liver glucose output	Increase plasma Volume, liver toxicity

Table 7. Thyroid Preparations for Replacement Treatment

	Average Daily Adult Dose (mg/d)	Comment
Levothyroxine (L-T_4)	150 μg	Best preparation
Triiodothyronine (T_3)	50 μg	Difficult to monitor, multiple doses required
Desiccated thyroid	90 mg	Variable potency

Gastrointestinal Drugs in Aircrew

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INTRODUCTION

Gastrointestinal diseases (GID) are common disorders in the general population. More than 50% of patients presenting with GID complaints are in the decades of life typical of military personnel, and GID represent some of the commonest reasons for medication waivers in military aircrew. The clinical course of most gastrointestinal disorders tends to be chronic, with unpredictable remissions and relapses, and a propensity for complications which may be acutely disabling or may chronically worsen the individual's general health. The development of GID by aviation personnel often leads to variable degrees of limitation in their flying duties, largely depending on the natural history of the disorder. The most common GID of aeromedical interest are: gastroesophageal reflux; peptic ulcer, both gastric and duodenal; chronic inflammatory disease of the bowel, predominantly regional enteritis and ulcerative colitis; and irritable bowel. Pharmacologic agents to treat GID include many of the most commonly used drugs in medicine, including antacids, histamine H2-receptor blocking agents, anticholinergics, proton pump inhibitors, antimotility agents, and antibacterials.[1]

Gastroesophageal Reflux (GER)

Heartburn is probably the commonest GER symptom. When heartburn and acid regurgitation become regular and persistent, appropriate medical therapy is necessary. Mild to moderate GER responds well to lifestyle advice and acid suppression.[2] To neutralize acidity, non-absorbable antacids such as magnesium and aluminum hydroxides are preferred, being associated with few side effects; diarrhea, the commonest, usually does not occur at a total daily dose <90ml. To reduce acid secretion, an H2 antagonist such as ranitidine 300 mg/day, or a proton pump suppressant[3] such as omeprazole 20-40 mg/day, may be used. Cholinergic agents such as domperidone,[4] cisapride, or metoclopramide may also be used to increase sphincter pressure.[5] Cessation of acute therapy after 4-8 weeks is associated with relapse in 70-80% of patients; thus, maintenance therapy such as ranitidine 150 mg/day is commonly employed for at least one month longer.

Aeromedical Concerns

GER normally responds well to medical therapy in 4-8 weeks. After the acute phase, subjects with mild to moderate disease may be fit to fly with appropriate limitations. For severe GER, flying, especially high performance aviation, may be a provocative factor and is contraindicated. Maintenance therapy with ranitidine or omeprazole is compatible with a return to unrestricted flying duties. Therapy with a prokinetic agent such as cisapride or metoclopramide is not, because of serious sedative and extrapyramidal side-effects.[6,7]

Peptic Ulcer (PU)

PU occurs most commonly in the proximal duodenum and along the lesser curvature of the stomach. Duodenal ulcer is commonest in young males. Both duodenal and gastric ulcers have a remitting/relapsing natural history and can be associated with serious complications, such as hemorrhage and perforation. Although the secretion of acid or pepsin into the stomach is the proximate cause of peptic disease, the great majority of cases are associated with *Helicobacter pylori* (Hp) gastritis. Hp is present in 90% of duodenal and 60-70% of gastric ulcers. Recent data show that in patients followed for three years after ulcer healing, eradication of Hp with antibiotics may prevent ulcer relapse in 80-87% of individuals. The goals of medical therapy are suppression of acid secretion and Hp eradication. H2 receptor antagonists and proton pump suppressors are used.[8] Cimetidine, 800 mg/d, ranitidine, 300 mg/d, famotidine, 40 mg/d, or nizatidine, 300 mg/d, lowers gastric acidity and promotes healing of duodenal and gastric ulcer in

4 to 8 weeks. Omeprazole, 20-40 mg/d, lansoprazole, 15-30 mg/d, or pantoprazole, 40 mg/d, can completely inhibit acid secretion and has a long duration of action; healing typically occurs in 100% of cases within 2 to 4 weeks. Additional agents include sucralfate,[9] which forms a protective coating in the base of ulcer, and bismuth-containing preparations, which have an action similar to that of sucralfate. Eradication of Hp can be achieved using antibacterial therapy, but antibiotic regimens are complex; the best regimen is a matter of debate which is beyond the scope of this monograph, particularly since the aviator would likely remain grounded during treatment.

Aeromedical Concerns

Aircrews suffering from PU require at least two months grounding for uncomplicated cases. At the end of this period, during which patients are unfit for flying duties, endoscopic evaluation must confirm the complete healing and eradication of Hp.[10] When both goals are successful, subjects have a very small risk of relapse and may return to unrestricted flying duties. All H2 antagonists have side effects of potential concern, such as drowsiness, tiredness, dizziness (cimetidine), vertigo, headache, diarrhea (ranitidine), fatigue (famotidine), asthenia, and sleepiness (nizatidine).[11,12] Several studies with evaluation of visual and motor performances, alertness and behavior, did not show any interference by cimetidine or ranitidine, suggesting that the use of H2 antagonists in aircrews should be limited to those two drugs.[13,14] Side-effects of proton pump suppressors,[15] such as visual disturbances (omeprazole) and, rarely, necrotic arthritis (lansoprazole), are of concern for flying personnel, and less information is available about these drugs. In cases complicated by hemorrhage or perforation, flying must be forbidden for one year, and endoscopic evaluation will be necessary at the end of that period. If Hp infection was documented and the organism is shown to be eradicated, the risk of future complications should be low.

Inflammatory Bowel Disease

Regional enteritis (Crohn's disease) and ulcerative colitis are characterized by chronic inflammation which may occur in any part of the gastrointestinal tract and have a natural history of remissions/ relapses. Both conditions may significantly compromise aviation personnel employability and always require full specialist evaluation.

Regional Enteritis (RE)

RE commonly affects the distal ileum and colon, but the entire small bowel may be involved. Most cases begin before age 40 and occur about equally in both sexes. RE is characterized by lifelong exacerbations, with a recurrence rate of almost 100% within 15 years.[16] Chronic diarrhea, associated with abdominal pain and fever, is the usual presenting symptom. Complications, both local and extraintestinal, are common, and include fistulas, abscesses, malabsorption, anemia and arthritis. No specific therapy exists. Antidiarrheal agents, such as loperamide (2-4 mg/day), may be used to relieve cramps and diarrhea. Aminosalicylate preparations are useful in suppressing mild or moderate disease, maintaining remissions, and preventing relapses; both sulfasalazine and mesalazine (known as mesalamine in the USA) should be administered with a low initial dosage (500 mg or 400 mg, respectively), then gradually increased up to 4-8 g or 2.4-4 g daily in divided doses, respectively.[17,18] In acute stages of disease, systemic corticosteroid therapy is usually added, such as oral prednisone, 40-60 mg/day, with gradual dosage reduction depending on response. Surgical intervention is mandated when recurrent intestinal obstruction or serious complications, such as fistulas or abscesses, are present.

Aeromedical Concern

A diagnosis of RE usually leads to a period of temporary grounding for a minimum of several months. In those cases in which remission is maintained for a prolonged time, a return to limited flying duties can be considered. Those subjects suffering from small intestine enteritis are usually assigned to restricted duties, and are generally unfit for solo-pilot. Others with uncomplicated RE limited to the colon and with remission for at least one year may return to less restricted flying categories. During maintenance therapy, aircrews may often need to be grounded because of side-effects of medical therapy, which are frequently dose-related. In up to 30% of subjects sulfasalazine may cause significant side effects such as vomiting, nausea, anorexia, headache, cutaneous rash, hemolytic anemia, blood dyscrasia, and, rarely, hepatitis. Mesalazine as a rule is usually better tolerated.

Ulcerative Colitis (UC)

UC is a chronic ulcerative disease involving the entire colon, and is characterized by frequent attacks of bloody diarrhea and repeated exacerbations and remissions. UC is more common in males and in the young, peaking between 15 to 30 years of age. Diarrhea attacks may present with varying intensity and duration. Hemorrhage and fistulas are common local complications; peripheral arthritis, uveitis and episcleritis are also common and emphasize the systemic nature of this disease. Colonoscopy and biopsy are useful to assess the extent of disease and distinguish ulcerative from regional (Crohn's) colitis. The therapeutic approach is similar to that used with RE.[19] Antidiarrheal agents, such as anticholinergics, loperamide, or codeine, may lead to symptomatic improvement, but should be used with extreme caution. Mild to moderate disease may respond to mesalazine or sulfasalazine. Severe disease requires systemic corticosteroid therapy with oral prednisone. Nearly a third of patients with extensive disease eventually require surgical extirpation of the colon.

Aeromedical Concern

A diagnosis of UC is cause for temporary grounding for a period of 6 months. Those patients in whom disease is restricted to the rectum or distal sigmoid, and show clinical remission without any evidence of complications or drug side-effects, may be returned to limited flying duties, usually restricted to flying in multi-crew aircraft. Serious and extensive disease, because of a significant incidence of complications and relapses, should be considered incompatible with flying.

Irritable Bowel Syndrome (IBS)

IBS is a very common clinical syndrome, representing about 50% of all gastrointestinal complaints. Motility disorders are associated with a variety of symptomatic presentations, most commonly abdominal pain, diarrhea, or constipation. By definition, no anatomic cause can be found, and the condition commonly represents a reaction to stress, emotional factors, diet, or occasionally drugs in susceptible individuals. In many cases, reassurance is all that is required. Regular physical activity is indicated to relieve stress, and a diet high in insoluble fiber may improve bowel function. Pharmacotherapy is usually indicated only in severe cases. In patients with diarrhea, loperamide (2-4 mg) may be given before meals. To relieve spastic symptoms, anticholinergic agents and a mild sedative may be temporarily used.

Aeromedical Concerns

The severity of symptoms can vary widely. IBS is usually compatible with flying, but severe and persistent symptoms, especially those requiring drug therapy, may require grounding.

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Malaria Chemoprophylaxis in Military Aircrew

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RESUME

La prophylaxie du paludisme chez les membres du personnel navigant militaire est une préoccupation majeure du médecin de l'air. L'article aborde les aspects aéromédicaux de la question en examinant les indications et les effets secondaires des principales molécules utilisables en prophylaxie palustre. La possibilité d'apparition d'effets secondaires neurosensoriels lors de l'emploi de certaines molécules est un critère essentiel dictant le choix final de la prescription. Les connaissances sur la chimioprophylaxie du paludisme à plasmodium falciparum étant évolutives, les régles de prescription sont susceptibles d'être adaptées ultérieurement. Dans tous les cas, la chimioprophylaxie doit s'intégrer dans une stratégie de gestion globale, comportant la mise en place de mesures antiparasitaires individuelles et collectives.

SUMMARY

Malaria prophylaxis of aircrew is one of the more frequent problems with which a flight surgeon has to cope. This article examines the aeromedical aspects of the topic by reviewing the indications and side effects of the available chemoprophylactic drugs. A potential for neurosensory side effects constitutes the most frequent reason to reject the use of a particular drug. Knowledge about malaria prophylaxis is in a constant state of change; thus, recommendations are liable to become rapidly outmoded. Whatever the chosen drug, chemoprophylaxis should always be integrated into a global management strategy which includes antivector measures on an individual and collective scale.

I. INTRODUCTION

Malaria is the most common parasitic disease around the world. According to the World Health Organisation (WHO), it is responsible for 300 to 500 million cases per year, as well as 2 million deaths.[13]

Historically, the combination of malaria with military operations has resulted in disastrous losses of personnel. The global management of this biological hazard by US forces during the Pacific campaign of World War II is widely accepted as one of the decisive factors leading to the Allied victory in those infested areas. Loss or unavailability of such highly qualified personnel as aircrew is particularly unacceptable, and thus it is imperative to determine the best way to prevent the disease.

Epidemiologic data indicate that, between 1993 and 1998, French Air Force aircrew and ground crew deployed to endemic areas experienced an annual malarial attack rate of 6.2%. In 1998, the entire French forces reported 562 malaria attacks, with unfortunately one death recorded, after an average rate of exposure of 12,350 personnel per year. Sick personnel were medically unfit for a mean time of 6.8 days. The majority of cases (77.4%) have begun overseas, while the remainder occurred following their return to France. Military personnel involved in rapid and frequent deployment are more likely to contract malaria than are those who permanently reside overseas (relative risk 5.6). The following statistics clearly show that the struggle against this parasitic disease is actually becoming more difficult as time goes by:

- 53% of malaria attacks have occurred after a stay in WHO group 3 countries (i.e., high risk of resistance), versus 47% for group 2 countries;
- although 16% of personnel display poor compliance with chemoprophylaxis as assessed by plasma drug concentration, 50% of cases have occurred among people who were taking chemoprophylaxis regularly; and
- resistance of *Plasmodium falciparum* to antimalarials, although still clearly dependent on geographic location, is spreading.

While treatment of a malarial episode is more or less established, the most logical defense continues to be prophylaxis, including disinsectation, the use of repellents to avoid *Anopheles* bites, and the use of chemoprophylactic drugs.[8,19]

The choice of adequate chemoprophylaxis relies on many criteria[5,6,8,16,21,24,25,43,47,48] and each one should be taken into account:

- the species of *Plasmodium* potentially encountered;
- the level of awareness/education of aircrew about this infectious hazard, including the risk, the absolute need for a medical examination in case of symptoms during and after exposure, and the potential failure of the chemoprophylactic agent;
- the assessment of the risk of infection according to the country, the season, the duration and the type of the stay, and the measures locally applied to fight the biological vector;
- the current state of resistance to antimalarial drugs encountered in the country, which is available in the annually updated WHO guidelines;[33]
- the practicability of the prophylactic regimen, which partly determines compliance; and
- the ease and the availability of self-treatment in case of suspicious symptoms.

An issue of particular interest to the flight surgeon is the potential side effect profile associated with the drug, particularly those adverse effects which may impair flight safety.

The main goal of this review is not to investigate the different antimalarial therapeutic drugs, or the practical measures undertaken to combat the biological vector. Rather, we will focus our interest on chemoprophylactic drugs. When discussing the indication, we will refer to the WHO classification for countries:

- Group 1: no resistance described in the considered country,
- Group 2: resistance described but still uncommon,
- Group 3: high risk of resistance.

The chemoprophylaxis policy of each nation participating in the Working Group will not be discussed. The reader may look for this information in the database built up by the Working Group and presented in this volume.

II. THE AVAILABLE PROPHYLACTIC DRUGS

Chloroquine (Nivaquine®)

Mechanism of action: This amino-4- quinoline is directly schizonticidal. The parasite accumulates the drug inside its digestive vacuoles, which stops the enzymatic degradation of hemoglobin, the main source of amino acids for the parasite. Resistance appears when the parasite is no longer able to accumulate the drug inside the vacuoles.[5,23]

Formulation: 100-300 mg tablets

Half-life (serum): 10-30 days

Chloroquine has a high affinity for pigmented tissue, where it is readily stored.

Range of dose:

- 100 mg per day, from the day before departure to 4 weeks following return from an endemic area
- alternate regimens are 300 mg per week, or 300 mg two times per week

Indication: Chloroquine is currently restricted to countries where chloroquine resistance has not yet been recorded (WHO Group I).

Side effects: According to many publications,[5,8,21,36,48] side effects are usually benign and rare during prophylaxis. Nevertheless, Steffen[46] found that side effects occurred in 19.9 to 22.2 % of a group of 12,272 travelers using 300 to 600 mg chloroquine per week, including two cases of psychosis. Neuropsychologic disorders, though

unusual, have included toxic psychoses, episodes of disorientation, hallucination, impaired consciousness, and seizures. Other commonly described symptoms include headache, digestive troubles, (nausea, diarrhea), pruritus (especially in dark-skinned races), lichenoid cutaneous eruption, vertigo, and deafness.

Ophthalmologic complications are of particular interest in the aviation environment. Accommodation problems and corneal deposits have been described with chloroquine; they may disappear after the drug has been discontinued. The side effect of most concern is the development of retinopathy. According to Easterbrook,[15,35] the visual prognosis of this retinopathy is excellent if the diagnosis is made at an early stage of the disease. The retinopathy develops in several stages,[17] with dyschromatopsia, loss of visual acuity, emeralopy, and maculopathy, with an "ox eye" aspect on angiography. Retinopathy has been described among patients treated with high doses of chloroquine or hydroxychloroquine for connective tissue diseases,[22] as well as among chloroquine abusers.[29] The greatest risk appears to be among those who were not under medical surveillance.

Retinopathy may appear with a cumulated dose of 100 g, but is more common at higher doses (300 g). The size of the daily dose is also important; daily doses should not exceed 250 mg, or 4 mg/kg/day. In a recent study, Levy et al.[27] argued that an ophthalmological survey was not necessary if the daily dose of hydroxychloroquine did not exceed 6.5 mg/kg. However, it should be noted that chloroquine may be more likely to cause retinopathy than hydroxychloroquine.[45] The maximal safe dose, daily or total, of chloroquine is still under debate; the main factor accounting for the differences between studies is probably the variation of retinal sensitivity to chloroquine between individuals.

In the French aeromedical experience, even in aircrew on the recommended dose of 100 mg per day, regular ophthalmologic evaluation is performed; this basic survey includes measurement of the visual acuity and color vision testing. Those parameters are recorded regularly during the career of a pilot. If necessary, determination of the contrast sensitivity curve, an automated visual field, funduscopy, and an electroretinogram could be performed. Despite the fact that none of the commonly used tests alone is satisfactory for detecting retinopathy, Ruiz et al.[37] have argued for a lesser survey, using a careful corneal examination, color vision testing, visual fields, and an Amsler grid test every 9 or 12 months.

During prophylaxis with chloroquine, the occurrence of retinopathy is distinctly unusual, with twelve cases recorded by French authors.[21] All of these patients had taken a total estimated dose of 360 g to 1300 g over many years. Since 1982, not a single case of retinopathy has been detected by the French Aeromedical Centers in aircrew taking frequent prophylactic courses of chloroquine (Corbé C., personal communication).

Cardiac toxicity may appear with accidental high doses. Voluntary poisoning with chloroquine carries a grim prognosis.

Amodiaquine (Flavoquine®)[7,10,36,48]

The use of this drug is no longer recommended because of the risk of toxic hepatitis and agranulocytosis.

Mefloquine (Lariam®)[4,5,7,8,16,23,25,36,40,41,48,49]

This aminoalcohol drug is closely related chemically to the amino-4-quinolines. It is schizonticidal for each type of *Plasmodium*. The site of action is the membrane of the erythrocyte; it has no effect on intrahepatocytic parasites.

Resistance to mefloquine was first described in Thailand in 1989, and is spreading. Failure of chemoprophylaxis has also been reported in Africa, but it remains rare on that continent. Resistant cases are the exception in other areas.

Formulation: 50 and 250 mg tablets

Range of dose: 250 mg per week, from 7-10 days before departure to 3-4 weeks after return

Indication: chemoprophylaxis for group 3 countries, if the length of stay is less than 3 months

Contraindication: previous history of seizure or psychiatric disorders

Side effects: Steffen[46] found a rate of side effects of 22.3% in 5342 travelers taking mefloquine for chemoprophylaxis. Usually the prevalence of side

effects varies from 15 to 40 % between studies. The following symptoms have been described and some of them are clearly of interest to aviation:

- digestive disorders (nausea, vomiting, diarrhea, abdominal pain syndrome)
- anorexia, asthenia
- pruritus
- headaches, seizure, sleep disorders[28]
- vertigo
- psychomotor coordination troubles, spatial disorientation
- transient memory failure[31]
- psychiatric disorders,[11] hallucination and depressive syndromes

Neurosensory and psychiatric side effects have been described, especially with the therapeutic use of mefloquine.[34] Bernard, Gourbat, et al[7] have reported a 39% rate of side effects with therapeutic doses of mefloquine. This study recorded three cases of encephalopathy with seizure; of note, seizures may be delayed. With the prophylactic use of mefloquine, the rate of frank psychiatric manifestations has been estimated at 1 per 15,000 to 20,000 (50); 90% of these side effects appear during the first 5 weeks.[34]

The aeromedical suitability of chemoprophylaxis with mefloquine has been discussed in some articles. According to Schlagenhauf[38] and Steffen,[46,47] the occurrence of side effects differs little between mefloquine and the chloroquine /proguanil combination. This may lead some to reconsider the use of mefloquine for aircrew. A study conducted with Swissair pilots[40] did not show a significant difference in performance between mefloquine and placebo. Shamiss[41] has compared the suitability of mefloquine versus doxycycline in Israeli aircrews sent to Rwanda. He recorded side effects in 13% of those on mefloquine, compared with 39% of those on doxycycline. Twenty-five percent of aircrew members on doxycycline discontinued chemoprophylaxis, compared to none using mefloquine. The author concluded that mefloquine was suitable for aeromedical use because of better tolerance and compliance.

Dutch authors[20] have used mefloquine in Cambodia; careful survey, including clinical examination, biological analysis and regular EKG to measure QT-intervals did not uncover any problems. During a controlled study of 95 volunteers, British experimenters[14] did not observe a significant difference between mefloquine and placebo in neurologic symptoms or on neuropsychological testing.

Against this, Barett[4] reported a 0.7% rate of neuropsychiatric disorders with mefloquine, compared to 0.09% with the chloroquine/proguanil combination. Another study[39] documented an 11% rate of significant side effects related to chemoprophylaxis with mefloquine.

One particular study has emphasized the fact that the use of mefloquine increases the risk of post-malaria neurological symptoms. According to these authors,[30] mefloquine should not be used after previous treatment of a severe malaria attack.

Although mefloquine has been considered capable of inducing serious side effects, recent studies comparing this compound to chloroquine/ proguanil[9,12] do not seem to confirm a more serious side effect profile than standard therapy. Whether mefloquine will prove to be useful in the future remains to be seen. At the present time, most NATO countries forbid the use of this drug for prophylaxing aircrew.

Sulfonamides: Sulfadoxine, Dapsone (Disulone®)[23]

Mechanism of action: These antifolic drugs inhibit dihydropteroate synthetase, crucial to the biosynthesis, from paraminobenzoic acid, of a metabolite essential for the parasite's growth.

Sulfonamides have no action on the gametocyte or the pre-erythrocyte form of the parasite. They are moderately active on the trophozoites and on the schizonts. They may potentiate the action of antifolinic drugs.

There is general agreement that sulfonamides should not be used as monotherapy, either for treatment or prophylaxis.

Pyrimethamine: Daraprim®, Malocide®[23]

Those antifolinic compounds have a schizonticidal action mediated by the inhibition of dihydrofolate reductase.

Resistance, which has now been widely documented, precludes their use separately from other drugs. The level of resistance is particularly high in Southeast Asia, in the Amazon basin, and in East Africa. Pyrimethamine is still effective in West Africa.

Side effects are primarily those of folic acid deficiency, including macrocytic anemia, aphthous ulcers, and stomatitis.

Proguanil: Paludrine® [23]

Its active metabolite is cycloguanil, an antifolinic drug. The mechanism of its schizonticidal action is identical to pyrimethamine.

Proguanil is no longer used separately because resistance, though less frequent than with pyrimethamine, is still a significant risk. Cross-resistance between pyrimethamine and proguanil has also been described.

Formulation: 100 mg tablet

Side effects:

- aphthous ulcers, stomatitis
- moderate digestive disorders
- alopecia
- pruritus, cutaneous eruption, depigmentation

Sulfadoxine and Pyrimethamine: Fansidar® [7,48]

This chemoprophylactic agent has been largely discarded because of the risk of serious side effects, including Lyell syndrome, Stevens-Johnson syndrome, and agranulocytosis.

Dapsone and Pyrimethamine: Maloprim® [48]

For reasons similar to Fansidar®, this combination is no longer used.

Chloroquine and Proguanil: Savarine® [1,8,43,48]

This schizonticidal combination was previously taken as separate tablets. Several years ago, the French Army Health Service developed a new formulation, combining 200 mg of chloroquine and 100 mg of proguanil, to aid in compliance. It has been widely used by French military personnel, including aircrew, in Africa. This formulation is now available for civilian use under the commercial name “Savarine®”.

Range of dose: 1 tablet per day, from the day before departure to 4 weeks after return.

Indication:

- Chemoprophylaxis for WHO Group II endemic areas.
- Chemoprophylaxis for WHO Group III endemic areas when mefloquine is not indicated or poorly tolerated, or when the length of stay is over 3 months.

Side effects: Side effects of the two parent drugs have been described previously.

According to the French Aeromedical Center’s experience, chloroquine plus proguanil has been commonly given to military or civilian aircrews. Even after repetitive use, side effects have been no more significant than those seen with chloroquine alone.

Doxycycline[5,8,23]

This antibiotic of the tetracycline group has a schizonticidal effect on *Plasmodium falciparum* by inhibiting the biosynthesis of the 70 S ribosomal protein. It is effective on either the intraerythrocytic or the intrahepatocytic form of the parasite. Until recently, resistance to doxycycline did not seem to have appeared.

Formulation: 100 mg tablet

Range of dose: 1 tablet per day, from the day before departure to 4 weeks after returning.

Indications: Usage currently recommended for particular geographic areas.

- forest areas between Thailand and Cambodia, and between Thailand and Myanmar
- WHO Group III endemic areas in Southeast Asia when mefloquine is poorly tolerated

Side effects:

- digestive disorders (nausea, epigastric distress, vomiting, diarrhea, abdominal pain syndrome)
- photosensitization
- vaginal candidiasis
- asthenia

During the previously cited trial with Israeli aircrews in Rwanda,[41] doxycycline prophylaxis was associated with worse compliance than mefloquine (75% vs 100%), as well as a higher rate of side effects (39% vs 13%). The majority of recorded side effects were digestive symptoms.

Doxycycline has been more effective than Savarine® in preventing *Plasmodium falciparum* malaria in French soldiers stationed in central Africa and in Cambodia.[3,32]

Primaquine [5,8,36,51]

This amino-8-quinoline may destroy the gametocyte, the pre-erythrocyte, and the intra-hepatocytic form of the parasite, including the hypnozoite responsible for late relapses.

Range of dosage:

- 15 mg per day until 2 weeks following return, or
- 45 mg per week for two months following return.

Indications: Primaquine can be used to prevent infection by *Plasmodium vivax* and *Plasmodium ovale*, both of which can induce late relapse. Primaquine may be combined with chloroquine. Two randomised studies have demonstrated its efficacy (94%) in non-immune travellers as a prophylactic drug for *Plasmodium falciparum* in Java and Columbia.[18,44]

Contraindication: The presence of glucose-6-phosphate dehydrogenase deficiency is an absolute contraindication because of the risk of hemolytic anemia. This defect is known to affect 10% of African-Americans.

Side effects:

- various digestive disorders (especially nausea)
- headache
- accommodation disorders
- agranulocytosis, anemia and methemoglobinemia

Drugs For The Future

Numerous drugs are currently under study for treatment of malaria, but relatively few studies are designed to address prophylaxis. Artemether (Paluther®), pyronaridine, and benflumentol[1] are presently under study for such a purpose.

Azithromycin[2,8] has emerged as a possible chemoprophylactic drug. At a dose of 250 mg per day or 1000 mg per week, it is effective on intrahepatocytic parasites, but it seems less protective than doxycycline.

Atovaquone[1,8,23] displays a unique mechanism of action by inhibiting the mitochondrial respiration of the parasite. Thus, it is active against all four species of *Plasmodium*. A synergistic action with proguanil has been shown, while an antagonistic action with quinoline compounds has been reported. Atovaquone cannot be used alone because of the risk of emerging resistance. Malarone® combines atovaquone (250 mg) with proguanil (100 mg). Its therapeutic action has been demonstrated on *Plasmodium falciparum*, but a prophylactic action has not been demonstrated for non-immune people. For immune people, two studies[26,42] from Kenya and Gabon have shown this combination to be effective and well tolerated despite several digestive side effects.

Other new drugs[1] are currently under study (partly at the Walter Reed Institute in Washington):

-- WR 250417 is chemically close to proguanil.
-- WR 99210 inhibits dihydrofolate transferase.
-- WR 238605 (etaquine) and WR 182393 belong to the amino-8-quinoline family; they seem to be active on the intrahepatic form of the parasite.
-- docetaxel (Taxotere®)
-- inhibitors of *Plasmodium* proteins.
-- inhibitors of *Plasmodium* lipid metabolism.

Some drugs appear to be capable of restoring sensitivity to chloroquine. Verapamil and an investigational compound (WR 268954) have shown such a property.

CONCLUSION

The choice of malaria chemoprophylaxis for aircrew should be seen as one of many steps towards a global management strategy for this biological hazard. The flight surgeon has in fact several different tasks to perform:

- to assess risk case by case;
- to make aircrew aware of the disease, by giving them clear and updated information during repeated briefings;
- to choose a prophylactic agent with the least deleterious side effects, keeping in mind that compliance with the drug should be optimal;
- to encourage aircrew to use physical and chemical barriers to vectors;
- to watch over the personnel he is responsible for during and after the stay; and
- to report problems with tolerance or efficacy.

Standby treatment, i.e., use of an antimalarial drug as therapy in case of suspicious symptoms, is another alternative. It could be used when aircrew are involved in frequent but short stays in endemic areas, as is often the case with civilian long-haul crews; such a circumstance which might otherwise call for almost continuous chemoprophylaxis.

Any prophylactic drug may induce side effects. The decision to use a malaria chemoprophylactic agent in military aircrew will be the result of a complex compromise between the expected efficacy and the potential for deleterious effects on flight safety. The avoidance of drugs with neurosensory side effects and of new, inadequately tested drugs seems to be the basic rule. In fact, the flight surgeon will have to choose between two different type of risks, the risk of ineffective prophylaxis, and the risk of a drug-induced mishap. A good knowledge of the available drugs, access to updated information, and rational judgment will help him to determine the most acceptable risk.

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Drugs and Air Operations

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INTRODUCTION

There can be little doubt that the performance of air personnel may deteriorate during intensive and sustained operations, and much thought has been given to the use of hypnotics to preserve sleep, and stimulants to enhance vigilance. The effect of these two possibilities may be complementary. Stimulants may be particularly useful for critical periods of work likely to involve impaired performance when used against a background of hypnotics to ensure adequate sleep in limited rest periods. However, the use of hypnotics and stimulants demands the most careful evaluation of each individual drug, and of their interactions.

In the case of hypnotics the overriding consideration, assuming efficacy, is duration of action which is dependent on the dose and the pharmacokinetic profile. Determination of the minimal dose is essential. Information on the pharmacokinetic profile is useful, though it is not possible to predict duration of action from such data with any certainty. It is often implied that the elimination half-life determines the duration of action, but duration of action also depends on rate of absorption and distribution, and so all three phases of the pharmacokinetic profile, as well as the minimum effective concentration for a particular effect, are involved. It is essential to carry out experimental studies to determine the minimum dose to produce sleep during a limited period of rest, and to ensure that impairment of performance does not extend into the work period.

In the use of stimulants attention must be given to the effect of the drug on performance as well as duration of action. It is vital to ensure that adverse effects on performance do not arise from the use of a stimulant, and for this reason a wide range of performance tasks must be included in the assessment. Dose is important, and the minimum dose necessary to maintain performance over the period of work must be determined. As with hypnotics studies must be carried out to determine duration of action to ensure that the use of a stimulant does not adversely affect the ability to sleep in the subsequent rest period, which may be critical in maintaining the continued effectiveness of the individual.

There are two broad approaches to studying the activity of hypnotics and stimulants to predict the effect which they may have on the performance of the individual. The profile of activity can be built up by using a variety of laboratory tests directed toward assessing specific skills relevant to the work of the individual, or the task itself can be simulated with as much accuracy as possible. Inevitably the question arises whether information obtained with performance tests carried out in the laboratory are relevant to day-to-day work. At first sight simulation maybe a more attractive approach, but there are serious doubts whether simulation provides data more relevant to the real situation. It is beyond discussion that laboratory studies provide accurate information on discrete skills and on persistence of effect, and it is, therefore, essential that simulation provides data of at least equal value.

It is true that studies using simulation may bring increased reality and motivation to the experimental set-up. However, uncertain or insensitive measures have no advantage over accurate measures from the laboratory. Simulators may merely test isolated functions in a complex, expensive and possibly uncontrolled way. Spurious confidence in the use of simulation must be avoided. Nevertheless, there is a measure of agreement between studies using simulation and laboratory tests, and it is the contention that laboratory tests do not provide such useful information as simulation which is in dispute. At present, laboratory tests remain essential, though the development of the means to measure more sophisticated skills, such as hazard perception using simulators, is welcome. Studies

using laboratory tests, hand in hand with simulation, provide the ideal approach.

Whatever the approach, change in performance needs careful interpretation as the central nervous system itself is modified. Other skills which may be of greater relevance to the task than those actually tested may be affected. On the other hand, an inability to demonstrate impaired performance does not necessarily mean a drug is free of adverse effects, as there is no test or group of tests which would indicate that human performance is preserved. It is, therefore, essential that a wide variety of data is considered in the use of hypnotics and stimulants in air operations, and that the operational scenario is well understood to ensure that these drugs will be used both effectively and safely.

As far as the use of such drugs is concerned, it must be appreciated that the overriding feature of some air operations may be several days of continuous action in an attempt to overcome defences or to repel the opposition. The exact implications for the forces involved depend on the scenario, but what is common to all is the need to maintain a round-the-clock capability in which each individual helps to meet the demands of the operation which itself is limited only by the endurance of the hardware. Such operations may involve interdiction or long range air support, a campaign to liberate an occupied country or a carrier-borne air operation. In all these cases, and in other examples of less intensive, but nevertheless sustained activity, there is the need to meet the operational requirement, and for individuals to sustain a workload far beyond that which may have been experienced previously. It is in such scenarios that the use of drugs to ensure sleep during limited rest periods and vigilance during critical duty periods arises. A brief review of some previous military operations where hypnotics and/or stimulants have been used may be appropriate.

Royal Air Force

The Royal Air Force (RAF) used the hypnotic temazepam during the South Atlantic Campaign to regain sovereignty of the Falkland Islands,[1,2] and during the liberation of Kuwait. The South Atlantic Campaign involved long range return flights from Ascension Islands of 6,000 - 8,000 miles and during the campaign some transport crews attained 150 flying hours within 24 days. This involved six long range missions lasting up to 28 hours each. Duty extended over two nights, and the mission was achieved with augmented crews involving a pilot and navigator. Some transport crews accumulated 360 flying hours within a three month period. Crews involved in maritime reconnaissance attained 100 flying hours within 14 days with flights which varied from 6 to 20 hours, and these were also augmented with a pilot and engineer. Temazepam was used widely. The majority of aircrew took 20mg to get to sleep at various times of the day and experienced good sleep without side or residual effects. They were advised to take the hypnotic at least eight hours before flight and whenever possible were given an initial dose to assess any untoward effect, though none was encountered.

United States Air Force

The United States Air Force (USAF) has used amphetamines and caffeine in support of air operations since the early 1960s. Amphetamine was used during the Vietnam War and during the air strike on Libya in 1986.[3] During the campaign to liberate Kuwait it was used occasionally by aircrew of the USAF Tactical Air Command who deployed from the United States by air-to-air refuelling for Operations Desert Shield and Desert Storm, and up to 5mg every four hours during tactical flying operations with each dose preceding a critical stage of the flight by 30 minutes. It was considered that dextroamphetamine was a safe and effective medication which improved aircrew cockpit performance and enhanced flight safety.[4]

United States Navy

The United States Navy has a cautious attitude to the use of amphetamines, at least as far as their carrier-based air operations are concerned. In Operation Southern Watch, which from 1992 involved operations over Southern Iraq, the policy of the United States Navy precluded the use of amphetamines to maintain performance, though caffeine was acceptable using protocols developed by the Naval Aerospace and Operational Medical Institute. Caffeine tablets (100-150mg) were taken as necessary up to 300-600mg in any 6 hour period, avoiding ingestion from 24 to 48 hours pre-flight to maximise the in-flight benefit. Caffeine was considered to be extremely helpful in maintaining capability with few, if any, adverse effects.[5]

RESEARCH IN MILITARY ESTABLISHMENTS

The use, and potential use, of hypnotics and stimulants in military operations is likely to be based on experimental work carried out in research establishments which directly support the military. Studies published by such establishments are particularly revealing as they not only indicate the drugs which are of interest to a particular service, but also the circumstances in which they may be used. Hypnotics are used for critical sleep periods, while an analysis of the data available suggests that as far as stimulants are concerned there are two broad scenarios. Stimulants could be used to counteract the effects of sleep deprivation (prolonged sleep deprivation), or to avoid impaired performance over a discrete period of time within a complex pattern of work and rest – usually involving duty overnight. The published studies from military establishments world-wide will be reviewed in these contexts.

HYPNOTICS

Efficacy and Residual Effect. Studies on the efficacy and possibility of residual effects of hypnotics were carried out by the RAF Institute of Aviation Medicine during the 1970s and '80s, and temazepam was selected as the drug of choice for aircrew. A rapidly absorbed formulation and a dose of 10 or 20mg provided useful hypnotic activity with freedom from residual effects. Temazepam has been used by both military and civil aircrew in the United Kingdom for the last 20 years.[6,1,2]

Studies on temazepam (20mg) have also been carried out by the Royal Australian Army Medical Corps, Oakey, Queensland, in relation to trans-meridian travel.[7] The rate of adjustment was not affected by temazepam, but it had a beneficial effect on sleep and alertness after transmeridian travel without detrimental effects on performance. Temazepam (20mg) has also been studied in individuals coping with an acute shift of their sleep-wake cycle. Porcu, Belltreccia, Ferrara and Casagrande (1997) from the Reporto Medicina Aeronautica e Spatiale, Aeroporto Pratica di Mare, Italian Air Force,[8] studied sleepiness during the night after a daytime administration of 20mg temazepam. Temazepam was effective in inducing and maintaining sleep without any significant carry over effect.

However, it is unfortunate that temazepam has, of recent years, been subject to abuse, and for this reason the use of temazepam, at least in the United Kingdom, is now subject to various controls. It could, therefore, well be appropriate to use an alternative hypnotic free of such medico-legal restraints. In this context zolpidem is clearly a candidate to be included in aircrew medication. The studies carried out by the Service de Sante, Base Aeronavale, Rochefort Aeromarine are of interest. Sicard, Trochera, Moreau, Viellefond & Court (1993)[9] evaluated zolpidem (10mg) for its residual effects on daytime wakefulness in navy fighter pilots. The absence of residual effects showed that zolpidem could be considered for operational use. These studies supported previous assessments carried out by the RAF Institute of Aviation Medicine.[10]

The usefulness of naps with placebo and with zolpidem (10mg) has been explored by the US Army Aeromedical Research Laboratory, Fort Rucker.[11] Subjects were exposed to three separate 38 hour periods of continuous wakefulness, each separated by 10 hours for recovery sleep, and the effect of a 2 hour evening nap on subsequent performance studied. Naps with placebo and especially with zolpidem attenuated the decrements normally associated with sleep deprivation, but post-nap impairment persisted in both cases, which the authors considered could compromise performance under operational conditions.

A hypnotic with a shorter duration of action than zolpidem would, perhaps, be more appropriate for use during naps. One possibility is zaleplon, which has a duration of action of around 1 hour. However, the usefulness of this compound has not been evaluated using simulations of operational scenarios, and such studies would be required before any recommendations could be made.

STIMULANTS

Prolonged sleep deprivation. The effects of stimulants on performance during prolonged sleep deprivation have been studied by the Walter Reed Army Institute of Research (WRAIR) and the Naval Health Research Center (NHRC), by the Defence and Civil Institute of Environmental Medicine (DCIEM), and by Centre de Recherches du Service de Santé des Armées (CRSSA), the Centre d'Etudes et de Recherches de Médicine Aérospatiale

(CERMA) and the Institut de Médicine Aérospatiale du Service de Santé des Armées (IMASSA). The Walter Reed Army Institute of Research and the Defence and Civil Institute of Environmental Medicine have been concerned with the effects of amphetamine. In the study at Walter Reed[12] subjects underwent total sleep deprivation for a period of 60 hours from 0730 hours on the first day of the experiment. Dextroamphetamine sulphate (5, 10 and 20mg) was given at 0830 hours on day three after 48 hours of sleep deprivation, and performance was measured over the next 12 hours. The effect of the drug was observed during the day after loss of two nights' sleep. Amphetamine led to dose-related increases in daytime sleep latencies and cognitive performance, and significant effects were seen with 10 and 20mg. The authors concluded that amphetamine was an effective agent for the rapid alleviation of the effects of sleep loss, but advised caution in the use of amphetamines under field conditions.

In the joint studies carried out by the Defence and Civil Institute of Environmental Medicine (DCIEM) and the Centre de Recherches du Service de Santé des Armées[13] the effects of 20mg d-amphetamine and 300mg modafinil were assessed during a period of 64 hours of continuous work and sleep loss. The drugs were given at 2330 hours and 0530 hours during the first and second nights of sleep deprivation and again at 1530 hours during the third day of continuous work. Amphetamine and modafinil improved performance in a similar manner, though modafinil led to fewer side effects than amphetamine. The authors concluded that modafinil could prove to be an acceptable alternative to amphetamine in counteracting the effects of sleep loss during sustained operations. However, further studies at DCIEM[14] have suggested that modafinil (300mg), but not amphetamine (20mg), may lead to overconfidence, and so these authors advise that a comprehensive understanding of the effects of this drug should be reached before it is used operationally.

Modafinil has also been studied by the Institut de Médicine Aérospatiale (IMASSA-CERMA). Modafinil at a dose of 200mg – lower than that studied by DCIEM and CRSSA – was given on six occasions at eight hourly intervals (2200, 0600 and 1400 hours), over a period involving 60 hours sleep deprivation from 0700 hours on the first day, with the first ingestion the same day at 2200 hours. The authors[15] concluded, from both subjective and objective evidence, that satisfactory levels of vigilance had been maintained free of microsleeps. In a discussion on the activity of modafinil,[16] Lagarde and Batejat pointed out that, though modafinil has a wakening effect similar to that of d-amphetamine, it is without the adverse mood effects of amphetamine observed by Newhouse *et al.*[12] They proposed that the lack of adverse effects on mood and on the cardiovascular system indicated that modafinil may be potentially useful for maintaining efficiency during prolonged wakefulness.

More recently a study has been carried out by the United States Army Aeromedical Research Laboratory (USAARL) on the effects of modafinil on aviator performance during 40 hours of continuous wakefulness.[17] Three 200 mg doses of modafinil were given over a period of 8 hours. Modafinil attenuated the effects of sleep deprivation, but vertigo, nausea and dizziness were associated side-effects, and these were problematic during simulator flights. Simulators tend to increase motion sickness in susceptible individuals, and it could well be that some of these difficulties would subside under actual flight conditions. It is also possible that side effects would be ameliorated by lowering the drug dosage over the 8-hour period. Although the experiment did not allow direct comparisons between modafinil and dextroamphetamine, it was considered that modafinil was the less efficacious of the two, and was more likely to produce side effects.

Studies at the Naval Health Research Center have been concerned with the use of pemoline.[18] Pemoline (37.5mg) was given on four occasions separated by 12 hours, commencing at 2200 hours, during a 64 hour period without sleep. Pemoline was consistent in counteracting the effects of sleep loss and of the circadian cycle on performance, and was free of any effect on mood. An important point made by the authors is that sleep deprivation should not be the only determinant of whether, or when, to administer a stimulant. An individual deprived of sleep for 50 hours may not benefit much from pemoline when given at 1000 hours, whereas an individual with minimal sleep deprivation may well benefit when given the drug overnight. Their data suggested that pemoline may predominantly ameliorate decrements in performance which arise with the circadian cycle. These observations are relevant to the studies carried out in the United Kingdom by the Royal Air Force School of Aviation Medicine and Defence Evaluation and Research Agency on the effects of pemoline on

prolonged duty overnight[19,20] which will be reviewed later.

The potential effects of methylphenidate on performance has also been investigated by the United States Naval Health Research Center. In the same experiment which studied pemoline, the activity of 10mg methylphenidate was assessed over a 64 hour period without sleep. In this study, although pemoline showed consistent effects, many of the differences between methylphenidate and the placebo group involved subjects performing worse on the drug than on placebo. Essentially 10mg methylphenidate was not particularly effective in counteracting the effects of sleep loss together with the nadir of performance associated with the circadian cycle. Limited effects on performance would be consistent with the studies cited in references 21 and 22, that methylphenidate only enhances performance during the day when performance is impaired by preceding sleep loss. It would, therefore, appear that methylphenidate, at least at the 10mg dose, neither enhances performance overnight nor during the day, and that any effect of the drug is limited to counteracting mild impairment of performance as would occur during the day after overnight sleep loss.

Several studies have been carried out by the Walter Reed Army Institute of Research and by the Institut de Médecine Aérospatiale (IMASSA-CERMA) on the activity of caffeine in relation to prolonged sleep deprivation.

The effect of caffeine (150, 300 and 600mg/70 kg PO) was studied, using sleep onsets and subjective assessments, after 49 hours without sleep. Caffeine led to significant alerting and long lasting beneficial mood effects.[23] Batejat, Lagarde, Pradella, van Beers, Schroiff and Sarafian[24] studied the effect of single doses on psychomotor performance during 30 hours sleep deprivation, while others[25,26] studied the effects of 300mg caffeine given every 12 hours during a 64 hour period of sleep deprivation. These studies established that time release caffeine (300mg) maintained cognitive performance up to 45 hours, increased spontaneous motor activity up to 48 hours and increased daytime sleep latencies up to 64 hours.

Duty Overnight. The above studies were concerned with prolonged sleep deprivation, but stimulants are more likely to be used operationally to reduce the effects of several hours of work alone or to ameliorate the effects of sleep loss together with the circadian nadir in performance during an overnight operation. Studies relevant to these scenarios have been carried out by the Royal Air Force Institute (later School) of Aviation Medicine and the Defence Evaluation and Research Agency (DERA), and by the Army Aeromedical Research Laboratory (USAARL), the Naval Aerospace Medical Research Laboratory (NAMRL) and the Army Research Institute of Environmental Medicine (ARIEM). In the context of the possible use of stimulants these laboratories have studied several compounds including pemoline, amphetamine, tyrosine and caffeine.

Studies carried out by the Royal Air Force Institute of Aviation Medicine during the 1980s used a model of an interdictor operation, in which a squadron of aircraft with an established aircrew-aircraft ratio was required to launch a number of missions at six-hourly intervals over a period of six to nine days.[27] With this scenario it was possible to define the pattern of work and rest which would be demanded of each individual crew. Essentially, each pattern of work was a random mix of duty periods varying between 6 and 18 hours and rest periods of 6 hours. The rest periods were critical, but even if it was assumed that each rest period provided good sleep (with or without the use of hypnotics) it was clear that some duty periods would involve low levels of performance. These were periods which involved duty of 12 to 18 hours overnight.

It was predicted from this model that, assuming the crew obtained refreshing sleep during each limited but critical rest period of six hours, about 15 interdictor missions could be operated over a nine day period, but that three or four of the overnight missions would involve low, and probably unacceptable, levels of performance. No doubt comparable scenarios could be obtained from land and sea operations, but, essentially, it is the effect of the adverse juxtaposition of many hours on duty and the circadian fall in performance overnight which is likely to lead to poor performance.

It is, therefore, in the context of sustaining air operations overnight that the question of the use of stimulants is most likely to arise. However, it must be borne in mind that the use of stimulants, as opposed to the use of hypnotics, modulates the individual while carrying out the task, and it is vital to ascertain that the stimulant does not itself give rise to unacceptable adverse effects. With the use of stimulants an attempt is made to maintain

vigilance at levels which exist during the day, and to avoid an excessive increase in arousal or adverse effects on cognition or mood which could impair the integrity of the individual.

During the 1980s the Royal Air Force Institute of Aviation Medicine attempted to establish which chemical entities would be most likely to be useful as stimulants. It was considered that stimulants whose activity was predominantly due to modulation of the noradrenergic or serotonergic systems were likely to be unsuitable in critical situations, as these drugs may give rise to unacceptable changes in cognition and mood. Suppression of REM sleep in man, independent of any reduction due to increased wakefulness, was used to exclude those drugs whose activity was likely to be predominantly noradrenergic or serotonergic, as modulation of these systems is known to suppress REM sleep in addition to any reduction induced by an alerting effect. The studies showed that drugs which did not suppress REM sleep (other than by increasing wakefulness) were unlikely to be noradrenergic or serotonergic in action,[28] and so for this reason the dopamimetic agent, pemoline, was assessed.

Turner and Mills showed that pemoline had the potential to sustain alertness and performance during work periods which involved continuous high workload overnight. Pemoline (30 and 40mg) had prolonged effects extending beyond the 12 hour period of duty, though 20mg maintained performance between 8 and 12 hours and was less likely to disturb any recovery sleep.[19] In further studies,[20] the dose range was extended down to 10mg. The study involved a 12 hour period of work during which subjective alertness and performance on a range of tasks were assessed at 1.5 hour intervals after ingestion at 2000 hours of pemoline (10, 20, 30 or 40mg). Work was preceded by a 6 hour rest period with temazepam (20mg) and was followed by 4 hour recovery rest without medication. Pemoline increased alertness and performance. With 30 and 40mg the onset of activity was delayed to 4.5 hours after drug ingestion and, again, the alerting effects persisted beyond the work period and disturbed recovery sleep. However, 10 and 20mg pemoline had no effect on recovery sleep. It was concluded that 20mg was likely to be the most suitable dose of pemoline for maintaining nocturnal performance. This dose was without adverse effects on recovery sleep and could be useful in the management of impaired performance overnight.

The Army Aeromedical Research Laboratory[29] studied the performance of helicopter pilots during simulated flights which commenced at 0100, 0500, 0900, 1300 and 1700 hours. Dextroamphetamine 10mg was given one hour before the first three assessments, which took place at 0100, 0500 and 0900 hours. Performance was improved during the 0500 and 0900 hours flights, though no effect was established at the 0100 hours flight. The study is of significance as it shows a useful effect of amphetamine when a relatively short period of sleep deprivation (say 6-7 hours) coexists with the nadir of circadian performance, and so is particularly relevant to the studies at references 18 and 20.

Amphetamine and tyrosine have also been studied by the Naval Aerospace Medical Research Laboratory.[30] In the studies with amphetamine a nine hour planning session was followed by four hours of rest and a 14 hour mission, and this was repeated after a six hour period of rest. A dose of 10mg (administered as 10mg/70kg) was given just over four hours into the second 14 hour session at 2035 hours. Amphetamine reduced fatigue without euphoria, improved performance, and lessened the tendency to shift from a conservative to a risky response strategy. The same laboratory studied the effects of tyrosine during a continuous period of night work. The study commenced at 1930 hours and ended the next day at 0820 hours. At 0130 hours the subjects were given 150mg/kg tyrosine which led to an amelioration of the decline in performance. There were useful effects on psychomotor skills, on vigilance and on monitoring functions, and ingestion was free of adverse effects on mood or on the cardiovascular system.

The UK Defence Evaluation and Research Agency Centre for Human Sciences has recently studied the efficacy of caffeine (300mg) in sustaining performance during prolonged duty overnight (unpublished data), in an experimental design in which performance was studied from 1500 hours to 0900 hours the next day, preceded by a 6 hour period of sleep with either placebo or temazepam (20mg). The ingestion of caffeine at midnight sustained performance throughout the remaining part of the night. The effect of caffeine was similar to that seen in other studies with monoaminergic compounds.

The studies on the activity of various stimulants on both prolonged sleep deprivation and duty overnight have established that many compounds

reduce the adverse effects of sleep loss and of the nadir of circadian activity on performance. Amphetamine, modafinil and pemoline in appropriate doses are probably equally effective. The choice of drug does, therefore, appear to depend on the adverse effects of the compound at the appropriate dose rather than on the primary activity of the drug itself. Many workers have cautioned against the use of amphetamine due to its effects on mood and the cardiovascular system. However, adverse effects are unlikely with the low dose (5mg) of amphetamine which has been used in air operations by the United States Air Force, though it must be borne in mind that experimental studies have raised the question whether such a low dose actually improves performance. Certainly 20mg amphetamine would appear to be high, so perhaps 10mg is the optimum dose. The balance between effectiveness and adverse effects may well favour modafinil, though questions have been raised concerning overconfidence after ingestion of this drug. At the time of writing modafinil has not been studied widely, and so the final decision must await further studies.

Pemoline (10-20mg) would appear to be a useful compound, possibly like modafinil, free of effects on mood, though it is unfortunate that hepatotoxicity in children has led to it being withdrawn in the United Kingdom, though not in the United States. With occasional use in intensive and sustained operations, the risk of hepatotoxicity appears to be remote, and so pemoline remains a candidate for occasional use in alleviating the effects of sleep loss or of the circadian nadir of performance. Studies in two countries (the United States and the United Kingdom) are encouraging. Pemoline is believed by the author to be particularly appropriate as it is dopamimetic, rather than noradrenergic or serotonergic, in action. In this context it would be of interest if the activity of modafinil were also shown to be primarily on the dopamimetic system.

Caffeine in an appropriate formulation would appear to be a most promising stimulant both in sleep deprivation and in maintaining performance during prolonged duty overnight. It could well be that caffeine will prove to be the drug of choice.

CONCLUSION

It is evident that hypnotics and stimulants have an important part to play in sustaining personnel during intensive air operations. They have a complementary role in ensuring sleep during critical and limited rest periods, and in preserving vigilance under conditions which will inevitably involve impaired performance. As far as hypnotics are concerned, temazepam has been used for many years, but in view of the constraint imposed by medico-legal regulations on handling the drug, zolpidem may well become the hypnotic of choice. The choice of a stimulant for air operations is less clear. Amphetamine, despite concerns about its adverse effects on mood, has been used successfully, and pemoline and modafinil are clearly useful drugs. However, it could well be that caffeine proves to be the most appropriate stimulant for military operations.

The Working Group has not reviewed policy on the use of hypnotics and stimulants in air operations, and has not assessed the evaluation of the military effectiveness of any such policies.

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Melatonin and Aircrew: Is an Operational Use Recommended?

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RESUME

Le syndrome de désynchronisation induit par le franchissement répété de fuseaux horaires ou «jet lag» induit des enjeux non négligeables en terme de performance et de sécurité des vols lors de déploiements rapides de forces. Si certaines solutions physiques et pharmacologiques ont été proposées, l'utilisation de la mélatonine pourrait à terme se concevoir. Après un revue de la littérature, les auteurs mettent en exergue les problèmes pratiques encore non résolus liés à l'utilisation de cette substance. L'absence de certitudes scientifiques rend actuellement nécessaire une certaine prudence avant son emploi dans le personnel navigant.

SUMMARY

The time difference-related desynchronization syndrome commonly called "jet lag" raises many issues in terms of performance and flight safety during rapid military deployments. Of several physical and pharmacological solutions recently proposed, the use of melatonin is generally considered to be a promising coping strategy. In this literature review, the authors have highlighted practical unsolved considerations in the use of melatonin. A conservative attitude, especially about its use in aircrew, currently remains necessary because of the lack of scientific certainties.

JET LAG: A SHORT REVIEW

The time difference-related desynchronization syndrome commonly called "jet lag" is an experience shared by millions of international travelers each year, as well as by the crews manning the aircraft transporting them. In the military field, jet lag may impair the performance of military personnel involved in a rapid overseas deployment. The pathophysiology of jet lag is not completely elucidated. Given that several time zones are crossed very quickly, local time upon arrival is not the same as local time at the point of departure, a calculation to which journey time must be added. At a physiologic level, the time difference induces a state of desynchrony in the individual temporal structure which leads to various symptoms.[51,33,24,16] The symptoms of jet lag are represented above all by disruption of the sleep-wake cycle, with nocturnal insomnia and diurnal drowsiness.[33,44,45] Other clinical manifestations can be associated with it, such as a sensation of unease, asthenia, irritability, diminished physical[19,20,39] and cognitive performance,[7] anxiety, the appearance of depressive phenomena, and finally digestive disorders.[52,8] These symptoms typically appear after a flight crossing five or more time zones, and are all the more pronounced the greater the number of zones crossed. The direction of the flight is significant; an eastward flight, which demands an advance in the sleep phase, is less well tolerated than a westward flight, which demands a delay in phase. Overall resynchronization capacity is estimated at l hour per day for an eastward journey, compared with 1 hour and a half per day for a westward journey.[21,8] Individual factors are also influential, as certain personalities, such as an "evening person" or "owl," rather than a "morning person" or "lark,"[18] as well as youth, favor rapid resynchronization.[31] Following arrival, the conflict between the subject's internal circadian rhythm and the action of external synchronizers in the environment fades progressively, as natural (light/ dark cues) and social (alternation of work/rest) synchronizers reset the various biological rhythms

more or less quickly. Consequently, various physiological strategies, possibly combined together, have been proposed to cope with jet lag, with physical exercise, bright light exposure, and modification of dietary intake being the most often cited. Physical exercise generally has a positive impact,[46] but the effect of bright light has not convincingly been demonstrated,[42] and there exists no controlled study using dietary adjustment. Furthermore, the application of such strategies is not always compatible with social activities. Gradually modifying bedtime before departure is also not advisable because it induces symptoms of jet lag before the journey.

PHARMACOLOGIC MANAGEMENT OF JET LAG

Any treatment able to alleviate jet lag and accelerate the resynchronization of biological rhythms would be of interest in terms of operational efficiency for the military, both for the sense of well-being of aircrew and travelers, and also in view of flight safety. Existing treatments appear to alleviate the symptoms of jet lag with varying degrees of success. Hypnotic drugs may be of benefit to avoid sleep disturbance. Benzodiazepines in particular have been extensively studied. They induce sleep and offer the individual a subjectively better night, but possible side effects like daytime drowsiness, lowered performance and anterograde amnesia are concerning. By taking the duration of action into account, the physician may be able to use such drugs under certain circumstances.[49] Among the benzodiazepines, temazepam has received the most attention and seen the widest operational use.[32] With a very short half life, zolpidem seems to have fewer side effects than benzodiazepines, and has been proposed to induce anticipatory or recovery sleep in aircrew.[47]

Interestingly, perhaps due to their restricted availability in many countries, stimulants have not been studied for jet lag therapy. Nevertheless, either amphetamines or modafinil could be of interest to sustain vigilance after arrival and speed up resynchronization.[22] Caffeine tablets are generally too short-acting to sustain vigilance for the entire diurnal period; slow-release caffeine offers a valuable alternative, but remains to be tested in this context.[23]

MELATONIN

Main Characteristics

Melatonin is a natural hormone, derived from serotonin, which is secreted by the pineal gland primarily during the hours of darkness. Melatonin is able to shift various biological rhythms by giving the internal clock an endogenous signal reflecting light/dark alternation in the environment;[25] such a property is known as chronobiotic.[14] Melatonin, the secretion of which is stimulated by darkness and inhibited by daylight, permits adjustment of the 25 hour periodicity characteristic of the suprachiasmatic nucleus to one of 24 hours. Thus, the pineal gland resynchronizes the master clock in the suprachiasmatic nucleus (SCN) by means of melatonin. The circadian rhythmicity of various hormonal (e.g., cortisol), vegetative (e.g., core temperature, sleep-wake cycle) and behavioral (e.g., activity) rhythms is then strengthened.[10]

The effects of melatonin are widespread but incompletely understood.[1] The secretion of melatonin at night reinforces the nadir of temperature[38] and coincides with sleep and low levels of cortisol secretion. It is clear, however, that melatonin is not the "sleep hormone," given that its secretion occurs at night even in nocturnal species such as rodents. Melatonin secretion begins at around 9-10 PM, reaches a peak around 3 AM (50-70 $pg.ml^{-1}$ in plasma), and disappears at around 7-9 AM. The melatonin secretion profile varies from one individual to another, but is relatively constant within the same individual from night to night. The melatonin rhythm is not very sensitive to masking effects, being little influenced by external stimuli save that engendered by light. The half-life of orally administered melatonin is 35 to 50 minutes; its major (90%) hepatic metabolite is 6-sulphatoximelatonin which, measured in the urine, provides a reliable method to assess the quantity of melatonin secretion in a noninvasive way.

Toxicologic studies in rodent models have been unable to determine an LD_{50}. In the absence of toxicity, exogenous melatonin administration at pharmacological doses has been carried out in humans in order to better understand its physiologic role and to determine its potential therapeutic use in circadian rhythm disorders. The power of exogenous melatonin resides in its capacity to modify

endogenous secretion in accordance with a phase-response curve in a dose-dependent manner,[25,15] and not by conventional feedback. Thus a dose of melatonin taken in the afternoon or evening brings about a phase advance - the peak of endogenous melatonin appears earlier and circadian rhythms are brought forward. A dose given in the morning or at midday entails a phase delay - the peak of endogenous melatonin appears later and circadian rhythms are postponed.[27] The strength of this chronobiotic effect is still under debate and it could be less important than previously assessed.[41] This point needs to be clarified in the future, since it clearly serves as the physiologic rationale for the potential use of melatonin as a jet lag therapy.

In the clinical field, melatonin has shown some success in delayed sleep phase syndrome, insomnia in the elderly, and blindness-related circadian disorders,[48] although the timing of administration needs to be optimized.[26]

Melatonin And Jet lag

The use of melatonin in preventing and treating jet lag has been investigated by relatively few controlled studies,[2,3,4,10,13,28,34,35,36,37] one of which was carried out under simulated conditions.[43] To our knowledge, the use of a melatonin agonist in the context of a jet lag protocol has not been published to date. The dose of melatonin used in these studies ranges from 5 to 10 mg, with 5 mg being the most commonly used. Administration of the agent varies between studies; the duration of treatment ranges between 3 and 9 days, beginning 3 days before the flight at the earliest, and the day after the flight at the latest, and ending 3 to 4, or even 5 to 7, days after the flight. In fact, prophylactic administration which takes place too prematurely may lead to drowsiness due to melatonin's sedative properties.[5] The time when the treatment is taken must be regular, in that before, during, and after the journey, it must correspond to bedtime in the country of destination. For an eastward flight, preventive doses will be taken in the late afternoon to achieve pre-synchronization, i.e., to induce a phase advance. Upon arrival, the treatment is taken at bedtime. Theoretically, a pre/post flight administration should be more efficient than a simplified protocol of post flight administration only, but study results remain inconclusive on this point. A significant alleviation of jet lag symptoms through the use of melatonin has been demonstrated in the course of these studies, but assessments were almost always subjective, using a sleep log, and visual analogue scales for jet lag tolerance, alertness, asthenia, and mood. The most objective studies, using actigraphy and/or performance tests,[33,14] demonstrated an increase in sleep duration and a faster resynchronization of subjects' rhythms (sleep-wake cycle, endogenous melatonin rhythm, temperature rhythm) when using melatonin compared to placebo. Cognitive and psychomotor performance of treated subjects were shown to be better than those of subjects receiving placebo.[14] Physical strength has never been evaluated in any study.

It should be noted that a small percentage (~10%) of subjects feel "worse" with melatonin, probably due to an administration timetable that is poorly adapted to the circadian clock of these subjects.[4,36] Interindividual variations in the flexibility of temporal organization may also account for such results. Ideally, physicians should assess the potential impact before giving any chronobiotic drug to a subject.[6] The majority of subjects experienced no side effects during these studies. However, drowsiness may appear 30 minutes after taking 5 mg of melatonin and may last approximately 1 hour.[3] According to Arendt, only higher doses of 50 and 80 mg of melatonin have demonstrated a clear hypnotic effect,[1] although Sack argues that there is a dose-response effect on sleep starting with lower supraphysiologic doses.[40] Dollins et al. agree that supraphysiologic levels of urinary 6-sulfatoxymelatonin are associated with cognitive performance impairment.[17] In jet lag studies, other minor side effects like nausea and headache have also been observed.[4] Recently, irregular sleep-wake cycle related to more prolonged melatonin intake has been described by Middleton et al.[2] Comperatore et al have tried to address the question of the grounding time of personnel after melatonin administration, and have noted that this grounding period should not exceed the time necessary for spontaneous resynchronization. They advised a 16 to 24 hour grounding time after a single administration of 10 mg at 2300 hours. A recovery sleep may shorten this duration.

CONCLUSION

The previous cited studies have shown that melatonin likely has an impact on jet lag symptoms, and demonstrate the presence of a chronobiotic effect, albeit a weak one. The potential usefulness of a compound like melatonin for military

deployments is obvious. Scientific literature has not yet provided clear answers to a number of practical considerations that need to be clarified:

- Administration timetable is still uncertain.
- Optimal dose is still to be identified; lower doses than those previously tested may be of interest, perhaps 3 to 5 mg maximum.
- Benefits in terms of sleep-wake resynchronization and performance sustainment should be confirmed.
- Side effects, especially transitory drowsiness, need to be clearly assessed, particularly if one is considering drug administration to active aircrew, and not just to passengers during the flight.

Future collaborative studies should address these questions before the optimal use of melatonin in the context of military operations can be ascertained.

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Medication for Motion Sickness

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MEDICATION

Over the years many medicinal remedies have been proposed for the prevention of motion sickness. The number of drugs that has been tested is large, but relatively few are effective (Table 1), and none can completely prevent the development of signs and symptoms in everyone in all provocative motion environments. When the motion is relatively mild and only 10% of the unmedicated population suffer from sickness, then use of a drug such as hyoscine (scopolamine) can increase protection so that all but 2% of the population remain symptom-free. But when the motion is of such severity and duration that 50% are sick when no drug is given, a large dose of hyoscine (1.0mg) still leaves 8% of the population unprotected.[1] In life-rafts, sickness rates approaching 100% have been reported, so it is not surprising that a significant proportion of the occupants will still suffer from sea sickness even when the dose of drug given is sufficient to cause side-effects.

None of the drugs of proven efficacy in the prophylaxis of motion sickness is entirely specific and all have side-effects.[2] Both the anti-histaminics (such as promethazine, dimenhydrinate or cinnarizine) and the anti-cholinergic, hyoscine, are also central depressants and can cause impairment of performance. Hyoscine, at all therapeutic doses, has been shown to cause a performance decrement on tasks requiring continuous attention and memory storage for new information, but only at doses greater than 0.8mg does it interfere with performance of a pursuit tracking task.[3] Promethazine 25mg and cinnarizine at doses greater than 30 mg have also been shown to impair psychomotor performance.[4,5] Other side effects of hyoscine, notably blurred vision, sedation, dizziness and dry mouth, may also contribute to performance decrement.[6]

There is thus good reason for the general rule that anti-motion sickness drugs should not be taken by aircrew, and should under no circumstances be taken by a pilot when required to fly. There is a place for the administration of prophylactic drugs to susceptible student aircrew, particularly during the early stages of flying training when accompanied by an instructor. However, there is evidence to suggest that hyoscine, whilst allaying symptoms, does interfere with the acquisition of protective adaptation. This is one reason why the continued dispensation of anti-motion sickness drugs to aircrew is to be deprecated; another is that such a pharmacological "crutch" is not compatible with operational duties.[7,8] An exception may also be made for aircrew who are not in primary control of the aircraft, such as rear crew members in maritime reconnaissance or hurricane penetration flights. For them the administration of one of the drugs whose side effects are slight (e.g., cinnarizine) may be entertained and could well be beneficial.

No such restrictions apply to the use of drugs by passengers for the alleviation of motion sickness. Paratroops and other personnel who must operate at peak efficiency on leaving the aircraft or at the end of a flight are a possible exception, though the putative performance decrement attributable to motion sickness and that due to drug side-effect is a dilemma to be assessed only with detailed knowledge of all facets of the operational situation. The choice of prophylactic drug is, in part, dependent upon the foreseen duration of exposure to provocative motion and, in part, upon differences between individuals, both in the efficacy of a particular drug and the severity of side-effects. So if, in practice, one drug is not effective or not well tolerated, then it is justifiable to give another drug or combination of drugs.

Where the therapeutic objective is to provide short-term protection, oral *l*-hyoscine (syn. scopolamine) hydrobromide (0.3 – 0.6mg) is the drug of choice. This acts within ½ - 1 hour and provides protection for about 4 hours. Side-effects can be troublesome and tend to be accentuated if repeated administration (at 4 – 6 hour intervals) is required for more prolonged prophylaxis. With the development of

transdermal drug transport techniques, it is now possible to provide a loading dose of 200 μg hyoscine, followed by controlled release at 10 μg/h for up to 60 hours, by means of a patch placed behind the ear (the Transdermal Therapeutic System or TTS). The protection afforded by TTS is reported to be comparable with that achieved by oral hyoscine, but there does appear to be greater inter-subject variability in both the efficacy and the incidence of side-effects than is found with repeated oral administration of the drug. When hyoscine is administered transdermally, peak blood levels are not reached until 8 – 12 hours after application of the patch, so it is necessary to anticipate a requirement for prophylaxis by at least 6 hours.[9] The antihistamines, promethazine and meclozine, when taken by mouth are absorbed more slowly than hyoscine and are not effective until about 2 hours after administration, but they provide protection for at least 12 hours. Other drugs in the same group, such as cyclizine, dimenhydrinate and cinnarizine, are absorbed at about the same rate although their duration of action is shorter, i.e., about 6-8 hours. Somewhat atypically, the peak therapeutic effectiveness of cinnarizine is not achieved until some 4 hours after ingestion even though the concentration of the drug in blood is at a maximum at 2 hours.

The demonstration that *d*-amphetamine increases subjects' tolerance to cross-coupled stimulation led to an evaluation of the use of this analeptic in combination with the established anti-motion sickness drugs.[10] It was found that there was a synergistic increase in prophylactic potency and a decrease in the sedation which is a common side-effect of hyoscine and the antihistamines. Ephedrine is almost as effective as amphetamine in enhancing the efficacy of the anti-motion sickness drugs and should be used in preference to amphetamine when prescription of this potentially addictive drug is contraindicated.

Assessment of therapeutic potency both in laboratory and in field trials has indicated that the combination of *l*-hyoscine hydrobromide (0.3mg) with ephedrine sulphate (5mg) is most effective for short-term (4 hours) protection. In situations requiring more sustained prophylaxis the combination of promethazine hydrochloride (25mg) with ephedrine sulphate (25mg) is recommended.[6]

Vomiting that is severe and repeated can lead to dehydration and loss of electrolytes. If this occurs in a survival situation (for example, on a life-raft) it may cause breakdown in morale, loss of interest in surroundings, and a loss of ability to co-operate with rescue attempts. In such cases attention should be given to the following:[11]

1. Maintenance of intake of fluids and electrolytes.

2. Use of drugs. These must be given parenterally. If given by mouth they may not be absorbed or will be returned with the vomit. The following preparations are recommended:

Drug	**Dose *(mg)***	**Route**
Hyoscine (scopolamine) hydrobromide	0.1-0.2	Intramuscular injection
Cyclizine lactate	50	Intramuscular injection
Promethazine hydrochloride	25-50	Intramuscular injection.

3. Supportive measures. Make the patient lie down, attend to general comfort and give reassurance.

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Table 1. Adult dosage and duration of action of anti-motion sickness drugs

Drug	Route	Adult Dose	Time of Onset	Duration of Action (hr)
Hyoscine HBr (Kwells®) (Scopolamine)	Oral	0.3 – 0.6mg	30 min	4
Hyoscine HBr	Injection	0.1 – 0.2mg	15 min	4
Hyoscine HBr (Scopoderm TTS®)	Patch	One	6 – 8 hr	72
Promethazine HCI (Phenergan®)	Oral	25 – 50mg	2 hr	15
Promethazine HCI	Injection	25mg	15 min	15
Dimenhydrinate (Dramamine®)	Oral	50 – 100mg	2 hr	8
Dimenhydrinate	Injection	50 mg	15 min	8
Cyclizine HCI (Marzine®)	Oral	50 mg	2 hr	6
Cyclizine lactate (Valoid®)	Injection	50mg	15 min	6
Meclozine (Sea-legs®)	Oral	25 – 50mg	2 hr	8
Cinnarizine (Stugeron®)	Oral	15 – 30mg	4 hr	8

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Modafinil: A Molecule of Military Interest

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ABSTRACT

Modafinil (Modiodal®) is a synthetic molecule prescribed for the treatment of narcolepsy and idiopathic hypersomnia. It could be used by armed forces for sustained or continuous operations. The wakening effect is potent: modafinil allows healthy volunteers to stay awake and efficient for more than 60 hours, without side-effects. The mechanism of action of modafinil is complex, involving the adrenergic system (central α1-postsynaptic receptors), associated with serotoninergic, GABAergic and probably dopaminergic systems. Moreover, the implication of excitatory amino acids was demonstrated. The anterior hypothalamic nucleus could be the main and specific target for modafinil. It could induce wakefulness by different mechanisms, as compared with other classical vigilance-enhancing drugs such as amphetamines. A neuroprotective effect against neurotoxic organophosphate agents was recently discovered.

Key words: Mechanism of action – Modafinil – Neuroprotection.

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INTRODUCTION

Modafinil (Modiodal®) was introduced in 1994 by the Laboratoire L. Lafon for the treatment of wake disorders such as narcolepsy and idiopathic hypersomnia. Because of its wakening properties, low toxicity and absence of tolerance-producing effects, it could be used by armed forces in sustained or continuous operations involving partial or total sleep deprivation, as in the Gulf War. The pharmacological properties of modafinil are very different from those of the vigilance-enhancing molecule of reference, amphetamine. Its mechanism of action is highly complex and incompletely documented at this time.

The goal of this article is to elucidate the specific mechanism of action of this molecule which does not fit into the classification system of Delay and Deniker and for which a new pharmacological category, "eugregorics" (from *eu*=good and *gregor*=arousal), has been proposed.

PHYSICO-CHEMICAL PROPERTIES, PHARMACOKINETICS AND TOXICITY

Modafinil, or 2-[(diphenylmethyl) sulfinyl] acetamide (Fig. 1), is an active metabolic derivative of adrafinil. Modafinil has proven to be more interesting than adrafinil for inducing wakefulness. It is essentially insoluble in water (which poses problems with respect to administration and bioavailability in experimental animals).

When modafinil is given orally in a single dose, absorption is slow; T_{max} is between two and four hours. The consumption of food with modafinil does not modify its pharmacokinetic profile. Modafinil metabolizes to modafinil acid, modafinil sulfone and hydroxy modafinil. Only the acid and sulfonic metabolites have been found in the plasma and urine of human subjects. Both of these metabolites are pharmacologically inactive. Urinary

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elimination of unconverted modafinil is low (approximately 10% of the administered dose). The elimination half-life of modafinil is somewhere between ten and thirteen hours. When multiple doses are given orally (200 mg/d), steady state plasma concentration is achieved within two to four days. Enzyme induction is not triggered at this dose level.

Modafinil has a low level of toxicity; its LD_{50} is higher than 1 g/kg in rodents (when administered orally) and approximately 400 mg/kg in canines. Acute and chronic toxicity levels are also low with modafinil: when it is administered for 25 weeks to rats in doses of 20 and 50 mg/kg/d, no toxic effects are observed. Similarly, *in vitro* and *in vivo* mutagenesis tests reveal no anomalies and life-long carcinogenicity studies conducted in experimental animals (rats and mice) have produced no suspicious signs of cancer.

PHARMACOLOGICAL INTEREST FOR HEALTHY SUBJECTS

Experiments involving healthy human subjects are comparatively rare. The data which is currently available concerns control group subjects who have participated in hypersomnia studies. In one such study, conducted by Benoit et al.,[1] a 200-mg dose of modafinil administered at 10 p.m. to a group of twelve young men was shown to reduce nocturnal sleepiness, (although the level of vigilance attained was less than the reference level), and to improve nocturnal psychomotor performance. In 1987, Goldenberg et al.[2] demonstrated that a group of twelve healthy subjects (five men and seven women) who had been given modafinil (200 mg three hours after breakfast) had multiple sleep latency test (MSLT), quantified EEG and analogue-visual-chart results that were not significantly different from those of the control group.

Much of the data currently available was produced in experiments involving subjects who had been deprived of sleep for periods of varying duration. The first of these experiments was conducted by Puech and Bensimon[3] with twelve healthy subjects who had been deprived of sleep for 36 hours. The investigators found that modafinil (at doses of 100, 200 and 300 mg/kg) antagonized the effects of sleep deprivation in a dose-dependent fashion. Lagarde et al. (1990 and 1992, published at a later date) have demonstrated the potent wakening effect obtained with modafinil when a 200-mg dose is administered for three consecutive days (Fig. 2), as well as the potentiation of the recuperative effect of short naps when the drug is taken during the day. The similarity of EEG results in subjects given modafinil and those given a placebo was confirmed by Saletu et al.,[7] as was the absence of side-effects when modafinil was administered in doses of 100 and 200 mg.[7,8] In 1994, Bourdon et al.[9] demonstrated that modafinil had no effect on heat production under neutral conditions, nor on body temperature regulation in subjects exposed to cold. More recently (1995), Pigeau et al.[10] and Buguet et al.[11] compared modafinil and d-amphetamine and showed, among other things, that the two substances were almost equally effective at stabilizing mood and maintaining performance.

The assessment of modafinil in healthy subjects offers a way to demonstrate the potent wakening effect of this molecule which permits the maintenance of optimum capacity, produces no side-effects at effective dose levels, and has the original property of inducing wakefulness without interfering with sleep.

MECHANISM OF ACTION

Hyperlocomotor activity, behavioural indices of arousal, and EEG results obtained after the administration of modafinil, have been examined in attempting to elucidate the mechanism of action which induces the wakening effect of this molecule.

Pathways of Waking

There are four main subcortical systems which can trigger waking at the level of the cerebral cortex (Fig. 3):

- a direct ponto-cortical pathway, issuing from the noradrenergic neurons of the locus coeruleus or the serotoninergic nuclei of the dorsal raphe;
- a ponto-basalo-cortical and ponto-hypothalamo-basalo-cortical pathway, issuing from the non-cholinergic neurons of the dorsolateral pontine tegmentum and the neurons of the posterior hypothalamus, (these neurons perform a relay function via the nuclei of the telencephalon), and ending in the cerebral cortex;
- a ponto or bulbo-hypothalamo-cortical pathway, issuing from cholinergic or non-cholinergic neurons in the magnocellular nucleus or dorsolateral pontine tegmentum, in which these neurons perform a relay function via the histaminergic neurons of the posterior hypothalamus which project to the cerebral cortex;

- a reticulo-thalamo-cortical pathway, issuing from the cholinergic neurons of the mesencephalic reticular formation which stimulate cerebral cortex activity through the intervention of the excitatory amino acid neurons (glutamate and/or aspartate) of the intermediate nucleus of the thalamus.

In short, these "waking neurons" call on many different neurotransmitters and share an essential anatomical characteristic; some of their extensions directly reach the cerebral cortex, while others connect with structures which in turn project to the cortex. Through these extensions, the cortex receives the transmitters which activate the "waking neurons." The neurochemistry of waking states is as complex as the neuronal circuitry on which it depends. Since knowledge in this area is developing at a rapid pace, one must be prudent about proposing simplified (and therefore inaccurate) configurations of the systems which govern the sleep-waking cycle.

Modafinil's chief pharmacological property is that it induces wakefulness, as opposed to stimulation, which has only occurred in mice and monkeys that were given high doses.[12,13] This distinguishes modafinil from psychostimulant amphetamines (the reference substances), which have different mechanisms of action and side-effects. In modafinil, the mechanism of action is particularly complex and enlists most of the transmitters involved in the neurochemical pathways of waking.

Adrenergic System

Central α1-adrenergic receptor antagonists (prazosin and phenoxybenzamine) diminish the electroencephalographic and behavioral wakening effects of modafinil in monkeys[14] and cats.[15] Alpha 2-adrenergic antagonists (yohimbine) and beta-adrenergic antagonists have no effect. Alpha-methyl-para-tyrosine, an inhibitor of catecholamine synthesis, has essentially no effect on modafinil-induced hyperactivity. In the context of the adrenergic system, modafinil appears to act as an α1-postsynaptic receptor agonist and does not require the participation of newly synthesized catecholamines. On the contrary, once monoamine reserves have been depleted by reserpine,[12] modafinil-induced hyperlocomotor activity is antagonized. It would seem that the mechanism of action of modafinil requires the participation of monoamine reserves. In addition, the effects of modafinil are not potentiated by noradrenalin re-uptake inhibitors (desipramine or maprotiline), nor by monoamine oxidase inhibitors (MAO inhibitors) such as nialamide and pargyline. Consequently the presence of "physiological" central α1-adrenergic tone is indispensable to the manifestation of the stimulant or wakening effects of modafinil.

Dopaminergic System

When modafinil is administered in low doses, its mechanism of action does not appear to require activation of the central dopaminergic systems.[16] In the rat, doses of up to 512 mg/kg given orally do not induce stereotypic or rotatory behaviors. In the dopamine-rich cerebral structures which regulate waking, such as the caudate nucleus, the striatum and the nucleus accumbens, modafinil (in doses of 16, 64 and 256 mg/kg) does not alter the maximum amplitude of catechol oxidation peaks. A dose of 30 mg/kg i.p. does not alter the concentrations of dopamine and its metabolites DOPAC and HVA in the dorsal striatum of the anesthetized rat.[17] At a concentration of 10^{-5} M, modafinil does not increase the spontaneous release of [^{3}H]-dopamine in mouse striatal synaptosomes. The dopaminergic system inhibitors haloperidol (0.125 mg/kg), pimozide (0.125 mg/kg) and sulpiride (32 mg/kg) do not modify modafinil-induced hyperactivity in rodents.[16]

However, behavioral and electroencephalographic studies conducted with Rhesus monkeys have demonstrated that pimozide (0.02 mg/kg) partially antagonizes the wakening effects of modafinil administered at doses of 12 to 45 mg/kg.[14]

Recent *in vivo* microdialysis studies in the anesthetized rat[18] show that modafinil (in doses above 100 mg/kg, s.c.) produces an increase in dopamine concentration in the posteromedial nucleus accumbens. Dopamine release occurs as a consequence of reduced GABAergic transmission, with the involvement of the serotoninergic terminals. In addition, Gold and Balster[19] demonstrated in 1996 that the administration of high doses of modafinil in the rat (250 mg/kg, i.p.) reinforced addictive behavior to cocaine (although at a rate 200 times lower than with amphetamine or ephedrine). An indirect increase in dopaminergic transmission, resulting from the cessation of GABAergic inhibition and/or the blocking of dopamine re-uptake, may contribute to the effects produced by modafinil at high dose levels.[18,19]

Serotoninergic System

In the guinea-pig, chronic administration of modafinil (30 mg/kg/day for seven days, s.c.) does not alter concentrations of serotonin in the parietal cortex and neostriatum.[20] In the mouse (30 mg/day for fourteen days, i.p.) and the rat (50 mg/kg, i.p.) modafinil does not alter serotonin concentrations but does cause an increase in the serotonin metabolite 5-HIAA, as well as an increase in the speed at which it renews itself in the striatum. In the guinea-pig, the repeated administration of modafinil (30 mg/kg/day, for seven days, s.c.) counteracts the decrease in parietal cortex serotonin concentration induced by the intracerebroventricular administration of 5,7 DHT (a toxin to serotoninergic neurons). In addition, administration of this serotoninergic antagonist causes a moderate increase in noradrenalin in the parietal cortex. This increase is potentiated by modafinil.[20]

Consequently, it appears that serotoninergic transmission is also implicated in the mechanism of action of modafinil.

Histaminergic and Cholinergic Systems

In vitro, modafinil does not modify the release of histamine (whether spontaneous or induced by depolarization) and does not counteract the inhibitor effects which histamine has on its own release. Modafinil acts as neither an agonist nor an antagonist to H3 histaminergic receptors. (H3 presynaptic receptor antagonists induce waking.)

In the guinea-pig, modafinil (3-30 mg/kg, s.c.) does not modify the outflow of cortical acetylcholine.[20]

Consequently, it seems unlikely that the histaminergic and cholinergic systems are implicated in modafinil's mechanism of action.

GABAergic and Cyclinergic Systems

Modafinil (3-30 mg/kg, s.c.) inhibits cortical γ-aminobutyric acid (GABA) outflow in a dose-dependent fashion in the unrestrained rat.[20] This result was confirmed in the anesthetized rat.[21] This inhibition of cortical GABA outflow is antagonized by the administration of methysergide (a 5-HT receptor antagonist) and ketanserine (a 5-HT2 receptor antagonist). It is not modified by the (i.p.) administration of prazosine (an α1-adrenergic receptor antagonist). Consequently, the reduction in cortical GABA release may contribute to the wakening action of modafinil. This modafinil-induced reduction in cortical GABA release does not occur when animals are pre-treated with 6-hydroxydopamine (a toxin to catecholaminergic neurons).[16] Therefore, the presence of catecholaminergic tone is essential. In fact, intracerebroventricular injection of modafinil increases GABA release in animals given 5,7 DHT (a specific neurotoxin to 5-HT neurons). The enhanced release of cortical GABA which modafinil induces in animals that have been pre-treated with 5,7 DHT is antagonized by prazosin.

These experiments show that modafinil-induced regulation of cortical GABA is linked to the balance between central serotoninergic and α1-adrenergic transmissions.

In addition, reduced outflow of cortical glycine has been demonstrated by microdialysis.[21] This inhibitory transmitter amino acid is often found in the same nerve endings as GABA.

Excitatory Amino Acids (EAA)

It is now recognized that excitatory amino acids (EAA) and their receptors participate in the systems that regulate waking.[22] It is also likely that EAA are implicated in the wakening and neuroprotective properties of modafinil. A proton study using two-dimensional NMR spectroscopy[23] in the rat has shown that modafinil (600 mg/kg, i.p.) increases the level of aspartate (72 $\pm$ 15%) and the glutamate-glutamine pool (28 $\pm$ 8%) in the cortex. A complementary microdialysis study[21] has demonstrated the occurrence of a moderate transitory increase, followed by a prolonged decrease, in the level of extracellular glutamate in the rat brain cortex. Modafinil also induces a prolonged and significant decrease in the level of extracellular aspartate. Finally, an actographic behavioral study conducted in mice[24] has shown that the increase in motor activity induced by modafinil (100 mg/kg) can be modulated by various glutamate agonists and antagonists. This would suggest that modafinil acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, a non-NMDA receptor agonist, and a metabotropic receptor agonist. However, the EAA-release inhibitor propentofylline has not been shown to antagonize modafinil-induced hyperlocomotion. Consequently, it would appear that the early release of glutamate observed in microdialysis is not the direct cause of modafinil-induced motor stimulation.

Metabolic and Energetic Effects

Two-dimensional NMR spectroscopy[23] of the rat brain cortex has shown that modafinil (600 mg/kg, i.p.) triggers an increase in the creatine-phosphocreatine pool. This phenomenon may play a role in the energy-dependent re-uptake mechanisms which are engaged following the massive release of EAA and, accordingly, may contribute to the neuroprotective effect of modafinil in physiopathological situations such as hypoxia or exposure to neurotoxic organophosphate agents.

In a complementary study using phosphorus-31 NMR, cerebral phosphomonoesters increased and cerebral phosphodiesters decreased following the administration of modafinil.[22] This may reflect the effects of modafinil on membranous phospho-lipids.[25]

Microdialysis following the administration of modafinil also showed a decrease in extracellular glutamine and alanine.[21] A decrease in the extra-cellular presence of these amino acids (which play a strictly metabolic role) may also contribute to the production of cerebral energy through the tricarboxylic cycle.

Site of Action

Determining the site of action of modafinil through the traditional method, which involves the displacement of receptor-labelled ligands, was not possible.[16] Every *in vitro* attempt produced a negative result, with the exception of dopamine-carrier binding sites in the striatum of the guinea pig and the rat, where modafinil displaced labelled ligands ([^{3}H]-WIN35,428 or [^{3}H]-mazindol).[26]

This led the team of professor Jouvet in Lyon[27] to investigate the proto-oncogene *c-fos*, a non-specific neuron activation marker. The Jouvet team observed that modafinil (1-5 mg/kg, p.o.) induces *c-fos* expression in the cat, where this largely occurs in the anterior hypothalamic nucleus. The vigilance-enhancing substances of reference, amphetamine and methylphenidate, do not induce *c-fos* expression in this structure but rather in the striatum and the whole cortex, which are dopamine targets. These results suggest that the anterior hypothalamic nucleus is the specific, privileged site of action of modafinil, inducing wakefulness through mechanisms which are distinct from those of traditional wakefulness-inducing substances.

In summary, although it is difficult to establish a hierarchy of the various neurochemical effects induced by modafinil, postsynaptic α1-adrenergic effects appear to be preponderant. At high dose levels, dopaminergic effects are induced and the transmitter amino acid system is brought into play. In addition, the effects of modafinil on energy metabolism within the cerebrum should not be overlooked.

NEUROPROTECTION

Modafinil has a protective effect against hyperoxic convulsions induced in the mouse.[28] More recent experiments with Rhesus monkeys[29] have strengthened arguments in support of the potential neuroprotective properties of modafinil. One month prior to the experiments, sixteen superficial electrodes were implanted in the animals in order to record electrical activity in the cortex (electro-corticogram). In addition, two electromyogram electrodes were implanted in the muscles at the back of the neck. Hypoxia lasting 60 minutes, corresponding to an artificial altitude of 5,500 meters (72% SaO_2), was induced in a hyperbaric chamber. Behavioral observation, as well as an analysis of electrical activity in the cortex of the Rhesus monkey in a state of hypoxia, demonstrated that modafinil (6 and 12 mg/kg) reduced sleepiness and increased vigilance. This led the investigators to hypothesize that the neuroprotective effects of modafinil may result from the modulation of several neurotransmission systems, in particular those which bring into play excitatory amino acids (EAA) and their NMDA receptors.

Neurotoxic organophosphate agents such as soman (potential tools of chemical warfare), target acetylcholinesterase (AChE) and cause the accumulation of acetylcholine (ACh). The acute administration of soman in laboratory animals brings about generalized convulsive seizures, as well as neuropathological sequelae in the subjects that survive. This occurs in all limbic areas, the hippocampus in particular. The occurrence of seizures is dependent on muscarinic cholinergic mechanisms. Recent studies[30] have shown that the massive release of excitatory amino acids (particularly glutamate) which follows soman poisoning likely plays a preponderant role in the propagation and maintenance of seizures, as well as in the delayed neuronal damage that occurs as a result of the activation of NMDA receptors. Consequently, soman poisoning appeared to pro-vide an excellent neurotoxicity model to objectively

test the neuroprotective properties of modafinil. Omega-3 sites are peripheral benzodiazepine receptors largely present in glial cells and macrophages, and mostly absent in neurons. The increased density of omega-3 sites is a reflection of glial reaction and macrophagic colonization, which are consequences of acute or chronic neuronal distress. Consequently, the density of omega-3 sites provides an indirect index of cerebral lesions. An initial series of experiments conducted in the mouse (Fig. 4) demonstrated that modafinil, administered at doses of 600 mg/kg, i.p., antagonized density increases in omega-3 sites in the hippocampus following soman poisoning (DL_{50}=220). However, modafinil doses of 150 and 300 mg/kg, i.p. did not antagonize density increases in omega-3 sites. A second series of experiments consisted of the microscopic examination (with cresyl violet coloration) of hippocampal sections in soman-poisoned rats, where some of the rats had been pretreated with modafinil and some had not. In view of the results previously obtained in the mouse, the test was conducted using only a dose of 600 mg/kg i.p. The hippocampus of the poisoned rats that had not been pretreated showed microscopic lesions or ruptures in the pyramidal cell layer as well as signs of cytolysis. In rats pretreated with modafinil, the CA1 and CA3 areas showed no visible microscopic lesions and the pyramidal cell layer had maintained its integrity. Hippocampal histologic sections in rats pretreated with modafinil were not visibly different from those of non-poisoned rats. These two studies, conducted at the Centre de Recherches du Service de Santé des Armées,[31] clearly show that, at a dose level of 600 mg/kg, modafinil plays a neuroprotective role, preventing hippocampal lesions induced by neurotoxic organophosphate agents.

The neuroprotective properties of modafinil may be linked to the prolonged decrease in extracellular EAA which it induces, as well as to its properties as an NMDA receptor antagonist and metabotropic receptor agonist.

These preliminary results, which provide an understanding of the neuroprotective mechanisms of modafinil, may have therapeutic applications, particularly in the context of exposure to neurotoxic organophosphate agents.

CONCLUSION

Because of its wakening effect, which is not associated with undesirable side effects, its recently discovered neuroprotective properties and its original mechanism of action, modafinil is a highly interesting molecule from the standpoint of military use. A number of aspects relating to the potential use of modafinil in an operational setting still have not been closely examined. Both the Centre de Recherche du Service de Santé des Armées and the Instituts are actively pursuing such investigations in order to ensure that combatants can conduct their missions safely and effectively.

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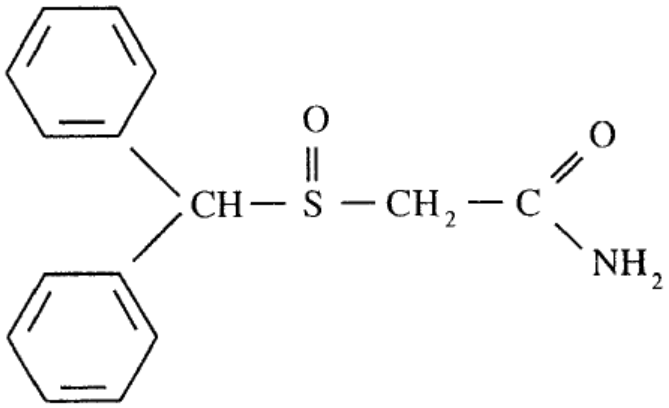
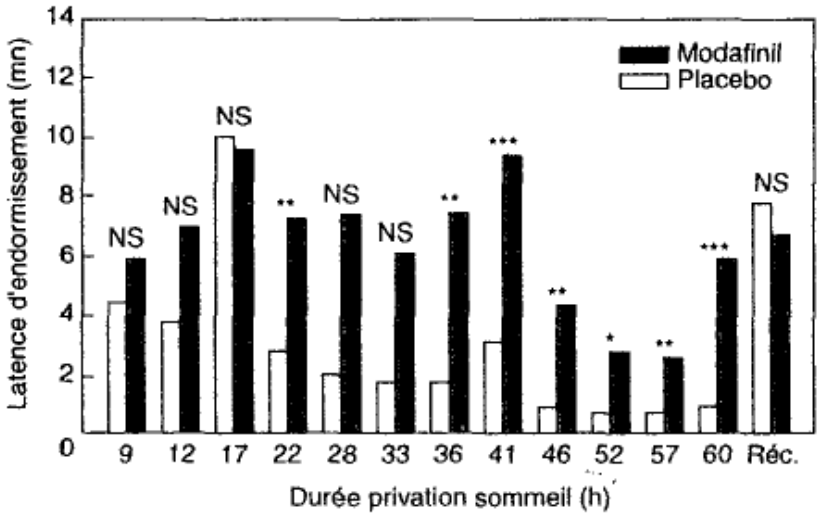
Figure 1: Modafinil Molecule



Molecular formula: $C_{15}H_{15}NO_2S$
Relative molecular mass: 273.36
Chemical identity: 2-[(diphenylmethyl)sulfinyl] acetamide
Commercial name: Modiodal®, Laboratoire L. LAFON
Characteristics:
White crystalline powder: practically insoluble in water, sparingly soluble in ethanol, soluble in methanol.
Modafinil melts at 150-155 degrees centigrade with thermal decomposition.

Figure 2: Mean Sleep Latencies in a 60-Hour Sleep Deprivation Experiment



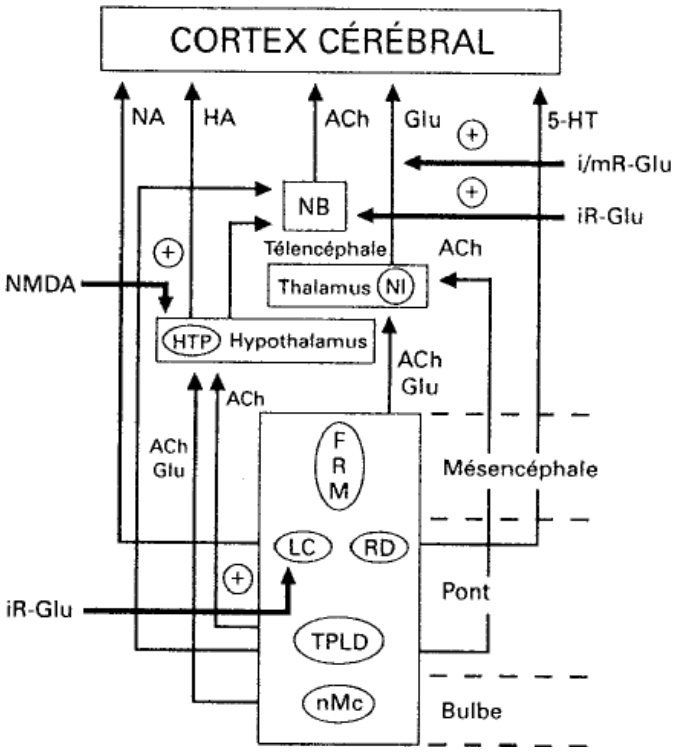
Vertical scale: Sleep latency period in minutes (0 to 14)

Horizontal scale: Period of sleep deprivation in hours – 0 to 60 hours

Multiple Sleep Latency Test (MSLT) with placebo and modafinil (200 mg/8 hrs). NS = not significant.

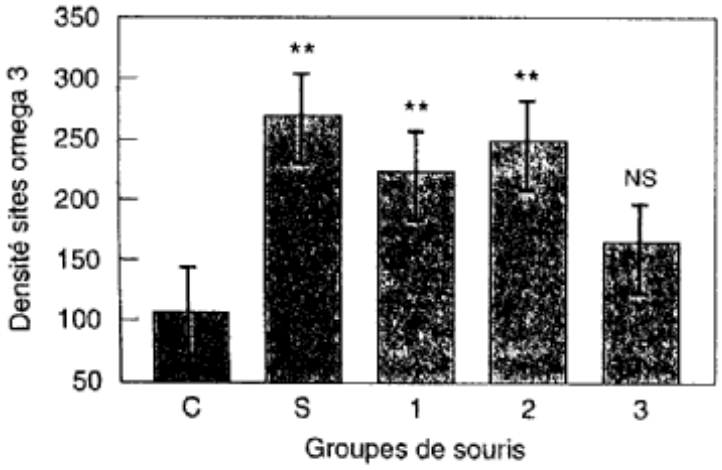
* $p < 0.05$; ** $p < 0.01$; *** p. <0.001.

Figure 3: Schematic Representation of the Neurochemical Pathways of Waking



ACh: acetylcholine	NMDA: NMDA receptors
Glu: glutamate and/or aspartate	MRF: mesencephalic reticular formation
HA: histamine	BN: basal nucleus
5HT: serotonin	IN: intermediate nucleus
NA: noradrenalin	LC: locus coeruleus
iR-Glu: ionotropic	MCn: magnocellular nucleus
glutamate receptors (NMDA and non-NMDA)	DR: dorsal raphe
mR-Glu: metabotropic glutamate receptors	DLPT: dorsolateral pontine tegmentum

Figure 4: Neuroprotective Effect of Modafinil.



Densité des sites ω3, dans l'hippocampe de souris, 48 heures après intoxication par le soman (moyennes ± e.s.m. exprimées en fmol/mg de protéine).
Groupes de souris : C = contrôle ; S = soman ; 1 = soman + modafinil (150 mg/kg) ; 2 = soman + modafinil (300 mg/kg) ; 3 = soman + modafinil (600 mg/kg).
Significativités exprimées par rapport au groupe contrôle :
** $p < 0,01$; NS : non significatif (Test de Mann et Whitney).

Vertical scale: Omega-3 site density (50 to 350)
Horizontal scale: Mouse groups (C – S – 1 – 2 – 3)

Omega-3 site density in the mouse hippocampus, 48 hours after soman poisoning (mean ± S.E.M. expressed as fmol/mg of protein
Mouse groups: C = control; S = soman; 1 = soman + modafinil (150 mg/kg); 2 = soman + modafinil (300 mg/kg); 3 = soman +modafinil (600 mg/kg).
Significance expressed in relation to the control group:
** $p < 0.01$; NS: insignificant (Mann and Whitney test).

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Section III: Current Usage of Medication in NATO Aircrew Medication Database

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INTRODUCTION

In April 1997, Working Group 26 undertook to facilitate international collaboration in determining the suitability of medications for use by military aviators. The group is focusing on two areas: 1) current knowledge and experience in use of medications by military aviators, and 2) means of international collaboration on the study of new medications for use by military aviators. To simplify the task, while still including the vast majority of drugs used in aviators, the group discussion decided to focus on eight disease categories: Hypertension, Malaria Prophylaxis, Asthma, Allergic Rhinitis, Allergic Dermatitis, Other Manifestations of Allergy, Hyperlipidaemia and Disorders of the Digestive System. Furthermore it was decided to see which drugs for operational use were thought to be important.

Attempts to get information from every NATO country resulted in responses from Belgium, Canada, France, Great Britain, Germany, Greece, Italy, Netherlands, Spain and USA. Later, the Czech Republic, Hungary and Poland also responded. Information about the fields of interest was gathered with the help of two questionnaires. The results of this "who is using what and when" will be explained in the rest of this article.

It must be noted that the information in this monograph concerning drug usage by different countries represents actual usage at one point in time, and may have changed even by the time of publication. The information is primarily useful to illustrate which drugs are generally considered safe, which are forbidden, and so on. It should also be noted that methods of approval vary between countries, some of which are detailed later under the "Matrices" section. For some countries, the listed medications represent defined policy; for others, whose practice may be to give their aviation medicine specialists guidelines as opposed to specific drug policy, the listed drugs represent actual usage.

QUESTIONNAIRE ON MEDICAL TREATMENT AND FLYING

For any drug used to treat one of the eight disease categories each country completed a questionnaire. (A blank questionnaire has been added as Annex A.) The following questions were asked:

a. Disease category. (Hypertension, Malaria Prophylaxis, Asthma, Allergic Rhinitis, Allergic Dermatitis, Other Manifestations of Allergy, Hyperlipidaemia, Disorders of the Digestive System).

b. (Main) indication(s) for the drug. While a drug may have a number of indications, only the main one is mentioned here. (Since we are directly concerned with the possible negative effects of the drug on the performance of the aviator, rather than the efficacy of the drug in the treatment of the disease, which is assumed, the same restrictions for use will usually exist even where the drug is used for more than one indication.)

c. Threshold (indications) for therapeutic use of the drug in military aviators. In many of cases, non-drug therapy will be used initially to treat a disease. Also, if drug treatment has an influence on performance, different threshold values may be used for flying and non-flying personnel.

d. Generic name of the drug. Since generic names are more likely to be identical than are proprietary names, the use of these names makes it easier to compare information.

e. Proprietary name if specified by the nation's policy. The proprietary name is considered to be important in unusual cases, when for some pharmacokinetic reason the same product made by different manufacturers gives different results.

f. Range of doses permitted for military aviators. The dosage range needs to be specified when higher doses might give (more) negative side effects in regard to flying performance.

g. Acceptable duration of use of the drug in military aviators. When the risk of a negative effect on health or performance increases over time, a limit on duration of use for a specific drug might be necessary. Other drugs might be used indefinitely as long as no side effects occur.

h. Required duration of grounding after initial use of the medication. For most drugs it takes time to reach a steady state, during which a number of unwanted effects might develop. This is particularly important for those drugs that show large inter-individual differences.

i. Required evaluation before clearance to perform flying duties while on medication. Every person reacts individually to a given drug. Therefore, testing might be indicated to determine whether the individual has reacted to the treatment as expected.

j. Required special evaluation before clearance while taking the medication. In some cases a pilot has to perform under extreme conditions, but it is usually impossible to predict in what way the performance under such conditions has been changed by his medication. Therefore, special tests may be needed, for instance to evaluate the effect of antihypertensive therapy on G tolerance in a controlled situation before allowing the aviator to return to the high performance environment.

k. Required restrictions on flying duties while using the medication. The ideal drug has no effect on flying performance, but the ideal drug does not exist. On the other hand, grounding everybody who requires drug therapy is not acceptable either. The side effect profile of a drug might preclude a pilot from flying in a high performance aircraft, but he might be able to fly transport planes.

l. Rules governing re-evaluation of an aviator using the medication (Required Monitoring). As always when treating a disease, it is necessary to monitor the progress of the disease under treatment, and to reassess whether the drug may affect flying performance at a later date.

m. Extent of aeromedical experience with the medication in military aviators. Number of Years in Aircrew. Number of patients. In order to be able to compare data from different countries it is important to know the aeromedical experience with this drug. With large numbers over a long time, the absence of side effects is significant.

n. Aeromedical research performed (in-house) on the medication. Not every country is able to perform research with every drug. Therefore it is helpful to know who can be contacted for detailed information in a specific area.

o. In use/no longer in use/in study. Self-explanatory.

p. Remarks. This section is for comments that did not fit in with any of the other questions, or perhaps for elaboration of an earlier answer.

The information that was gathered this way was combined into a electronic database for easier access and distribution. In this database three extra fields were added:

q. Country. Self-explanatory.

r. ATC code. ATC stands for Anatomical, Therapeutical and Chemical. This code has been developed by the World Health Organisation (WHO) to be able to compare all kinds of data concerning drugs. Drugs are divided into fourteen major groups, depending on the organ system targeted. Within each division, there are further levels of clarification based on therapeutic use. The fifth and last level identifies the specific drug. More information about the ATC code can be found on the Internet at www.whocc.nmd.no, the WHO Collaborating Centre for Drug Statistics Methodology.

s. DDD. The daily defined dose, the average daily maintenance dose in adults when a drug is used for its main indication, has a relation with the ATC code and is used in drug statistics to be able to compare consumption.

MATRICES

The database contains a plethora of information. To simplify this, for seven disease categories (no information had been submitted for “Other Manifestations of Allergy”) a matrix was created with the countries listed above, and the drugs listed along the left margin. Then, starting with the information from the database, and later completed

by the members of the Working Group for each drug the following codes were added:

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no specific information

The first two categories are reasonably self-explanatory. "Used for aircrew" means that the drug is approved/used in aviators without restriction to certain types of airframe, or restriction to as or with co-pilot status, or similar constraints; routine aeromedical oversight, such as a grounding period for observation, et cetera, still applies in these cases. "Used with restriction" means that some restriction, such as usage limited to aircraft not capable of sustained high G maneuvers, is in place. "Forbidden" implies that the approval authority had specific reason to prohibit the use of that drug in their aviators. "No specific information" means that, while there is not reason to specifically prohibit the use of that drug, it is not employed for any of a number of reasons, such as lack of availability in that country, or lack of interest in it because an equivalent drug has successfully been used with good results.

Thus, it is possible to see at a glance what type of medication is used or forbidden by what country. For more detailed information, particularly about restricted use, one could then go back to the database. The matrices have been added as Annexes C through H.

As noted earlier, these lists are useful to determine which drugs are widely deemed to be safe, and which drugs are specifically forbidden. It is unwise to directly compare lists across countries, since methods of approval vary. In Greece and France, aviators are evaluated at a central location at least annually. If an aviator is begun on a chronic medication by his flight surgeon, the choice is made locally, although in the Greek Air Force there is a guideline that recommends certain drugs. In neither case is there a forbidden list, although local flight surgeons are kept updated about drugs that are likely to be disapproved after central review. Italy follows a similar policy, although any time a chronic drug is begun, a package must be submitted immediately to the central authority. In the US Air Force, with rare exceptions listed in the applicable regulation, medication use is disqualifying, and waiver must be applied for; thus, although medical examinations are not routinely performed at a central location following training, medication usage is tracked. The governing regulation does list drugs that are routinely waivered, and others that are not considered waiverable, but this list is not considered comprehensive. Flight surgeons in the Canadian forces are provided with a list of approved medications, and a list of forbidden drugs. If an aviator is begun on an approved drug, no central oversight is required. Drugs which are on neither list may be approved by exception after submission to the central authority. Aviators do not undergo regular periodic re-evaluations at a central location. In the UK, written guidelines concerning drug usage are provided by the Surgeon General, with specific drugs being allowed, and other drugs or even groups of drugs being specifically forbidden. Again, if an aviator is begun on an approved drug, central oversight is not required, and aviators do not undergo regular periodic re-evaluations at a central location.

OPERATIONAL MEDICATION

A second questionnaire was submitted to find out what medications were of interest for operational use.

Definition: Operational medications are those pharmacological agents administered to healthy people to improve force effectiveness, in areas as diverse as vigilance, performance enhancement, and circadian adaptation. The Working Group decided not to address prophylaxis for chemical agents. Agents for disease prophylaxis, such as anti-malarials, are in a curious position. Since they are widely viewed as therapeutic drugs, they were addressed under the previous section, and yet for military purposes they are used more in an operational manner, in that they are typically supplied to large numbers of healthy personnel in a particular operational environment.

The questionnaire contains the following items (See also Annex B):

a. Operational purpose. What is one trying to achieve with the use of this drug?

b. Criteria for use. Who is allowed to use it? Under which circumstances is he allowed to use it?

c. Generic name of the drug.

d. Proprietary name if specified by the nations policy.

e. Range of doses permitted for military aviators. Here even more than in therapeutic use of drugs the dose is important because of possible side effects, and because titration of dose to the individual is likely to be impractical.

f. Acceptable duration of use of the drug in military aviators. Under operational circumstances, an indefinite period of use is almost never an option. Indeed, sometimes only a single dose is acceptable.

g. Restrictions on repetitive use. Can a drug be used whenever it is thought to be necessary? Can it only be used a certain number of times? Does one have to wait a certain amount of time before it can be used again?

h. Required ground testing prior to operational use. Sometimes an individual adverse response is likely to a given drug, such that ground testing is considered mandatory.

i. Operational restrictions on flying duties while using the medication. Does using the drug mean operational restrictions have to be made?

j. Follow-up reporting required. Does the pilot have to report his experience with the drug to a flight surgeon?

k. Extent of aeromedical experience with the medication in military aviators. How many years has it been used in aircrew? How many people have used it?

l. Research / observations including drug-interactions. Did the country do any research or did it rely on, for instance, literature? What kind of reactions did the flight surgeon see?

m. In use / no longer in use / in study.

o. Remarks.

This information was not combined into an electronic database for two reasons. First, it concerned only a small number of medications, and second the information given by the different countries was likely to be sensitive. Thus, only a paper review has been made. This review shows the fields of interest in this area and can point out recommendations for further studies.

FUTURE DEVELOPMENT

The database and the matrices for therapeutic medications contain a lot of information. It is very important to keep this information up to date. This means not only working on the current categories but also adding new ones. It needs to be a living document.

In order for this to occur, a person or institute has to take the responsibility of asking the member countries on a regular basis whether or not their information is still correct. Also, it should be determined how each country can get the information. The Internet is a fast way, but not a safe way, and some of the information, even about therapeutic drugs, although not highly classified, might be sensitive. Another possibility is a custodian who sends the information on request on a disk or (if necessary, encrypted) by e-mail.

Which direction this effort should take has to be determined.

ANNEXES

A – Questionnaire therapeutic medications
B – Questionnaire operational medications
C – Matrix asthma
D – Matrix allergic dermatitis
E – Matrix allergic rhinitis
F – Matrix disorders of the digestive system
G – Matrix hypertension
H – Matrix hyperlipidaemia
I – Matrix malaria prophylaxis

Annex A

Information Questionnaire AMP/Working Group 26

Subject: Therapeutic Medications

Disease Category:	Hypertension	Allergic Dermatitis
	Malaria Prophylaxis	Other Manifestations of Allergy
	Asthma	Hyperlipidaemia
	Allergic Rhinitis	Disorders of the Digestive System
(Main) indication(s) for the drug:		
Threshold (indications) for therapeutic use of the drug in military aviators:		
Generic name of the drug:		
Proprietary name if specified by the nations policy:		
Range of doses permitted for military aviators:		
Acceptable duration of use of the drug in military aviators:		
Required duration of grounding after initial use of the medication:		
Required evaluation before clearance to perform flying duties while on medication:		
Required special evaluation before clearance while taking the medication:		
Required restrictions on flying duties while using the medication:		
Re-evaluation rules for the restrictions while flying using the medication (Required Monitoring):		
Extent of aeromedical experience with the medication in military aviators. Number of Years in Aircrew: Number of patients :		
Aeromedical research performed (in-house) on the medication:		
In use / no longer in use / in study		
Remarks:		

Annex C

Asthma **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
acetylcysteine	u	u		u		u	u	u	**				
beclometasone	u	u		u		u	u*	u	**	u			
bromhexine	u	u		u		u	u	u	**		u		u
budesonide	u	u		u			u	u	**	u			
carbocysteine	u	u		u		u	u		**		u		
clobutinol						u			**				
cromoglicicacid	u	u	u*	u	u*	u	u	u	**	u			
desensitization		u	u	u			u	u	u	u			u
fenoterol		u*		u		u	f		**				u
inhaledbeta-2agonist	f	u*	u*	u	u*	u	f	u*	**	u*			
inhaledcorticosteroids	u	u	u*	u	u*	u	u*	u	**	u			
ipratropiumbromide		u				u	u*	u*	**	u*			
nedocromil		u		u				u	**	u			
oxolamine						u			**				
prednisone(oral)		f		u		f	u	f	**	f			u
salbutamol	f	u*		u*	u*	u*	u*	u*	**	u*			

Be	Belgium	It	Italy	CZ	Czech Republic
F	France	NL	The Netherlands	Hun	Hungary
GB	Great Britain	Sp	Spain	PL	Poland
Ge	Germany	USA			
Gr	Greece	CA	Canada		

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no policy or no experience
**	For the USA, asthma is disqualifying for flying; control by medications, since rarely complete, is considered inadequate to allow a return to flying status

Annex E

Allergic Rhinitis **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
astemizole	f	f	f	f				u*	f	f			u
beclometasone	u	u	u*	u		u	u	u	u	u			
budesonide	u	u	u*	u	u		u	u	u	u			
cetirizine	u	u*	f	f		u	f	u	f	u*			
cromoglycicacid	u	u	u	u		u	u	u	u	u	u		
fexofenadine			f						u	u			
flunisolide		u				u	u		u	u	u		
fluticasoneproprionate	u				u		u	u	u	u			
levocabastine				u*			u			u	u		
loratadine	f	u*	u	u*	u	u	u*	u	u	u			
nacetylaspartylglutamique		u											
naphazoline	u	u				u				u			
nedocromil		u			u			u					
oxymetazoline	u	u				u	u	u	u*	u			
rhgnatriichloridi0,9%							u	u		u			
steroids/decongestants		u	u	u		u		u*		u			
terfenadine	f	f	f	f			f			f			
triamcinolone	u	u						u*	u	u			u
xylometazoline		u		u		u	u			u			u
prednisolone(oral)		f	u				u*		f				

Be	Belgium	It	Italy	CZ	Czech Republic
F	France	NL	The Netherlands	Hun	Hungary
GB	Great Britain	Sp	Spain	PL	Poland
Ge	Germany	USA			
Gr	Greece	CA	Canada		

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no policy or no experience

Annex F

Disorders of the digestive system **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
alginatesodium		u					u	u					
alizapride	f	f				f	f						
antacids	u	u	u	u	u	u	u	u	u	u	u		u
bismuth(subsalicylaat)	f			u		u			u	u			u
butylscopolamine	f	f		f		f	f			f			u
cimetidine	f	u		u*		u	u*	u		u	u		u
cisapride	f	f		f		u	f	u	f	f	u		
codeine		f	u*	f		f	f	u*	f	f			u
difenoxylate	f		f					u*			u		
domperidone	u	u*				u	u	u					
doxycycline		u		u	u	u	u	-	u	u			u
famotidine	u	u		u*		u	u*	u		u			u
flavoxate	f			f		f							
floroglucinol	f	u											
isopropamide	f												
lansoprazole	u	u	f			u		u		u			
loperamide	u	u	u*	u*		u	u	u*		u	u		u
mebeverine	u	u		u		u	u	u					
mesalazine	u	u*	u*	u	u*	u*		u*	u	u			
metoclopramide	f	f		u*		f	f	u*	f	f			u
misoprostol	f	f						f		u			
nizatidine	u	u					f						
norit	u						u						
omeprazole	u	u	u*	u*	u	u	f	u	u*	u	u		
otiloniumbromide	u					u							
oxybutynine	f	f							f				
pantoprazole	u	u				u		u					
pinaverium	f	u				f							
propantheline	f	f				f	f		f				
ranitidine	u	u	u*	u*	u	u	u*	u	u	u			u
silymarine													
sucralfate	f	u		u		u	u	u	u	u			
sulfasalazine	u	f		u		f	u*	u*	u	u*			u
tiëmonium	f	f											
trimebutine	u	u				u							

Be Belgium
F France
GB Great Britain
Ge Germany
Gr Greece
It Italy
NL The Netherlands
Sp Spain
USA
CA Canada
CZ Czech Republic
Hun Hungary
PL Poland

u used for aircrew
u* used with specific restrictions or recommendations
f forbidden
blank no policy or no experience

Annex G

Hypertension **(Current as of 01 September 2000)**

Drug		Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
alpha1blockers	α1SL	f	f	f		f	f	f		f	f			
prazocine	α1SL	f	f				f	f	f					u
terazosine	α1SL	f					f							
urapidil	α1SL	f					f	f	f					u
yohimbine	α2SL	f					f	f						
fenoxybenzamine	αSL	f					f	f	f					
fentolamine	αSL	f					f	f	f					u
acebutolol	β1SL				u		u				u*	u		u
atenolol	β1SL	u	u	u*	u	u*	u	u*	u*		u*	u		
betaxolol	β1SL											u		
bisoprolol	β1SL		u		u	u*	u					u		
metipranolol	β12SL											u		
metoprolol	β1SL	f	u		u		u	u*			u*	u		u
propranolol	β12SL	f					u	f			f			u
nadolol	βSL(?)	u												u
pinacidil	(?)	f												
benazepril	Aceinhibitor	f												
captopril	Aceinhibitor	u	u		u	u	u	u*	u					u
cilazapril	Aceinhibitor	u												u
enalapril	Aceinhibitor	u	u	u*	u	u	u	u*	u		u	u		
fosinopril	Aceinhibitor	u			u						u			
lisinopril	Aceinhibitor	u	u	u*	u	u	u	u*	u	u	u			
perindopril	Aceinhibitor	u	u									u		u
quinapril	Aceinhibitor	u				u	u				u			
ramipril	Aceinhibitor	u	u		u	u					u	u		
trandolapril	Aceinhibitor											u		
amlodipine	Caantagonist	u*	u*	u*		u*	u	f				u		u
diltiazam	Caantagonist	u*			u		u	f	u			u		u
felodipine	Caantagonist	u*	u*			u*	u	f						u
isradipin	Caantagonist							f				u		
nifedipine	Caantagonist	u*			u		u	f						
nimodipine	Caantagonist	u*					u	f						u
noxonidine	Caantag.(?)													
verapamil	Caantagonist				u		u	f				u		u
candersartan	Angiotensin II antagonist													
losartan	Angiotensin II antagonist	u	u				u							
valsartan	Angiotensin II antagonist													
spironolactone	Diuretic	u*				f	u							u
triamt.&epitizide	Diuretic							u						
triamtereen	Diuretic				u			u		u	u			u
furosemide	Diuretic	f	f				f	f	f					u
bendrofluazide	Thiazide			u										
Chlorothiazide & amiloride	Thiazide		u			u		f	u			u		
Hydrochlorothiazide & triamterene	Thiazide	u*			u			f	u	u	u			u
hydrochlorothiazide	Thiazide	u*	u	u	u	u	u	f	u	u	u	u		u
indapamide	Thiazide	u*					u	f						u
thiazides	Thiazide	u	u	u	u	u	u		u	u	u	u		u
diazoxide	Vasodilatantia	f				f	f	f	f		f			

Drug		Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
hydralazine	Vasodilatantia	f			u		f	f	f		f			
minoxidil	Vasodilatantia	f					f	f	f		f	u		u

Be	Belgium	It	Italy	CZ	Czech Republic
F	France	NL	The Netherlands	Hun	Hungary
GB	Great Britain	Sp	Spain	PL	Poland
Ge	Germany	USA			
Gr	Greece	CA	Canada		

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no policy or no experience

Annex H

Hyperlipidaemia **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
acipimox	f					f					u		
atorvastatin		u							u				
bezafibrate	f	u		u		u							
ciprofibrate	u										u		
clofibrate	f									f			u
colestipol	f			u			u	u	u				u
colestyramine	f	f	u*	u	u	f		u	u	u			u
fenofibrate	u	u		u		u				u	u		f
fibrates		u	u*			u				u	u		
fluvastatine	u	u		u		u		u		u	u		
gemfibrozil	u	u		u		u	u		u*	u	u		
lovastatin				u*		u		u	u	u	u		
nicotinicacid	f			f					f	u*			u
omega3oilyacid		u								u			
pravastatin	u	u	u*	u	u	u	u	u	u	u	u		
resins		f						u	u	u			
simvastatin	u	u		u*	u*	u	u	u		u	u		u

Be	Belgium	It	Italy	CZ	Czech Republic
F	France	NL	The Netherlands	Hun	Hungary
GB	Great Britain	Sp	Spain	PL	Poland
Ge	Germany	USA			
Gr	Greece	CA	Canada		

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no policy or no experience

Annex I

Malaria Prophylaxis **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp	USA	CA	CZ	Hun	PL
atovaquone&proguanil													
chloroquine	u	u		u	u	u	f	u	u	u			
chloroquine&proguanil	u	u		u			f	u					u
doxycycline	u	u				u	u		u	u			u
mefloquine	f	f	f	f	u	u	f		f				
primaquine								u	u	u			u
proguanil	u			u		u	u	u					
pyrimethamine													u
pyrimethamine&dapson										u			

Be	Belgium	It	Italy	CZ	Czech Republic
F	France	NL	The Netherlands	Hun	Hungary
GB	Great Britain	Sp	Spain	PL	Poland
Ge	Germany	USA			
Gr	Greece	CA	Canada		

u	used for aircrew
u*	used with specific restrictions or recommendations
f	forbidden
blank	no policy or no experience

Annex D

Information Questionnaire AMP/WG26

Subject: Operational Medications

Operational medications are those pharmacological agents administered to healthy people to improve force effectiveness in areas as diverse as vigilance, performance enhancement, circadian adaptation and disease prophylaxis.
Operational purpose:
Criteria for use:
Generic name of the drug:
Proprietary name if specified by the nations policy:
Range of doses permitted for military aviators:
Acceptable duration of use of the drug in military aviators:
Restrictions on repetitive use:
Required ground testing prior to operational use:
Operational restrictions on flying duties while using the medication:
Follow-up reporting required:
Extent of aeromedical experience with the medication in military aviators Number of Years in Aircrew: Number of people : few / often used / …….
Research / observations including drug-interactions:
In use / no longer in use / in study
Remarks:

Allergic Dermatitis **(Current as of 01 September 2000)**

Drug	Be	F	GB	Ge	Gr	It	NL	Sp[2]	USA	CA	CZ	Hun	PL
betamethasone	u	u		u	u	u	u	u		u			
clobetasol	u	u		u		u	u	u					
desoximetasone	u	u		u	u		u						
hydrocortisone	u	u		u	u	u	u	u	u	u	u		u
prednisolone(oral)		f	u	u		u	u*	f	f	f			u
triamcinolone	u	u		u		u	u	u		u			u
cetirizine		u*	f				f		f				

Be Belgium
F France
GB Great Britain
Ge Germany
Gr Greece
It Italy
NL The Netherlands
Sp Spain
USA
CA Canada
CZ Czech Republic
Hun Hungary
PL Poland

u used for aircrew
u* used with specific restrictions or recommendations
f forbidden
blank no policy or no experience

[2] Only topical treatment

Annex B

Current as of 01 September 2000

Operational Medications	USA	USA	USA	USA
Operational purpose:	Avoiding motion sickness in student pilots	Counteract fatigue on long deployments; maintenance of alertness during extended missions	Sleep induction in operational environment	Sleep induction in operational environment
Criteria for use:	Student pilots with motion sickness which has become a conditioned response	Single pilot aircraft, only on deployments / redeployments which exceed 8 hours. Can be approved for individual mission use by Director of Operations – generally extended mission with long return flight.	Deployment or redeployment across time zones – may be employed in other operational scenarios – authorization by Major Command surgeon only	Deployment or redeployment across time zones – may be employed in other operational scenarios – authorization by Major Command surgeon only
Generic name of the drug:	Scopolamine patch	dextroamphetamine	temazepam	zolpidem
Proprietary name if specified by the nations policy:	Trans-Derm Scop	Dexedrine®	Not specified (Restoril® available)	Not specified (Ambien® available)
Range of doses permitted for military aviators:	1.5 mg patch to be used 4 hours before flight, and discarded afterwards	5 mg begun at onset of fatigue, then 5 mg q4h till just prior to landing	15mg - 30 mg	10 mg
Acceptable duration of use of the drug in military aviators:	Any flight, up to 3 flights before solo	Determined by mission length	Not more than 7 consecutive days	Not more than 7 consecutive days
Restrictions on repetitive use:	Same	Not expected – for deployment /redeployment only	No more than 20 days in 60 day period	No more than 20 days in 60 day period
Required ground testing prior to operational use:	None	5 mg at least 8 hours into a duty day, followed by another tablet 4 hours later	Single dose ground test	Single dose ground test
Operational restrictions on flying duties while using the medication:	May be used only by student pilot while flying with instructor – must be discontinued for the last three flights before solo – only recommended when motion sickness has become a conditioned response – otherwise prefer that students adapt through exposure	Not for use on operational missions – once begun, medication should be continued until landing	May fly no sooner than 12 hours post dose	May fly no sooner than 12 hours post dose
Follow-up reporting required:	Documented in medical record of student	Post mission debrief questionnaire after use	After action reports of deployments will document medication use	After action reports of deployments will document medication use
Extent of aeromedical experience with the medication in military aviators. Number of Years in Aircrew: Number of people: few / often used / …….	15+ unknown	15+ yrs (intermittent) unknown	15+ unknown	1+ unknown
Research / observations including drug-interactions:			No	No
In use / no longer in use / in study	In use	No longer in active use Potentially usable, but not used in years	In use	In use
Remarks:	Generally fails as a primary treatment for motion sickness, since it delays natural adaptation – useful when nausea has become a conditioned response to the flying environment	presently approved for use under above criteria	zolpidem preferred	zolpidem preferred to temazepam

Operational Medications	France	France	France	France
Operational purpose:	Vigilance sustainment in sleep deprivation context	Vigilance sustainment in sleep deprivation context Jet-lag therapy.	Prophylactic or recovery sleep period induction	Prophylactic or recovery sleep period induction
Criteria for use:	Operational conditions with no opportunities to take rest (wartime). Survival conditions (peacetime).	Operational conditions with no opportunities to take rest. Survival conditions.	SUSOPS & CONOPS	SUSOPS & CONOPS
Generic name of the drug:	modafinil	Slow release caffeine	zolpidem	Temazepam
Proprietary name if specified by the nations policy:	Modiodal®	To be defined	Stilnox®	Normison®
Range of doses permitted for military aviators:	100 to 600mg per day	300 to 600mg per day	5mg	
Acceptable duration of use of the drug in military aviators:	48 hours	48 hours	No prolonged administration	
Restrictions on repetitive use:	15 hours free of drug including a minimum 8-hour sleep period is necessary before an other waking period with modafinil could be planned	To be defined	See above	
Required ground testing prior to operational use:	Not necessary but desirable	Not necessary but desirable	Highly desirable	
Operational restrictions on flying duties while using the medication:	No restrictions	No restrictions	6 hours between the intake and take-off	
Follow-up reporting required:	Not necessary but desirable	Desirable	Desirable	
Extent of aeromedical experience with the medication in military aviators Number of Years in Aircrew: Number of people: few /often used / …….	7 years Few	Not applicable	Not applicable Few (self medication, flight surgeons)	Not applicable Self medication is probable in aircrews.
Research / observations including drug-interactions:	Modafinil may lower the power of hormonal contraception. Restriction of use in case of hypertension.	To be defined	Avoid other CNS drugs for potentiation effect	
In use / no longer in use / in study	U*	S	S	NI
Remarks:	Not applicable	Not applicable	Not applicable	

Current as of September 2000

Operational Medications	France	France	France	Great Britain
Operational purpose:	Vigilance sustainment in sleep deprivation context	Vigilance sustainment in sleep deprivation context	Jet-lag therapy.	Sleep disturbance in aircrew
Criteria for use:	SUSOPS & CONOPS	SUSOPS & CONOPS	Rapid oversea deployment	Sleep disturbance
Generic name of the drug:	Amphetamines	Pemoline	Melatonin and melatonin agonists.	Temazepam
Proprietary name if specified by the nations policy:			To be defined.	Normison (Wyeth)
Range of doses permitted for military aviators:			5mg for melatonin	10-20mg
Acceptable duration of use of the drug in military aviators:			To be defined.	As required
Restrictions on repetitive use:			To be defined.	Operational requirement only
Required ground testing prior to operational use:			To be defined.	7 days before om first occasion
Operational restrictions on flying duties while using the medication:			To be defined.	Usually not less than 12 hours prior to duty
Follow-up reporting required:			To be defined.	No
Extent of aeromedical experience with the medication in military aviators Number of Years in Aircrew: Number of people: few /often used / …….			Not applicable Self medication is probable in transport aircrews.	15 years
Research / observations including drug-interactions:				Extensive experience over 15 years
In use / no longer in use / in study	NA, NI	NA, NI	NA, I, S	use
Remarks:				

Current as of September 2000

Operational Medications	Germany	Canada	Canada	Canada
Operational purpose:	Malaria prophylaxis	Maintain crew alertness/wakefulness	Sleep aid in operational setting	Circadian rhythm adjustment; sleep aid
Criteria for use:	mission to endemic areas	Contingency ops only	Operational setting only	Operational only, transition to ops with sig circadian shifts
Generic name of the drug:	Chloroquine and Proguanil	Modafanil	Zopiclone	Melatonin
Proprietary name if specified by the nations policy:	Resochin/Palludrine		Imovane	
Range of doses permitted for military aviators:	Chloroquine 500mg/week – 750mg/week acc. to body weight < or > 70kg; no duration defined	200-300mg	7.5 mg	1-10 mg
Acceptable duration of use of the drug in military aviators:	no duration defined	? extended duty day to 36 hours max	During operation only	During operations only
Restrictions on repetitive use:	Ophthalmological controls in long-term use of Chloroquine	Max 3 doses in aircrew		No
Required ground testing prior to operational use:	only general precautions	Preferred	Single dose on off-duty cycle preferred	No
Operational restrictions on flying duties while using the medication:	Considering possible gastrointestrial side effects intake of Chloroquine only on days w/o flying duty	No operational restrictions	No restrictions. Miinimum 8 hours prior to duty	No restrictions
Follow-up reporting required:	no	Yes – through Flight Surgeon	Yes- through Flight Surgeon	Yes – through Flight Surgeon
Extent of aeromedical experience with the medication in military aviators Number of Years in Aircrew: Number of people: few /often used / …….	no specific data at the institute	No operational experience	No operational experience	No operational experience
Research / observations including drug-interactions:	none	DCIEM sustained ops studies	DCIEM study demonstrated no performance decrement	DCIEM experiment demonstrated no performance decrement
In use / no longer in use / in study		IS	IS	IS
Remarks:		CF preference over amphetamines or caffeine based on experimental data only		Operational study in preparation

Current as of September 2000

Operational Medications	Canada	Canada		
Operational purpose:	Prevention of airsickness	Prevention of airsickness		
Criteria for use:	Non-pilot aircrew in training; Trained aircrew in maritime patrol	Non-pilot aircrew in training; Trained aircrew in maritime patrol		
Generic name of the drug:	Scopolamine+ ephedrine	Promethazine+ ephedrine		
Proprietary name if specified by the nations policy:		Phenergan		
Range of doses permitted for military aviators:	Scopolamine 0.3mg Ephedrine 30 mg	Promethazine 25 mg Ephedrine 30 mg		
Acceptable duration of use of the drug in military aviators:	Limited use in non-pilot aircrew during training Non-flight deck aircrew in maritime patrol under Flight Surgeon supervision	Limited use in non-pilot aircrew during training Non-flight deck aircrew in maritime patrol under Flight Surgeon supervision		
Restrictions on repetitive use:				
Required ground testing prior to operational use:	Yes. Single dose on non-flying day	Trial on non-flying day		
Operational restrictions on flying duties while using the medication:	Non-pilot aircrew only	Non-pilot aircrew only		
Follow-up reporting required:	Report to Central Medical Board	Report to Central Medical Board		
Extent of aeromedical experience with the medication in military aviators Number of Years in Aircrew: Number of people: few /often used / …….	20 years Infrequent use	20 years, infrequent use		
Research / observations including drug-interactions:				
In use / no longer in use / in study	IU	IU		
Remarks:				

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Section IV: Expanding the Usage of Medication

Ethical Considerations in Use of Medications by Military Aircrew

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Those who make decisions employ a moral component in the process of rationalizing a chosen course of action – ethics. Military flight surgeons often find themselves making decisions involving competing interests, those of the military service whose mission they support (and by whom the flight surgeon is generally employed), and the best interests of the individual military aviator with whom exists a physician-patient relationship. In this respect, military flight surgeons and occupational medicine physicians share a common challenge. However, when the employer is a military service and the employee/patient is a military aviator, the ethical issues for the physician take on added dimensions beyond those typically encountered in the practice of occupational medicine.

Samuels wrote of absolute moral imperatives as the foundation for ethical decisions by individual physicians and stated that preservation of life and freedom are absolute moral imperatives.[3] Military physicians certainly support these two moral imperatives, but must do so in a culture where risk of loss of life is accepted at a much higher level than can be found in civilian occupations. In the use of medications in military aviators, the flight surgeon balances mission factors, the interests of the military service, and the interests of the long-term health of the aviator.

Lee and Rom wrote of three interrelated spheres of influence in decision-making: law, scientific fact, and ethics.[1] In the paragraphs that follow, we will briefly explore the ethical sphere and the act of striking an intelligent balance between these spheres of influence. Our discussion will touch on third party relationships in military aerospace medicine, conflict of interest, established ethical codes, and some ethic-driven duties for the military flight surgeon when making decisions.

Established Codes of Ethics

Because aerospace medicine is the science of medically supporting those who practice their occupations in the aerospace environment, occupational medicine is the closest match when seeking a template code of ethics for the practice of aerospace medicine. Generally such codes hold foremost the principle of giving the health and safety of the worker the highest priority. Table 1 contains the Code of Ethical Conduct established by the American College of Occupational Medicine. Neither this code, nor the code for occupational health services established by the Canadian Medical Association, fits military aerospace medicine precisely, because of the access permitted to commanders in most military services to specific medical information about the health of military members, and because of the higher level of generally accepted risk in military operations. However, several basic principles prevail in these codes: 1) priority for the health and safety of the worker, 2) honesty, 3) accurate risk communication, 4) confidentiality within the law, and 5) proper balance in judgments to avoid undue influence by third party interests. In a wartime setting, the balance of the basic principles shifts towards a greater degree of acceptable risk, but the ethical commander will continue to apply the basic principles, adjusting the balance in accordance with operational imperatives.

Some would add to these codes the principle of informing the worker of those who have legal access to their health information, which we will discuss further in a later paragraph. Some would question the practicality of the principle of objectivity as stated in the codes, especially in third-party relationships. As Samuels points out, judgment is never fully objective.[3] It's best to acknowledge and be aware of personal values and

third-party relationships, and to be aware of how they may influence our judgment and affect our ability to consider the options from a detached perspective. Judgment also entails acknowledging when our own objectivity is inadequate for a particular decision.

The Military Service as a Third Party

As stated earlier, occupational medicine physicians must balance the best interests of the worker and the employer. In most instances, these interests are not conflicting – what's best for the health and fitness of the worker is also in the best interest of the employer. When practiced in a military service, some significant factors warrant consideration by the physician, particularly in aerospace medicine. First, the modern military unit depends on its individual members for operation of technologically sophisticated weapon systems, and the performance of each individual is becoming increasingly crucial to mission success and the safety of fellow operators. This factor reinforces the importance of medications for operational prevention, such as malaria prophylaxis; likewise, this factor can also lead to interest in the use of medications as fatigue countermeasures. Since no medication is completely risk-free, the flight surgeon must weigh both mission benefit as well as risk to the aviator (and to the mission if the medication produces a side effect). Second, military members, particularly aviators, are quite mission-focused and often fail to consider their own personal long-term health when they require medical therapy or operational use of medications. At times, the flight surgeon may be the only person fully considering the member's long-term well-being, and may be pressured by the member to employ sub-optimal therapy because it is more mission expedient, or to employ an operational drug which enables the member to remain in the mission. In fact, pressure of this sort is probably more common from the military aviator than from the unit commander. However, particularly since the Persian Gulf campaign, we have seen that significant concerns may arise after military operations about the health effects of those operations – a concern that certainly encompasses operational use of medications. Such concerns do arise in members even though mission focus may have led them to actively seek a medication prior to the mission. The flight surgeon must not allow pre-mission enthusiasm on an aviator's part to lead to circumvention of the basic duty to communicate and manage risk.

Rosenstock and Cullen stated, "In addition to being a potential source of health risk, work is also a central and crucial component of life for most adults, encompassing both positive and negative aspects."[4] Military members, aviators in particular, identify strongly with their occupations and often consider the need for therapeutic medication a threat to their ability to continue in their occupation; conversely they often see operational medication as a means to enhance or ensure performance. The military flight surgeon must be aware of these short-term perceptions, but must also ensure the use of medication is not a detriment to the long-term health of the aviator. When selecting a therapeutic medication for a chronic condition, the flight surgeon seeks a medication compatible with continued flying duties while providing disease control in accordance with existing standards of care. The flight surgeon often must also explain to the unit commander that the long-term health of the aviator is actually in the best interest of the military service, although occasional mission emergencies in actual conflict may on occasion force a short-term focus.

Confidentiality

As we mentioned previously, a common theme in occupational medicine ethics is preservation of confidentiality regarding a worker's health by limiting access by third parties to that permitted by law. However, even legal access may lead to significant consequences for the worker – a fact most aviators (civil and military) fully appreciate. In the context of therapeutic use of medications, the military aviator must be informed of the impact of the treatment on his or her fitness to perform in accordance with the directives of the service, and of who must be informed of the treatment. Most military services allow commanders access to details of the health of aviators because the importance of a fit and healthy aviator to the mission and safety of others is deemed a greater good that overrides individual confidentiality - analogous to the greater good of a public health concern in civilian practice. While use of health information by the employer to determine job qualification in civilian industry is often regarded by law as discrimination, such a practice is commonly legal in military services due to mission and safety requirements for high levels of physical performance.

Obligation to Inform and Obtain Consent

The duty to inform the patient of the details of his or her condition and the various treatment options available is fundamental to the relationship between a physician and patient. This takes on added importance in military aerospace medicine because chronic conditions requiring therapy frequently affect the patients' ability to perform in their occupation. The flight surgeon has the moral duty to fully inform the aviator of the long-term health implications of all treatment options, and the occupational ramifications of each. Likewise, the flight surgeon has the duty to inform the unit commander and the service qualification authority of the aviator's condition and its impact on the aviator's ability to perform safely and effectively. Commensurate with the duty to inform is the duty to document. In most military medicine settings the medical record is the property of the service, but the member has access to information within the record. Accurate documentation by the flight surgeon is essential to the interests of the military service and the aviator.

When using medication for operational indications, the flight surgeon is prescribing for other than therapeutic reasons. In most instances, the medication is taken to prevent maladies such as endemic infectious disease. However, in some missions, factors such as fatigue and circadian desynchronization can pose significant threats to the ability of the aviator to perform. Such effects can be mitigated by use of medication, and the flight surgeon must balance the safety of the medication against the threats posed by fatigue to the aviator's safety and to the mission. The flight surgeon has the duty to inform the aviator and the unit commander of risks inherent in the use of operational medication.

Some nations require voluntary consent by the military member when using medications in military operations for reasons other than those formally approved by the respective national drug certification body. The flight surgeon has the duty to ensure such consent is truly voluntary. Samuels outlined three recommended safeguards for voluntary consent: 1) protection for those who might refuse consent; 2) effective efforts to educate; and 3) oversight of the process through a community or other relatively neutral structure.[3] When the flight surgeon is in a situation requiring voluntary consent for use of a medication, application of such safeguards helps avoid an atmosphere of coercion.

Military flight surgeons should consider carefully each of the three spheres of influence when prescribing medications for therapeutic or operational use by aviators: scientific fact, law, and ethics. Physicians classically devote great time and energy to building factual knowledge, and flight surgeons work hard to know applicable laws and service directives, but we devote little time to formal knowledge of the moral component to decision-making in aerospace medicine. Ethical issues in aerospace medicine are particularly important because the relationships between the three primary parties (the aviator, the flight surgeon, and the military service) are unique in terms of acceptable risk, confidentiality, and motivation. The flight surgeon who understands the relationship and his or her own values and interests will be most likely to optimally balance the three spheres of influence when making decisions.

All flight surgeons encounter the situation in which the aviator desires a therapeutic plan that is not in the best interest of the aviator's long-term health. Generally the aviator in such a situation is giving heaviest consideration to near-term qualification to perform and is concerned about a potentially disqualifying treatment. Flight surgeons should search diligently for a therapeutic plan that adequately addresses the health risks posed by the underlying condition while enabling the aviator to remain qualified for flying duties. In most cases, standards require that a condition be adequately treated in order to qualify for continued flying duties. However, in many systems conditions such as untreated hyperlipidemias and mild hypertension remain acceptable for flying duties. When faced with an aviator requesting substandard treatment in order to avoid a qualification issue, the flight surgeon must consider the ethical duty to serve the best interests of the long-term health of the aviator. Often a second opinion from another flight surgeon or clinical specialist is useful in clearly defining the best treatment plan which balances the spheres of influence.

The flight surgeon must be mindful of the basic ethical duties within the context of applicable laws and directives: the duty to serve the best interests of the long-term health of the aviator, the duty to support mission accomplishment, the duty to keep information confidential, the duty to communicate risk, the duty to document, the duty to avoid the

influence of conflict of interest, and the duty to obtain voluntary consent.

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1. Lee J, Rom W. *Legal and Ethical Dilemmas in Occupational Medicine*. Ann Arbor Science Publishers; 1982.

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3. Samuels S. On the Ethical Practice of Environmental and Occupational Medicine. in *Environmental and Occupational Medicine,* Third Edition. Lippincott-Raven; 1998.

4. Rosenstock L, Cullen M. *Textbook of Clinical Occupational and Environmental Medicine*. Saunders; 1994.

5. Beauchamp T, McCullough L. *Medical Ethics: The Moral Responsibilities of Physicians*. Prentice-Hall; 1984.

TABLE 1: Code of Ethical Conduct for Physicians Providing Occupational Medical Services
(American College of Occupational Medicine)

These principles are intended to aid physicians in maintaining ethical conduct in providing occupational medical service. They are standards to guide physicians in their relationships with the individuals they serve, with employers and workers' representatives, with colleagues in the health profession, and with the public. Physicians should:

1. Accord highest priority to the health and safety of the individual in the workplace;
2. Practice on a scientific basis with objectivity and integrity;
3. Make or endorse only statements which reflect their observations or honest opinion;
4. Actively oppose and strive to correct unethical conduct in relation to occupational health service;
5. Avoid allowing their medical judgment to be influenced by any conflict of interest;
6. Strive conscientiously to become familiar with the medical fitness requirements, the environment and the hazards of the work done by those they serve, and with the health and safety aspects of the products and operations involved.
7. Treat as confidential whatever is learned about the individuals served, releasing information only when required by law or by overriding public health considerations, or to other physicians at the request of the individual in relation to work, but employers are not entitled to diagnoses or details of a specific nature;
8. Strive continually to improve medical knowledge, and should communicate information about health hazards in timely and effective fashion to individuals or groups potentially affected, and make appropriate reports to the scientific community;
9. Communicate understandably to those they serve any significant observations about their health, recommending further study, counsel or treatment when indicated;
10. Seek consultation concerning the individual or the workplace whenever indicated;
11. Cooperate with governmental health personnel and agencies, and foster and maintain sound ethical relationships with other members of the health professions; and
12. Avoid solicitations of the use of their services by making claims, offering testimonials, or implying results which may not be achieved, but they may appropriately advise colleagues and others of services available.

Approach to Aeromedical Drug Evaluations

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INTRODUCTION

Therapeutic drugs acceptable for military aviation are those agents which, without significantly affecting occupational proficiency and safety, may be administered to aviators to alleviate disease which is not itself disqualifying for aviation, or which may allow return to flying status as a result of therapy. This is in contrast to operational medications, pharmacologic agents administered to healthy members to enhance force effectiveness in areas as diverse as vigilance, performance enhancement, Circadian adaptation, and prophylaxis. As a rule, while operational medications may be an issue in any military member, therapeutic agents are of particular concern only in aviation or other high-performance, high-risk occupations, where subtle alterations in psychologic or physiologic performance might have profound effects on performance or safety. For other military members, the standard assessment of clinical efficacy and tolerability which occurs prior to the marketing of a therapeutic agent is usually sufficient for treatment decisions. In the case of operational medications, subtle drug-induced alterations in the aviator are certainly of interest as well, but the relative lack of clinical experience and medical literature means that, as a rule, even the most basic questions of efficacy and safety need to be answered first.

While a large number of medications may be used for treatment of a temporarily grounded aviator, the primary concern here is with therapeutic medications which may be safely employed while the aviator is flying. With the exception of a few over-the-counter drugs which the aviator is specifically allowed to self-administer, medication use by the aviator should be under the direct supervision of the flight surgeon. (This also applies to herbal remedies; drugs derived from botanical sources are no less active for being "natural", and indeed pharmacotherapy first began with the use of such toxic alkaloids.) Aeromedical supervision is required not only by the disease, which obviously was significant enough to require pharmacotherapy in the first place, but also by the use of the medication, with the attendant risk of early or late toxicity. Follow-up must be based on aeromedical requirements. Clinical indications for surveillance are based on a presumption that patients will self-identify in the case of a symptomatic adverse reaction, and thus surveillance need only be directed at serious side effects which, at least in the early stages, are asymptomatic. In contrast, aviators cannot be presumed to self-identify even with symptomatic side effects, and clinically minor effects, whether symptomatic or not, may have a major impact in the aviation environment.

SELECTION OF DRUGS

Therapeutic Agents

The first consideration to be addressed in selecting therapeutic agents for aeromedical evaluation is whether one could select a class of drugs, or should study individual agents. The former approach is fraught with problems. To begin with, it's difficult to determine what constitutes a class of medications. Classes are most often based on mode of action, such as receptor blockade. As an example, H_1 antihistamines are generally considered to be a class of medications, yet while the mode of action of these drugs is similar, the incidence of sedation is dramatically different. Calcium antagonists are generally considered a "class", but the benzothiazepines and diphenylalkylamines cause significant decrease in cardiac inotropy, and are usually considered disqualifying. Chemical similarity might serve as a further class definition, but individual compounds necessarily differ from one another in some fashion. How many side chains or aromatic rings could be substituted, and with what moieties, and still allow a compound to be considered part of a class for aeromedical purposes? Even then, drugs that are chemically similar can be strikingly dissimilar in side effects. Loratadine is

closely related to azatadine, but the former is considered a non-sedating antihistamine, while the latter is a first generation antihistamine which has been used as a verum to induce sedation. Minocycline is in the same "class," by any accepted definition of that term, as tetracycline and doxycycline, but the vestibular toxicity it causes renders it unacceptable for aeromedical use. Temafloxacin was one of the quinolone anti-microbials, like ciprofloxacin and ofloxacin, yet fatal cases of hypoglycemia caused it to be removed from the market within four months of release. Assumptions about the acceptability of medications based on "class" are generally unwarranted. Drugs for aeromedical use need to be evaluated individually.

The following represents a basic approach for evaluating therapeutic agents intended for chronic use in aircrew.

Licensure
While an aviator with a life-threatening disease is as much a candidate for an investigational new drug as any other clinical patient, such use should preclude flying until the condition has sufficiently resolved and the medication is no longer needed. Therapeutic medications considered for use in an aviator on flying status should be licensed for clinical administration in the aviator's individual country.

Clinical Efficacy
Disease in the aviator should be treated to the clinical standard of care; the therapeutic agent under consideration should be generally acknowledged to be effective in treatment of the given condition. As a rule, the medication should be shown to be efficacious in the individual aviator before he or she is evaluated for return to the cockpit.

Clinical Experience
While stringent drug testing such as that demanded by national drug licensing agencies requires clinical trials involving several hundred to several thousand subjects, a tremendous amount of additional knowledge about indications, precautions, and adverse effects is gathered in the first several years following a drug's release. This is principally due to the hundreds of thousands of prescriptions typically written for many drugs in the first years of availability. In addition, use of the medication in less controlled circumstances than that typically found in clinical trials may play a role in eliciting unexpected complications. Sometimes these are serious enough to result in the withdrawal of the drug from the market, such as occurred in the recent past with felbamate and temafloxacin. In short, there is no substitute for experience. Unless there are strong reasons to consider a drug for immediate aeromedical use, it seems most prudent to explore the role of a therapeutic medication in aviation after a reasonable body of clinical experience has accumulated.

Alternatives
Other forms of therapy need to be considered. For example, the small risk of *torsades de pointes* involved in administering terfenadine to otherwise healthy individuals of aviator age had often been considered a reasonable risk in the past. However, fexofenadine, the active metabolite of terfenadine, does not prolong the QT_c interval; when this agent became available, the small chance of arrhythmia with terfenadine appeared to be an unnecessary risk. Nonpharmacologic alternatives should also be explored. For example, omeprazole appears to be a safer drug than originally predicted, since the ECL-cell hyperplasia and the increased risk of gastric carcinoid seen in animal studies have not been observed in human subjects. Nonetheless, many gastroenterologists would consider it unwarranted to commit a healthy young person with chronic gastroesophageal reflux to a lifetime of anti-secretory medication, and that surgical correction would be a much preferable option in such an individual.

Potential for Misuse
The potential for misuse or overuse of a medication should be considered. Although the usual clinical concern, i.e., misuse of a mood-altering substance, is an unlikely scenario with respect to waiverable drugs, other situations may arise which are unique to aviation. Certain medical conditions, such as allergic rhinitis, may directly impede the aviator's ability to fly, and incomplete control of the condition by a medication could prompt the aviator to take a higher dosage. Such an event occurred aboard *USS Nimitz*. During the investigation of an accident that cost fourteen lives and millions of dollars, the aircraft pilot was found to have a level of brompheniramine eleven times therapeutic level. In this case, of course, the aviator was taking an unapproved medication, but he also significantly overdosed on it in an attempt to control upper respiratory symptoms. While the risk that an aviator may take extra doses of medication is beyond the control of the flight surgeon, whenever

possible the probability of such an event should be taken into account when considering medication to approve for waiver. For instance, an antihistamine that has been shown to be nonsedating across its dosage range is probably a better candidate for therapeutic use than another, otherwise equivalent, agent, which is nonsedating only at lower dosages.

Operational Agents

Guidelines for selecting operational agents are necessarily less clear. While national licensure is preferable, in some cases it may be desirable to begin operational study while the initial research required for licensure is still incomplete. It is also possible that the compound of interest may not be considered to be a drug by all countries (e.g., melatonin). Clinical efficacy and experience may not apply, since in many cases the intended military use has no obvious parallel in civilian medicine. Obviously, alternatives need to be considered, but the operational armamentarium is so restricted that the agent of interest may be under study to provide an alternative to an older, problematic drug. For a number of operational drugs, the potential for misuse is almost intrinsic to the action of the drug, and policies for minimizing that potential are already in place.

AREAS OF CONCERN

Therapeutic Agents

In general, medication effects needing aeromedical evaluation are those that may affect flight performance and safety, yet which are of insufficient clinical importance to have warranted inclusion as part of the original drug studies. Unfortunately, for most medications, effects of aeromedical concern have not been tested as part of these initial trials. Potential areas include systems affecting ability to fly, such as cognition and special senses, and systems affected by unusual aspects of the flight environment, such as physiologic responses to acceleration.

Perhaps the most important potential side effect requiring evaluation is the effect of medications on higher central nervous system function. The critical nature of cognition, alertness, and coordination in the aviator goes without saying; unfortunately, the effects of most medications on these functions has also “gone without saying”, since there is not routinely any attempt at cognitive evaluation during initial clinical trials. It is not enough to rely on self-reporting of symptoms; it is axiomatic that the individual with impaired cognition is often incapable of recognizing such impairment.

Like cognitive processes, information about the impact of a given medication on special senses is rarely available, and proper function of at least some of these systems is critical to aviation. In particular, visual, auditory, and vestibular functions are crucial to successful flying. Impairment of the special senses may, or may not, be recognized by the affected individual.

Cardiovascular effects of drugs are of particular concern in the high-performance aviator, where degradation of acceleration tolerance by a medication which affected vascular tone or sympathetic reflexes could lead to disastrous results. The other cardiac effect of concern is the occasional appearance of arrhythmia, particularly polymorphic ventricular tachycardia, associated with prolongation of the QT_c interval.

Besides acceleration stress, other physiologic stresses routinely encountered in aviation include the barometric and hypoxic effects of altitude. While interaction of medication with the former is unlikely, there are at least some theoretic concerns about drugs and hypoxia. A study of first generation antihistamines at altitude suggested a synergistic effect between hypoxia and drug-induced effects on mentation; however, it does not necessarily follow that a nonsedating drug might potentiate the effects of hypoxia. As a separate issue, drugs which affect vascular tone usually affect the pulmonic as well as the systemic vasculature, which could in turn affect hypoxic pulmonary vasoconstriction, and thus perhaps maintenance of arterial saturation. In addition, drugs might disrupt Circadian rhythms, or might affect the organism’s response to temperature or climatic extremes. Evaluating a drug for such specific interactions would be indicated if there were a particular concern about the medication.

Operational Agents

Operational drugs present some unique areas of concern. First and foremost, efficacy in most cases cannot be assumed, and must be established through controlled studies. The absence of central nervous system effects, usually a highly desirable attribute for a therapeutic drug, is a contradiction in terms when applied to stimulants or sedatives; at most, one could hope for a beneficial effect on the targeted neural functions, and a minimal effect on

others. Concerns about other side effects, such as those involving special senses, do apply to operational drugs, but even there one cannot rule out the possibility of evaluating operational agents for their possible enhancement of such abilities (e.g., the putative effect of bilberry extract on night vision).

METHODS OF EVALUATION

The classic controlled study is usually the method of choice for evaluating medications for efficacy and adverse effects. With the use of placebo (negative) controls, one is able to separate real drug effects from inherent variability in tests or populations, ensuring the validity of positive results. With the use of verum (positive) controls, particularly in CNS testing, one can verify that the test method was capable of detecting a difference, thus supporting the validity of negative results. For operational drugs, such research is, for both practical and ethical reasons, mandatory. The intent with such drugs is to be able to employ them under particular operational conditions and for specific mission requirements; opportunities to preclude adverse effects in those aviators who needed to use the drug would be limited or, in many cases, nonexistent. Thus, advance study is required to define the risk of side effects of aeromedical significance, as well as to establish efficacy.

When applied to evaluation of therapeutic agents for aircrew, the use of the controlled study presents certain negative aspects. First, there is always an assumption that the tested sample represents the treated population; unlike initial clinical trials, however, issues of aeromedical concern do not usually involve more than 20-30 subjects, because they require intensive, time-consuming testing, and because funding is not so readily available. (As a rule, the same limitation of subject numbers applies to operational drug studies.) Second, a drug waiver cannot reasonably be recommended until all areas of concern have been addressed (e.g., cognitive effects, acceleration interaction, etc.), so there is often considerable delay in approving a medication. Lastly, drugs with a limited potential for use, best described as “aeromedical orphans”, would likely never be evaluated through the use of controlled studies; the labor and resources required to properly evaluate a medication would not change regardless of whether the drug would be used by two aviators or two hundred aviators.

While the difficulty of evaluating an “aeromedical orphan” via controlled studies is understandable, the loss of even one or two aviators is potentially serious, particularly in an era of fewer aircrew who are more intensively trained in advanced weapon systems. The choices have usually been to either disqualify the individual, use another drug which is established but less suitable (otherwise it presumably would have been used in the first place), or take the chance that a lack of self-reported side effects is adequate for flying safety. An alternative approach for therapeutic medications required by a limited number of aviators is that of an individual occupational evaluation, where the aviator is evaluated before and after starting a drug, in the same way one might perform hepatic or renal function tests before and after beginning drug therapy. Another advantage of such an approach is that it avoids any concerns about a representative sample. There are also certain disadvantages to this approach. For one thing, it only gives information about that individual. Furthermore, it is only possible to explore a null hypothesis; inferences from apparent effects are very limited in the absence of a placebo control. One must evaluate for effects using established tests, previously validated with positive and negative controls, and with enough population norms to interpret individual results. Lastly, one can only obtain answers that have direct relevance to the question of flying status, adhering to an aeromedical/operational standard of care.

Gold Standard Tests

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INTRODUCTION

While drug toxicity which targets internal, especially excretory, organs is aggressively evaluated in laboratory and clinical trials prior to marketing, adverse effects on systems of interest to aviation, e.g., the special senses, are only rarely evaluated. It is the intent of this guideline to recommend tests which have been successfully employed in earlier research to detect medication effects. Where that proved impossible, tests were chosen that were known to be sensitive in detecting abnormalities typically caused by medications (e.g., contrast sensitivity function for visual abnormalities). Also, tests with a history of use in clinical medicine were preferred, since they were more likely to be available, well validated, and familiar to potential investigators, although for some areas such as cognitive testing this was impractical. Since baseline testing should be readily available when investigating drug effects, tests with a higher degree of sensitivity and reproducibility were preferred to those with greater specificity. Note that some tests have been discussed, not necessarily to be recommended. Also, even for those tests that are recommended, we do not mean to imply that all tests be done on all drugs; the testing regimen should be tailored to potential areas of concern.

The following sections are arranged by physiologic category, consisting of cognitive functions, special senses, critical organs, and physiologic responses to environmental demands such as acceleration.

CNS ASSESSMENT

Before designing a test protocol, the first question to answer is the following one: is use of the drug intended to allow the subject to alleviate a physiological stress in a physiological way, i.e., in a way he would spontaneously adopt to cope with the situation, or is it to allow the subject to exceed the limits of human stamina and endurance for a certain period of time? For example, multiple layovers, extended duty time, jet-lag, or continuous or sustained operations will lead to a sleep debt and a performance decrease. The use of hypnotics or chronobiotics in that situation may allow aircrew to get some recovery sleep and thus maintain performance; the primary goal is to avoid residual effects of hypnotics after waking up. In contrast, the use of a psychostimulant to cope with sleep deprivation entails a totally different approach. If we want to alleviate the detrimental effect on performance of military operators in a particular situation, time appears to be the critical factor. How long does the drug act? Assessing the duration of the drug effect compared to placebo is not as simple as it may appear. Different physiological, psychophysiological and performance effects will not change at the same rate; furthermore, the changes are not linear, nor do they include a “steady state” plateau. This problem is multiplied by the number of tests which are used, each of the resulting curves having its own characteristics. Thus, determining the duration of effect will involve a degree of subjectivity on the

part of the scientific team, even if optimal testing has been thoroughly carried out.

Determining safe limits of use is even more complicated. One should first list the different mental functions the drug is able to modify and then choose a test which will offer the best scientific conditions of validity and fidelity. Other characteristics may be of importance, especially usability under laboratory or field conditions. The choice of the different mental abilities to be explored should ideally rely on a task analysis or on the knowledge of aircraft handling and complex system management. The job of military pilots is changing rapidly; higher mental abilities, such as task sharing, workload management, decision making, and mission planning, are now as necessary to the success of a mission as basic perceptive and psychomotor abilities. Psychology has not yet produced tests able to assess such higher cognitive functions. The use of simulators offers an option, even if it gives only global performance data. Although we tend to focus on evaluating a drug from a purely cognitive point of view, one should not forget mood and feelings, since detrimental effects on the affective domain may lead to a performance decrement or risk-taking behavior. Finally, a last point of interest should be mentioned. Deleterious effects induced by operational drugs must be put in the context of the likely use of the drug. Military operations produce intense strain on personnel, and the resulting stress reaction may partially compensate for some side effects that appear under laboratory conditions, a point that should be kept in mind before rejecting a candidate drug.

Assessment Methods

This section will list some of the recommended tests and parameters used to assess drug effects and side effects on the CNS during laboratory or field experiments.

Vigilance Assessment by EEG Methods

Continuous or ambulatory EEG is the best means to measure the level of cortical arousal during the subject's activities. Besides constituting the central component of nocturnal polysomnography, as well as daytime nap studies, EEG can also be used in the daytime to detect drowsiness.[1,2]

Sleep Scoring: Rechtchaffen & Kales' manual is the reference routinely used for staging and scoring sleep studies.[3] For scoring micro arousals, which may appear during any sleep episode, an American Sleep Disorders Association (ASDA) task force has recommended guidelines.[4] Micro sleeps, defined as an abrupt decrease in vigilance, have been described in the laboratory[5] and during various field experiments. Detecting them in a military setting is of particular interest, as they may be responsible for a sudden decrease in performance. Established scoring rules do not exist for this type of event, but it is generally accepted that they present as a burst of 4 to 7 Hz rhythm for 1 to 10 seconds.[6] In the French experience, especially with several studies on stimulants, a micro sleep was defined as a period of stage 1 or deeper sleep which occurred after a minimum of 15 seconds of wakefulness, and lasted between 3 and 14 seconds. After a first micro sleep, another period of wakefulness of at least 15 seconds was deemed necessary before one could score a second micro sleep. These rules are similar to those used to score micro arousals, although the situation is reversed. The defined duration is a compromise, since it seems difficult to score events which last less than 3 seconds, especially on a continuous recording; however, if different events with a cumulative duration of more than 3 seconds were documented during the same epoch, a single micro sleep was registered. A cumulative index of micro sleeps during a period of sustained sleep deprivation seems to be a valuable parameter to assess the power of a stimulant.[7]

Multiple Sleep Latency Testing/Maintenance of Wakefulness Testing: Designed by Carskado and Dement in 1977, multiple sleep latency testing (MSLT) is now widely used. The ASDA scoring rules offer a standard methodology.[8] The maintenance of wakefulness test (MWT), first described by Mitler et al. in 1982,[9] aims to assess the ability to remain awake under soporific circumstances. There is a relative lack of reference data in the general population, although recent progress was made by Doghramji et al.,[10] who defined normative data with a lengthened duration of test. If these data are confirmed, it will be possible in the future to use MWT as a routine test. The use of combined MSLT and MWT is also possible using the MAST technique described by Erman et al.[11] It has been shown that the MWT has a higher discriminative power than the MSLT to assess the effect of psychostimulants in narcolepsy.[12] MWT will likely become the reference test for psychostimulants in the near future, but for hypnotics it seems preferable to continue using the standard MSLT.

Actigraphic Data

Many actigraphic devices are now available to evaluate physical activity. The main problem with actigraphic data lies in establishing a suitable method for processing the results. For drug studies, one method is to compare mean level of activity during defined periods under two pharmacological conditions, but there exists a feeling of dissatisfaction with this type of processing. In the future the dichotomy index, which aims to measure the contrast between wakefulness and sleep, may prove to be a valuable alternative;[13] its calculation will probably be included in the software of actigraphic devices.

Subjective Data on Sleep Wake Rhythms

Visual Analogue Scales (VAS) are commonly used to measure the subject's own assessment of alertness and mood. Within the many scales available, one can choose the Bond and Lader VAS,[14] the Stanford sleepiness scale,[15] or the Epworth sleepiness scale. The last is more useful to evaluate sleepiness related to sleep disorders.[16] The Bond and Lader VAS includes 16 dimensions which can be clustered into three major categories, consisting of vigilance, mood, and stress level. It has been used satisfactorily during sleep deprivation experiments, and also during field research investigating aircrew fatigue during multiple layovers.

Sleep logs are routinely used as well, as they provide valuable information on subjects' behavior.[17] In the case of field research, the subject may be asked to write down additional information such as stimulant or medication consumption, hours of work and rest, and type of work, such as in flight or on the ground.

The Horne and Ostberg questionnaire is also used for the assessment of subjects' chronotype.[18] It is useful to avoid the recruitment of extreme subjects, such as extreme “morning” and “evening” types, whose chronobiologic characteristics may impair the homogeneity of the studied population.

Mental Performance

The main test battery employed in military research laboratories is the AGARD STRES Battery, which was specifically developed to assess the effect of environmental stressors on mental performance.[19] The STRES battery includes 7 different tests:

- Reaction times (simple and complex),
- Mathematical processing,
- Memory search,
- Spatial processing,
- Unstable tracking,
- Grammatical reasoning, and
- Dual task (unstable tracking with concurrent memory search).

172 scientific references about these different tests are available in the AGARDograph. The STRES battery has been used satisfactorily during numerous laboratory experiments performed by the French aeromedical centers, three of which are listed.[2,20,21] The battery has also been implemented on desktop computers for field studies. However, these tests have become less standardized between countries than originally planned. Two main reasons may account for this. Firstly, some laboratories have forsaken the use of some tests to shorten their experimental protocols. Secondly, differences between computers, especially in terms of processor speed, may lead to unexpected variation between time or score measurements. This point is of particular interest in the case of collaborative studies.

Focused attentional performance may be assessed with the BATP test[22,23,24] of the "Etablissement d'Application Psychotechnique," one of many tests available to assess attentional performance.[25,26] The subject must detect targets embedded in distractors, the shapes of which are very similar. The test lasts 10 minutes, and puts significant strain on the subject. It has been widely used in a paper and pencil version during sleep deprivation experiments. Recently, a software version has been developed and validated.[27]

VISUAL ASSESSMENT

Spectrum of Ophthalmic Toxicity of Systemic Drugs

Ocular toxicity from systemic medications may present in any of several ways. The following system follows a largely anatomic classification, with some examples of agents under each heading which are known to present in such a fashion.

1. Cornea – corneal deposits
   - amiodarone, antimalarials, indomethacin

2. Anterior chamber – autonomic effects
   - antihistamines, antihypertensives, innumerable other drugs

3. Lens – cataracts
   - allopurinol, clomiphene, sulfonamides

4. Retina – retinopathy/maculopathy
   - antimalarials, thioridazine, canthaxanthine, tamoxifen, niacin

5. Optic nerve – toxic optic neuropathy
   - ethambutol, chloramphenicol, lithium

Testing Visual Function

Baseline testing is crucial, since early ocular toxicity may manifest as a minor decrement in testing which at that point may still be within normal range. Furthermore the normal range of a healthy population is not well established for all tests, and baseline testing also allows one to identify minor preexisting abnormalities which might otherwise be blamed on the drug. Since ocular toxicity may not manifest equally in each eye, tests should be administered in a monocular fashion.

Corneal and lenticular opacities are relatively rare, and usually readily identifiable by standard biomicroscopy. Visual blurring due to autonomic drug effects is very common, but because it is readily reversible, there has been little effort devoted to evaluating screening tests. However, testing for high and low contrast visual acuity should readily identify drug toxicity presenting in this fashion.

For a number of reasons, considerably more effort has been expended on screening tests for drug-induced retinopathy, particularly that due to antimalarials. The changes may not be reversible and may even progress off therapy. Also, retinal changes may not be visible until permanent damage has occurred. Furthermore, some patients with established retinopathy are asymptomatic. However, despite the large body of research, the literature is confusing and controversial.[1] This may be due in large part to a lack of agreement as to what defines the earliest stages of retinopathy, and also to a lack of studies which have followed patients over the long term. Goldman perimetry[2], Amsler grid testing[3], electroretinography[4], and electro-oculography[5] have all been evaluated as screening tests for early chloroquine retinal toxicity, but results have been inconsistent. In many cases, the results have correlated well with established retinopathy, but less well with what was felt to represent early retinopathy. As noted earlier, this may be due to a lack of criteria for what actually constitutes early retinopathy, and to the practical and ethical dilemma of following patients over the long term to determine whether definite retinopathy actually developed.

Literature concerning toxic optic neuropathies is more limited, consisting largely of clinical findings noted in established cases. Definite cases of ethambutol optic neuropathy have displayed symmetric, central scotomata. Acquired color vision deficit has been a consistent finding, particularly a green weakness.[6] Joubert et al showed significant deutan errors in patients on ethambutol early in the course of treatment, while tritan errors appeared later, in those who had been on the drug for more than two months[7].

Defective color vision overlaps several of the earlier categories, particularly retinopathy and optic neuropathy. Many drugs are known to affect color vision (see Table 1, from WG-24). Probably because dyschromatopsia is defined by the results of functional testing, there is general agreement about optimal testing procedures. The Farnsworth-Munsell 100 Hue (FM-100) test has been used successfully to screen for solvent exposure[8], and digoxin toxicity[9], both revealing a dose-response relationship. In the former study, the Lanthony D-15 desaturated panel appeared to be a useful field screening tool, but did not provide as detailed an assessment as the FM-100. The prevalence of blue-yellow deficiencies by FM-100 in patients on phenytoin and carbamazepine correlated well with the presence of neurotoxicity;[10] tritan screening plates also identified dyschromatopics, but this was to be expected, since deficiencies in this study were confined to the blue-yellow axis (Type III).

Besides color vision, a number of vision tests depend on the integration of multiple ocular functions, but contrast sensitivity function (CSF) testing is particularly sensitive to a large number of abnormalities, including neuropathy, retinopathy, amblyopia, and glaucoma, as well as any abnormality affecting standard high contrast acuity.[11] Perhaps because of this broad sensitivity and lack of specificity, CSF testing has not been commonly employed in screening for drug-induced retinopathy or neuropathy. However, for evaluating drug effects over the short term in a relatively healthy

population, this lack of specificity should pose little problem. CSF testing has been shown to be sensitive to blood alcohol level in a dose related fashion (average level .09%), whereas perceived intoxication did not correlate to blood level.[12] CSF testing has also been shown to be enhanced by dopaminergic drugs.[13]

Given the increasing reliance on nighttime military operations, the effect of a drug on night vision is of obvious interest. No standardized test exists to evaluate visual acuity under scotopic conditions. There are standardized tests for evaluating contrast under low mesopic conditions, using instruments such as the Mesoptometer or the Nyktometer, but these tests evaluate a limited range of contrast levels, and to our knowledge neither instrument has been used to test for drug effects. It is possible to identify deficiencies in dark adaptation, by bleaching out rhodopsin under bright light, and then measuring the return of gross scotopic vision under dark conditions. This is a cumbersome test of doubtful sensitivity, and will not identify short term alterations; as an example, it has been used in cases of vitamin A malabsorption, where rhodopsin levels have become seriously depressed over a long period of time. Despite the fact that there appears to be a lack of validated testing techniques for scotopic vision, such a deficiency is of questionable significance in the area of drug testing, since the group is not aware of any drug which is thought to degrade scotopic vision in the absence of frank retinopathy or other structural disease.

Degradation of visual acuity with night vision goggles (NVG) is a distinctly separate issue, since NVGs involve low photopic rather than scotopic vision; the fact that the screen itself is green is evidence of that. The present generation of NVGs contain a phosphor screen which emits light of a defined wavelength, or narrow band of wavelengths, in the green spectrum, with the resulting low contrast image formed by varying intensities of green light. One would suspect that deficits in CSF testing might correlate with NVG acuity, and recent results have indeed demonstrated such a correlation, albeit not a strong one.[14] It is possible to test NVG acuity directly. As long as illumination levels are strictly controlled, and the identical NVG device is used, results have been reproducible, but the amount of shift that would constitute a significant change would vary depending on the device and conditions.

Recommended Visual Function Tests

The following tests are recommended for evaluating ocular effects of therapeutic drugs in aviators.

Visual Acuity: High contrast visual acuity, far and near, using standard methods such as Snellen or Bailey-Lovie charts, performed at baseline, 3 days, and 6-12 months. A decrement of two lines on the Snellen chart is considered a significant change from baseline.

Ophthalmoscopy: Biomicroscopy with indirect ophthalmoscopy to evaluate for corneal deposits, cataracts and fundus changes, performed at baseline, and at 6-12 months. Any such findings are potentially significant.

FM-100: Standard saturated 85 chip panel, under 6750° K light source, performed at baseline and at 6-12 months. A difference in square roots of Total Error Scores exceeding 2.274 is considered to be a significant change.

Contrast Sensitivity Function Testing: Less available data, but other tests for screening visual function appear to sacrifice sensitivity for specificity. While Vistech or Pelli-Robson charts are simpler to administer, they measure larger incremental changes (0.12 log units) in CSF when compared with cathode ray tube-based tests. CSF testing should be performed at baseline, 3 days, and 6-12 months. A decrement of 0.05 log units is considered a significant change.

VESTIBULAR ASSESSMENT

In general, the vestibular system is part of the human equilibrium system. Information about position and movement is obtained by the vestibular, the visual and the somatosensory systems. Each of these systems covers a particular range in the frequency spectrum. In case of damage to, for instance, a semicircular canal system, compensation takes place within the central vestibular system itself. But it is also observed that in these cases patients rely much more on vision and on somatosensory information. In case of a bilateral loss, such as may occur due to gentamicin toxicity, one may observe a much stronger response from the other sensory systems. This has even lead to discussions about whether the vestibular system still has a vital function, or merely fine-tunes equilibrium; such a misinterpretation probably

occurs because of a lack of awareness that loss of other systems may elicit equally strong responses. When monitoring subjects for vestibular function, one has to be very careful to ensure that the system purportedly being examined is truly being evaluated.

When monitoring vestibular functioning, several important issues need to be understood.

Anamnesis: Because damage to the vestibular system due to drugs usually affects both labyrinths, the most important tool in standard diagnostic practice, the anamnesis, falls short. In the usual clinical situation, a vestibular deficit is suspected if a subject complains about vertigo, and a "quick and dirty" examination of eye movements shows spontaneous nystagmus, indicating a unilateral vestibular hypofunction. With a bilateral decrease of vestibular function, however, there is no spontaneous nystagmus and no vertigo is reported. The patient may be unsteady, but since he/she is often already in the hospital because of underlying illness, this finding is often misinterpreted even by trained otolaryngologists. (As an example, because patients treated with gentamicin were monitored with audiograms showing no decrease in function, and because the patients did not report vertigo and no spontaneous nystagmus was observed, the gradual decrease of vestibular function was often completely missed until the loss was complete.)

Reproducibility: If vestibular tests are carried out, they should take place on the same part of the day, in a reproducible manner, preferably by the same examiner, and a high level of arousal should be maintained during all examinations. It is known that test results may be influenced by the instructions before the test, and by whether the subject is kept busy during the test, for instance by performing mental arithmetic. In tests of the vestibulo-ocular reflex, the subject should be examined with the eyes open in a completely dark room; eyes closed versus eyes open in darkness may lead to different results. As another example, in case caloric irrigation is used, this should always be done with the same temperatures and with the same medium, not for instance alternately with water and air. Although this seems obvious, if examinations are done in different laboratories, the results may be difficult to compare because of these discrepancies.

Data Analysis: Because it is not always clear what sort of function deterioration might happen, it is advisable not to rely only on automatic data analyzing programs, but to also perform direct visual inspection of the data.

Tests for the Vestibulo-Ocular Reflex

Caloric Irrigation: Irrigation of both ears with water of 30 and 44 degree Celsius is the standard laboratory technique to assess a difference in function between the left and the right labyrinth. The test requires consistent laboratory practice because there are many factors which may influence the final result. A disadvantage of the test is poor patient acceptance, because nausea is easily provoked, and thus the test is not a good candidate to routinely monitor vestibular function. However, in order to assess vestibular function prior to a particular trial the caloric test may be quite useful.

Rotating Chair: A sudden stop from constant velocity yaw rotation with 90 degrees about the vertical axis results in a vestibular nystagmus, which disappears gradually. There are several characteristics which can be determined from this nystagmus response. The response can be described by an amplitude A and a time constant T (as a first order approach, neglecting the phase 2 response where the nystagmus reverses its direction). The test is not nauseating for the subject, but the inter- and intra-individual variability is great, demanding consistent test performance if any conclusions about decrease of vestibular function are to be drawn with sufficient certainty. This test is useful for monitoring vestibular functioning.

Although the time constants for pitch and roll rotation are different from the one obtained by yaw rotation, there is no indication that pitch and roll rotation should be monitored as well. Moreover, this requires special test devices to keep the head in the center of rotation during rotation about the vertical axis, and even more complex devices when other axes than the vertical axis are considered for rotation. As with pitch and roll, there is no indication that using other axes would give more useful information than that obtained by yaw rotation about the vertical axis alone; furthermore, rotation about other axes is rather provocative in terms of motion sickness.

Sinusoidal rotation at different frequencies is also useful, but it does not add more to the test results

obtained with the sudden stop test, with one exception; if visual suppression of vestibular nystagmus is examined, sinusoidal rotation provides a better evaluation than either sudden stop tests or caloric examination. (In fact, examining fixation suppression during caloric nystagmus should not be done at all; one loses the information from the vestibular nystagmus that has to be suppressed at that particular moment, hampering the computation of the suppression coefficient. This coefficient is the quotient from the nystagmus slow component velocity during fixation and the nystagmus slow component velocity without fixation. A coefficient exceeding 0.1 is usually judged as abnormal.)

For bedside testing Frenzel glasses can be used, the head being rotated to and fro by the patient him/herself. One has to be careful here, because the cervico-ocular reflex adds to the response. For instance, patients with a bilateral loss of vestibular function, a likely pattern with drug toxicity, may show an enhanced cervico-ocular reflex, which means that the resulting nystagmus pattern is hardly different from the one in healthy subjects. The same applies for stepping in place, rotating, because then the somatosensory information from the stepping itself is much more pronounced in these patients and may hamper the proper interpretation of the eye movements.

Tilt Chair: In order to look at ocular torsion of otolithic origin, subjects are tilted over angles up to some 60 degrees. Here again, strict adherence to testing technique is crucial, the more so since the response is in general rather small, with static eye torsion angles of 6-8 degrees being common. The within-subject variability is large. Preventing torsion of the recording device with respect to the head requires much attention, because that can easily account already for 2 or 3 degrees of torsion if not fixed appropriately. The otolith information is corroborated by the somatosensory information from pressure on the body, which also contributes to the eye torsion. Some experimenters try to avoid the cumbersome tilting of the whole body, by requiring the subject to only tilt his head; however, then the neck contributes to the torsion as well. The fact that one necessarily deals here with different sensory systems makes the interpretation of this test very difficult, to say the least. Although subjects find the tests easy to perform, this test doesn't seem to be appropriate for monitoring vestibular function.

Examining the subjective vertical is good in dealing with a unilateral vestibular deficiency, but in case a bilateral loss is suspected, the subjective vertical is not affected, although the accuracy in the settings decreases.

Tests for Postural Control

(Sharpened) Romberg Test The advantage of measuring and comparing postural stability, with the subject standing with the eyes open and closed, is that it is a physiologic test situation. From the sway pattern a measure of stability can be derived, demonstrating whether standing was easy or required much energy. It is not necessary to measure EMG; with the available force measuring platforms, head trackers, or video equipment, one is readily able to record postural sway. When the system is put under pressure, for instance by having subjects standing on a layer of foam rubber and/or with the head in extension, everyone must put some effort into the process in order to stay upright. One should realize, however, that in all these posture tests training effects can be seen, not only during a single session, but also over several days. Nevertheless, the difficulty of the test can be adjusted to each individual subject, and the test is not provocative. If the precautions about standardization are taken into consideration, this test is a good candidate for monitoring the equilibrium function.

A simplified version of this test is the sharpened Romberg test; with the subject standing with the feet in tandem position, the number of side steps necessary to prevent falling during a trial of one minute is taken as a measure of stability. Although severe disturbances are easily recognized this way, it is also possible to minimize the number of side steps by trying hard to remain upright. This is not reflected in the number of side steps, making this test unreliable for monitoring purposes.

Modern tests on postural control vary the visual surroundings, apart or in combination with tilt of the platform on which the subject is standing. Although these rather complex tests throw some light on the subject's equilibrium system, the interpretation of the test results requires a lot of experience. It definitely elucidates how the subject uses sensory information, but it should be realized that the system in case of some disturbance always prefers to rely on the visual information first; apparently that is the easiest way to handle the situation. It is not immediately obvious that these tests provide more information on the equilibrium

system than the Romberg test with additional foam rubber.

Stepping Around: In normal daily life activities such as walking, information of all sensory systems is available and integrated to guarantee optimal postural control and a unique spatial orientation. In fact, analysis of the normal postural and gait activities gives the best impression of the functioning of the equilibrium system. For detailed analysis of the functioning of the different subsystems involved, complex apparatus is required. Generally, the tests are not demanding for the subjects, but the analysis of the data is quite demanding for the examiner. These tests could be indicative of diminished vestibular activity, and are very valuable to follow-up compensation processes for damage to a subsystem. They have proven their value for showing functional compensation by the other subsystems. For instance, the somatosensory contribution to the nystagmus during stepping in circles depends on the contribution of the semicircular canals; the bigger the lesions, the higher the gain of the somatosensory nystagmus slow component velocity. Although these tests perfectly reflect normal daily life situations, technical problems prevented widespread application. Today technical progress has allowed further elaboration of these tests. There is increasing interest primarily because of the increasing applications of virtual reality, but also for diagnostic purposes.

Central Vestibular Function Testing: Optokinetic nystagmus, pursuit and different types of spontaneous or provocative nystagmus are easily recorded, but do not reflect a bilateral decrease in vestibular function.

Coriolis-effects as a Sign of Vestibular Function: The simplest way to establish the presence of vestibular function is to have a subject, during constant velocity rotation with the eyes closed, tilt his head toward his shoulder. If the sensation perceived is one of tilting the head to the shoulder, the chance that vestibular areflexia is present is rather high. If this can be done with velocities up to 135 or 180 degrees/sec without any problems, the conclusion is straightforward, and no vestibular function is present. If the vestibular system is still intact, the effect of tilting the head during rotation with the eyes closed is rather disturbing to the subject; he/she feels as if falling over with the chair, and often nausea develops immediately. The Coriolis Stress Test using this paradigm to determine how many head movements can be sustained by the subject without vomiting is, for obvious reasons, not useful for monitoring vestibular function on a regular basis.

CARDIOVASCULAR ASSESSMENT

Spectrum Of Cardiac Toxicity Of Systemic Drugs

Only a few of the many potential cardiotoxins, specifically certain of the antineoplastic agents, mood-altering drugs, anti-infective agents, antihypertensive drugs, and vaccines, have been shown to result in clinical heart disease. These drugs may have a direct toxic effect on the myocardium or the coronary vasculature, or they may disturb primarily the functions of impulse formation and conduction. Others affect the heart indirectly by altering autonomic regulation. In the case of those drugs that exert a direct toxic myocardial effect, the extent of damage tends to reflect the intensity and duration of exposure.

In addition to those agents that evince toxicity, there are also drugs that have the potential to induce a generalized hypersensitivity reaction. The heart may become a target organ during such reactions, and may suffer significant inflammatory injury.

Cardiovascular Manifestations of Adverse Reactions to Drugs

ECG Changes: Electrocardiographic changes induced by drugs may include ST-segment depression, prolongation of P-R interval, prolongation of the Q-T interval, T-wave inversion, appearance of U waves or increased U-wave amplitude. Examples of drugs which have been clearly documented to induce ECG changes include the antiparasitic drugs emetine, used in the treatment of amebiasis and schistosomiasis, and chloroquine used in the prophylaxis and treatment of several parasitic diseases, as well as psychotropic drugs, especially phenothiazines and tricyclic antidepressants.

Of the ECG changes noted earlier, the one receiving the most attention has been the QT interval, since drug-induced lengthening of cardiac depolarization has been to blame for a number of deaths.

Cardiac Rhythm Disturbances: These include extrasystoles, both supraventricular and ventricular, and tachycardias, both supraventricular and

ventricular, bradycardias, either sinus or due to A-V block. Ventricular arrhythmias can be caused from ventricular irritability due to direct effect of the drug on the myocardium, or due to prolongation of the Q-T interval noted above. Examples include antiparasitic agents, psychotropic drugs, antibiotics such as erythromycin, terfenadine, thyroid hormone, sympathomimetics, and anticholin-esterases.

Cardiomyopathy: Cardiomyopathy can arise from direct damage of the myocardium by the drug, such as with antineoplastic drugs, emetine, phenothiazines, lithium, or sympathomimetics, or due to hypersensitivity reactions, which have been documented with antibiotics and vaccines.

Pericarditis: Certain drugs, such as emetine and methysergide, may induce pericarditis, either in conjunction with underlying myocarditis, or as a manifestation of mesothelial damage, in which case it may be associated with other manifestations such as peritonitis.

Alterations in Blood Pressure: Drugs may affect the heart indirectly through altering blood pressure, causing either hypotension such as with antihypertensive drugs, or hypertension, such as with oral contraceptives or sympathomimetics.

Recommended Cardiovascular Function Tests: To evaluate potential cardiotoxicity, the following tests are recommended. To be able to delineate effects which are actually induced by medication, testing is advisable prior to initiation of the drug.

ECG: A resting baseline ECG must be done to identify pre-existing abnormalities. Specifically, careful measurement of the Q-T interval must be done. This interval, measured from the beginning of the QRS to the end of the T wave, indicates the approximate total duration of ventricular systole. It varies with heart rate, sex and age; several formulae have been used to take these variables into account and provide a "corrected" Q-T measurement (Q-Tc). Certain drugs are known to cause Q-T prolongation, a list which seems to get longer by the month. A prolonged Q-T means that there is delayed repolarization of the ventricular myocardium, and this is associated with an increased predisposition to reentry phenomena, thus favoring the development of serious ventricular tachyarrhythmias, syncope, and sudden death. Even when corrected for heart rate (QTc), this measurement displays considerable spontaneous variation. When evaluating for drug-induced prolongation, one should obtain three tracings before instituting drug treatment, and three tracings after reaching a steady state. An average change in QTc of greater than or equal to 35 msec is considered to be a significant difference, and unlikely to be due to chance.[1]

Holter 24-Hour Rhythm Monitoring: Holter monitoring allows one to detect changes in rhythm conduction, as well as changes in heart rate variability, which serves as an index of autonomic nervous system function. Asymptomatic episodes of sinus bradycardia (with the heart rate as low as 30 beats per minute), sinus pauses of up to 3 seconds, and Möbitz type I second degree atrioventricular nodal (Wenckebach) block should be considered to be normal variants.[2]

Echocardiography: This is the premier diagnostic tool for the early diagnosis of cardiomyopathy and pericarditis caused by drugs.

Exercise Testing: This may be performed periodically in aviators to assess exercise capacity and to evaluate for coronary disease. It could be used to screen for adverse effects of drugs on exercise capacity, the blood pressure response to exercise, and/or provocation of arrhythmias. Maximal exercise capacity in normal individuals is influenced by familiarization with the test equipment, the level of training, and ambient conditions during the testing. When estimating functional capacity, the amount of work performed (or exercise stage achieved) should be measured, rather than the minutes spent exercising. Hypotension following exercise, defined as a drop in systolic pressure below the standing level pre-exercise, occurs in normals with an incidence of 1.9%, and may be symptomatic. Hypotension occurring late in exercise, or during the recovery phase, can be due to medications.[3] Effort-induced supraventricular or ventricular arrhythmias may develop during exercise testing in normals, and may be symptomatic.[4] The possibility of false-positive results must be considered if exercise testing is performed as part of drug testing.

Tilt table testing: Head-up tilt table testing can be used to screen for abnormal blood pressure or heart rate responses during treatment with medications. When the test is performed in the absence of provocative pharmacologic agents, it appears to discriminate between symptomatic patients and asymptomatic control subjects; the specificity of the

test when performed at angles of 60 -70^0 is about 90%, with a relatively low false-positive rate in the population tested.[5,6,7]

PULMONARY ASSESSMENT

For certain classes of pharmacotherapeutic agents, pulmonary function assessment should be included as part of a comprehensive aeromedical assessment. In particular, for drugs that may affect airway function or the pulmonary interstitium, appropriate pulmonary function testing should be included.

Table 2 lists possible adverse pulmonary reactions of drugs with potential application in the aerospace environment. (derived from the Medical Letter 32, 827; Current Medical Diagnosis and Treatment 39th edition 2000).

Many other therapeutic agents besides those listed may have adverse pulmonary effects, and adverse effects may emerge in new medications observed over time. When considering the introduction of a new medication for aircrew, the possibility of a known or unknown adverse effect on pulmonary function should always be considered.

Aeromedical Concerns Related to Pulmonary Dysfunction

The primary aeromedical concerns with respect to pulmonary dysfunction include:

- aggravation of hypoxia
- compromise of G – tolerance
- possible pulmonary barotrauma

Hypoxia is a ubiquitous threat in aviation. Pulmonary dysfunction may aggravate hypobaric hypoxia by creating ventilation-perfusion mismatch through either small airways dysfunction, or by affecting regional lung compliance through inflammation, edema, fibrosis, or emphysema. Mild degrees of arterial desaturation, e.g., 90%, may occur in individuals with perfectly healthy lungs at moderate altitudes (e.g., 9,000–10,000 feet), reflecting alveolar oxygen tensions on the cusp of the oxyhemoglobin dissociation curve. In such circumstances, even moderate degrees of pulmonary dysfunction may result in significant further desaturation converting a tolerable degree of mild hypoxia to significant desaturation with resulting performance decrements.

While G-tolerance is primarily based on systemic perfusion, desaturation caused by G-related ventilation-perfusion mismatch may play a contributory role in G-endpoints. Because it is the least structurally supported organ, the distortable elastic lung may well represent the eventual limiting factor in man's tolerance to radial accelerative forces. In this setting, small airways disease and interstitial lung disease may play a significant role in G-tolerance and in creating the substrate for acceleration atelectasis.

Pulmonary barotrauma is an unlikely event, but may occur with explosive or rapid decompression in the presence of trapped gas, as with agents that have the potential to cause an asthmatic reaction.

Pulmonary Function Assessment of Drugs for Use in Aircrew

Since pulmonary function testing is a specialized evaluation requiring trained technicians and carefully calibrated equipment, testing for an aeromedical pharmacotherapeutic assessment should be carried out in an accredited pulmonary function laboratory with appropriate quality control. Specific technical details will not be addressed in this monograph.

Pulmonary function assessment of pharmaco-therapeutic agents being assessed for use in aircrew should consider assessment of:

1. airways function,
2. lung volumes, and
3. diffusing capacity.

Assessment of Airway Function

Small airways caliber is affected by mechanisms including neural pathways, humoral control, direct physical and chemical effects, and local cellular mechanisms. Assessment of airway function should be included in the aeromedical assessment of any pharmacotherapeutic agent that may affect the autonomic nervous system (parasympathetic or sympathetic), or that may affect the release of vasoactive polypeptides which modulate nitric oxide production.

The following tests comprise a basic assessment of airway function.

- Forced expiratory volumes

- Flow-volume curves including low gas density spirometry

Additional tests may be added depending on the potential side-effects of the pharmacotherapeutic agent:

- low gas density spirometry
- tests of airway reactivity
  - before and after bronchodilator
  - bronchial provocation tests
- other specialized tests
  - single-breath nitrogen washout
  - frequency dependence of compliance

Forced Expiratory Volume (forced vital capacity volume-time analysis): From a forced vital capacity (FVC) maneuver, the volume expired in a given time during the forced vital capacity is measured and a plot derived of expired volume against time. Primary derivatives including the FVC (forced vital capacity) and FEV_1 (volume expired in 1 second) are recorded, as well as secondary derivatives including the FEV_1/FVC ratio and $FEF_{25-75,}$ (average flow rate during the middle half of the FVC).

Airways obstruction due to inflammation, broncho-spasm, or loss of elastic support (emphysema) result in decreased values for $FEV_{1,}$ and the FEV_1/FVC ratio. However, these parameters may remain relatively well preserved in early small airways disease, and the sensitivity of the FEV_1 and the FEV_1/FVC ratio in detecting early small airways disease is low. On the other hand, a decrease in the ratio below 75% has a relatively high specificity for identifying airways disease, either reversible (as in asthma) or fixed (as in emphysema).

Flow-Volume Curves: Expiratory flow rates are plotted against expired volume change during an FVC. Both inspired and expired flow rates are plotted. Parameters measured include peak inspiratory (PIFR) and expiratory (PEFR) flow rates, and flow rates when 50% (FEF_{50}) and 75% (FEF_{75}) of the vital capacity have been expired.

The shape of the maximum expiratory flow-volume (MEFV) curve from about the last 75% of the FVC down to RV is largely effort independent, and is determined by the elastic recoil properties of the lung and the flow-resistive properties of the small airways (<2mm). In healthy subjects, this segment is generally linear, but in subjects with small airways disease (e.g., asthma) or loss of elastic recoil (e.g., emphysema), the shape of this segment is "scooped" with a decrease in FEF_{50} and $FEF_{75.}$

Low Gas Density Spirometry: Flow volume curves are obtained with the subject breathing air, and then repeated after breathing a low gas density mixture of 80% helium and 20% oxygen. The resultant curves are superimposed by matching at RV. The difference in flow rates on helium versus air at 50% vital capacity ($V_{max\ 50}$) is measured, as is the volume at which expiratory flows converge (VisoV). The basis for this test is that turbulent flow in the larger central airways is density dependent, while flow in small airways (<2mm) is laminar and density independent. In normal lungs, small airways contribute only about 20% to total expiratory flow resistance, and so breathing gas of low gas density produces a significant increase (>20%) in $V_{max\ 50}$ by improving flow in large airways; since the curves converge late, VisoV is normally 10-20% of the FVC. In individuals with small airways disease or dysfunction, small airways contribute a much larger share to total airflow resistance, and when such individuals breathe low density gas, there is little or no (<20%) change in $V_{max\ 50}$, and VisoV is increased.

Specialized Tests of Small Airway Function: Other specialized tests used to assess small airways function include the single-breath nitrogen washout curve (Fowler's test), and the frequency-dependence of compliance. These tests are generally available in research laboratories but not in routine clinical pulmonary function laboratories.

Sensitivity/Specificity of Tests of Small Airways Disease: The sensitivity and specificity of various pulmonary function markers of small airway function have been assessed and correlated with histopathologic findings in a number of studies. Low gas density spirometry and the single-breath nitrogen washout curve (closing capacity and slope of phase III) appear to provide the highest sensitivity. FEF_{50} and the MMFR show changes earlier than the FEV_1 or the FEV_1/FVC ratio, but are less sensitive than the earlier tests. All suffer from a problem with interindividual variability, which makes their clinical utility small. They do appear to be reasonably reproducible in a given individual.

Assessment of Airway Reactivity:

Before and After Bronchodilator: Assessment of FVC and expiratory flow rates at baseline and after administration of a beta-adrenergic bronchodilator such as salbutamol (albuterol) may demonstrate reversible airflow obstruction suggestive of asthma or reactive airways disease. An increase of 15% or greater in FEV_1 is indicative of reversible airways obstruction, but changes in other parameters including FEF_{50}, FEF_{25-75}, or specific airways resistance may also be suggestive.

Bronchial Provocation Testing (BPT): BPT is used to objectively assess airway reactivity. Various challenges may be used; the most commonly used and best standardized is the methacholine challenge test. After obtaining a best effort baseline FEV_1, subjects breathe increasing doses of nebulized methacholine with repeat FEV_1 determinations after each dose. The test is terminated when a 20% fall in FEV_1 compared with baseline has been achieved. The methacholine dose at which this occurs may be expressed as the cumulative dose (PD_{20}) or concentration (PC_{20}).

Measurement of Lung Volumes

Lung volumes may be affected by agents and diseases which cause

1. interstitial changes – e.g., edema, pneumonitis or fibrosis
2. loss of elastic recoil – e.g., emphysema
3. gas trapping – e.g., asthma, emphysema

Interstitial changes generally result in *decreased* lung volumes (restrictive lung disease), while loss of elastic recoil and gas trapping are reflected in *increased* lung volumes (obstructive lung disease).

Lung volumes are measured by

- gas equilibration techniques such as nitrogen washout (open circuit system breathing oxygen) or helium (closed circuit), or by
- body plethysmography, which calculates total thoracic gas (VTG) based on volume or pressure changes using Boyle's law.

The gas equilibration techniques measure only the volume of those areas in the lung in ventilatory communication with inspired gas, while the body plethysmograph measures the total volume of intrathoracic gas. By comparing lung volumes measured by both methods, an estimate can be derived of gas trapping by comparing the functional residual capacity (FRC) from plethysmography with the gas equilibration technique. FRC_{box}/FRC_{gas} may be used as an index of gas trapping, with values greater than one suggesting gas trapping.

Diffusion Tests

The carbon monoxide diffusing capacity (D_{LCO} or D_{CO}), also known as transfer factor, measures the transfer of a diffusion-limited gas (CO) across the alveolocapillary membrane. Carbon monoxide combines with hemoglobin about 210 times more readily than oxygen. In the presence of normal ventilatory function, and normal amounts of hemoglobin, the primary factor limiting diffusion is the alveolocapillary membrane. Diffusing capacity is essentially a measure of conductance of CO across that membrane. The D_{LCO} is reported in milliliters of CO per minute traversing the alveolo-capillary membrane per millimeter of mercury of driving pressure.

Many factors other than the alveolocapillary membrane may affect the diffusing capacity. These include

1. Hemoglobin concentration
2. Elevated carboxyhemoglobin – e.g., in smokers
3. Pulmonary capillary blood volume – increased volume increases the D_{LCO}
4. Alveolar carbon dioxide concentration
5. Altitude
6. Technical variations

The most commonly used technique is the single breath – modified Krogh technique. Because there are many technical pitfalls and sources of variability in measuring D_{LCO} in conducting serial measurements in an aeromedical assessment, careful attention to technique in an accredited pulmonary function laboratory is especially important.

Diffusing capacity is generally decreased in interstitial lung diseases such as the pneumoconioses, or oxygen toxicity. D_{LCO} is also reduced in diseases causing loss of parenchyma such as emphysema. Many drugs may cause reductions in D_{LCO} because of their effects on the alveolocapillary membrane.

Recommendations for Pulmonary Function Assessment in Aeromedical Pharmaco-therapeutic Evaluations

For drugs which have known or are suspected of having an effect on pulmonary function, pulmonary function testing should be included as part of the testing protocol. The precise PFT protocol may vary depending on whether the drug primarily has an effect on airway or interstitium. As a minimum, the following is recommended for baseline and serial evaluation.

- Assessment of airflow limitation – maximum forced expiratory curves
- Assessment of lung volumes – gas equilibration or body plethysmography
- Assessment of gas transfer – Single-breath diffusing capacity

Depending on the pharmacology and potential known adverse effects of the medication in question, the pulmonary function profile may be expanded to include:

- Assessment of airway reactivity and small airway function
  - low gas density spirometry
  - single-breath nitrogen washout
  - forced expiratory curve before and after bronchodilator
  - bronchial provocation testing
- Lung volume measurements with body plethys-mography AND gas equilibration assessment for possible gas trapping

ENVIRONMENTAL ASSESSMENT

NATO air operations may require aircrew to deploy and operate in a wide range of environmental conditions, and may involve physiologic challenges including acceleration (G forces), altitude exposure including decompression and hypoxia, and extremes of thermal exposure. Life support equipment including PPG and CBW ensembles, flotation devices and cold water survival garments complicate physiologic responses. Medications for aircrew intended to enhance performance or for prevention or treatment of medical conditions may require assessment in such situations, where complex physiologic responses may occur in response to extreme environmental conditions. The extent to which any individual medication must be assessed in terms of environmental responses will depend on the potential for altering responses in such environments, based on its chemical composition and mechanism of action.

RTO Working Group 26 recommends that an assessment of a medication being approved for unrestricted use in aircrew should consider the following:

a. G-tolerance testing
b. Thermal responses
c. Hypoxic interactions

Thermal Responses

Air operations may impose high thermal strain on aircrew (such as were experienced in the Gulf War), or aircrew may face serious heat loss in cold ambient air or cold water immersion survival situations. Personal protective equipment such as PPG ensembles (Combat Edge, STING, AEA) or immersion suits may add to performance capability and/or survival on the one hand, but may compromise heat tolerance, and aircrew taking medications may be further compromised physio-logically in such environments.

There are no established, standardized tests to assess heat or cold tolerance. Assessment of the potential impact of medications in hot or cold environments requires comparison with a placebo under clearly defined conditions. Test conditions should simulate to the extent possible those projected to occur operationally. The variables to be defined include:

a. temperature
b. humidity
c. wind chill
d. clothing and protective equipment worn
e. physical activity – sedentary, workload – intermittent or continuous
f. monitoring (depending on conditions)
   - core temperature; rectal probe, esophageal probe or radiotelemetry pill
   - skin temperature – number of sites
   - ambient temperature/dew point/humidity
   - heart rate
   - body heat gain

- sweat production
- evaporative efficiency

The Air Standardization Coordinating Committee has defined certain “Standard Environments” for the physiologic evaluation of personal thermal conditioning systems (ASCC AIR STD 61/62 Feb 88). These may be useful as guidelines to help define environments in which to assess the effect of medications. The guiding principle for assessing the thermal impact of medications in aircrew should be to simulate as closely as possible the most probable extremes of operational conditions.

Altitude

Altitude exposes aircrew to a potential threat from both hypoxia and decompression. Sudden loss of cabin pressurization or oxygen supply at high altitude represents an uncommon in-flight emergency which requires urgent aircrew action. Since this is an uncommon occurrence, with obvious action required, assessment of the incremental risk for decompression sickness or severe hypoxia is not considered essential in an aeromedical drug protocol, but may be included should the pharmacology or mechanism of action of the drug in question suggest a potential significant interaction in such circumstances.

Mild hypoxia, however, occurs routinely during normal air operations and the effect may be confounded by medications to create a significant flight safety and/or operational concern. Assessment of the environmental aeromedical effects of medications should include assessment of the potential interactive effects of mild hypoxia on cognitive function and performance.

Study design should be based on a double-blind crossover protocol to assess the interactive effects of mild hypoxia and medication on both performance and ability to learn new tasks (corresponding to the ability to respond to novel situations). Experimental design should ideally include an exercise component to simulate the physical workload of pilots (25W). Physiologic monitoring should include as a minimum heart rate and oxygen saturation. Performance tasks should include as a minimum a spatial orientation task (SOT, Manniken task), a serial choice reaction time (SCRT – e.g. Hamilton K et al), and a logical reasoning task (LRT- e.g., Baddeley). Study design should include a group trained to asymptote on tasks before the hypoxia/drug intervention, and a second naive group who are first exposed to the tasks during the interventions (in a cross-over fashion) to assess the impact on novel task learning. Studies should ideally be performed at several altitudes ranging from 5,000-12,000 feet, but to minimize the probability of a type 2 error if a single altitude is chosen, 12,000 feet (3658 m) is recommended.

To assess performance differentially across subjects trained to asymptote versus those novel to the tasks, i.e., for subjects trained to asymptote, a learning curve demonstrating asymptote for the subjects is the normal pre-requisite to experimental manipulation. Subsequent to this demonstrated asymptote, the subjects are exposed to the experimental condition and perform multiple trials under the influence of the stressor in question. The performance results under the stressor are compared to the last trial or last few trials of the asymptote to determine the impact of the stressor.

Subjects who are novel to the task should perform multiple trials (without any previous exposure to the task) under the influence of the stressor, and these results are plotted over trials to produce a performance curve which is compared to the average learning curve (done by the other subjects i.e., the previously trained subjects), the difference in the curves showing the direct impact of the stressor on learning efficiency.

Acceleration

Centrifugal accelerative forces are a frequent physiologic challenge to fast-jet pilots, occurring to some degree on virtually all sorties. Protective systems have evolved since introduction of the g-suit over 50 years ago, with a see-saw balance between aircraft performance and human capability. Current generation aircraft with rapid onset high-G capability can produce G-LOC without warning and a series of accidents occurred until offset by G-training programs and improved G-protection. In the last few years the “push-pull” effect or negative to positive G-transition has been more clearly defined as a physiologic threat. New generation G-valves are being developed to provide protection based on G-history rather than just absolute G-levels. Future generation aircraft now in development will produce new challenges. In this challenging, changing scenario, every effort must be made with the introduction of a medication not to tip the balance against the human in the system.

Assessment of the impact on G-tolerance must be part of the investigation for any medication considered for use in fighter aircrew.

G-tolerance is best assessed on the human centrifuge. Various biometric assays for assessing G-tolerance have been published, but may not reflect the performance characteristics and physiologic demands of newer generation aircraft. There is significant intra-subject variability (Ludwig, Krock), and various end-points can be used including vision change (peripheral light-loss or central vision dimming), blood pressure or ear opacity. G-tolerance may be measured as +Gz intensity tolerance, or +Gz duration tolerance. Gz intensity tolerance may be measured in a relaxed state without straining, or with various +Gz protection including the AGSM (anti-G straining maneuver) and/or protective equipment from a standard G-suit to a full PPG protective ensemble.

WG 26 does not propose to define a precise methodology of assessing the effects of a medication in the acceleration environment, but rather to define a general approach. Such studies will by their nature be carried out in one of a few institutes or laboratories with human centrifuge capabilities, and researchers in such laboratories generally have extensive experience in biometric acceleration assays. The following concepts are outlined as general guidelines.

As a general guideline, a study to assess the effects of a pharmacologic agent on G-tolerance should be based on a double-blind cross-over design using subjects as their own control. Pharmacologic agents to be assayed, which will be prescribed in other than a single-dose regimen (e.g., pyridostigmine) should be given over a period long enough to reach a pharmacologic and physiologic steady state.

The following parameters constitute minimum recommended monitoring during a pharmacologic study assessment:

- electrocardiogram
- blood pressure (e.g., Finapres, with the cuff level standardized for all exposures at the third intercostal space)
- ear opacity monitor
- EMG activity from vastus lateralis, rectus abdominis and intercostal muscles to confirm that subjects are relaxed

Assessment of G-endpoint can be based on one or a combination of:

- peripheral visual loss
- central visual loss
- ear opacity

The following guidelines are recommended for assaying G-tolerance:

- Subjects should receive sufficient exposure and experience to be comfortable centrifuge riders.
- Baseline G-tolerance should be defined on at least three different days
- The intervention study (placebo, pharmacologic agent) should follow shortly after (within one week)
- G-tolerance profiles should include
  - -- relaxed gradual onset run with an onset rate of 0.1 G/sec
  - -- relaxed rapid onset runs with G-onset rates of at least 2 g/sec to plateaus with a maximum separation of 0.5 g

In addition to obtaining information on possible effects on G-tolerance in controlled studies, it is recommended that aircrew to whom long-term medications are prescribed undertake a standard G-training program once stabilized on the medication before returning to operational flying duties. This would allow individual aircrew to assess in a controlled environment any idiosyncratic drug effect on individual G-tolerance before returning to the operational environment.

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TABLE 1

DRUG	CHROMA-TOPSIA	DEFICIT TYPE	TINGE OR HALO	NOTES
Analgesics				
Acetaminophen			yellow	
Salicylates	+	I	yellow	
Antibiotics				
Chloramphenicol		II	yellow	Total dose > 100g or > 6 weeks
Chlortetracycline		III		The only tetracycline that affects color vision
Erythromycin		III	red, green	
Ethambutol		II, III		For 3-6 months, defect persists
Ethionamide				Heightened color perception
Isoniazide		II		
Penicillamine		II		
Streptomycin	+	II	yellow	
Sulfonamides	+	II	red, yellow	Transient myopia
Salazosulfapyridine		I		
Antifungal				
Griseofulvin			green	
Antipyretics				
Ibuprofen		II		Colors appear faded
Phenylbutazone		II		
Salicylates	+	I	yellow	
Antimalarials				
Atabrine	+			
Chloroquine	+	III +	yellow	Purple spots / white background
Clioquinole		II+, III		
Quinidine		II		
Quinine	+	I, II, III		
Antineoplastics				
Mercaptopurine		II		
Vincristine		II		
Antirheumatics				
Ibuprofen		II		Colors appear faded
Indomethacin		III		
Antispasmodics				
Atropine			red	Ocular administration
Cardiac and Vascular				
Amiodarone			halo	Glare from lights
Ergotamine	+	II	red	
Nitroglycerin			halo blue, yellow	
Rauwolfia alkaloids			yellow	Mainly reserpine
Digoxin		III	halo blue, red, yellow, green	Blue-yellow is early toxicity indicator
Digitalis	+	I+, II, III		
CNS effects				
Alcohol (ethanol)	+	II	halo blue	
Alcohol (amyl)	+	II		
Amphetamines			blue	

DRUG	CHROMA-TOPSIA	DEFICIT TYPE	TINGE OR HALO	NOTES
Barbiturates	+			
Isocarboxazid				
Methaqualone		I, II, III	yellow	
Oxazolinediones				Prolonged dazzle in light, objects seem snow covered
Pentobarbital			green, yellow	
Pentylenetetrazol			yellow	
Phenothiazines			halo blue yellow	Rare in low doses
Diuretics				
Thiazides			yellow	Yellow spots in white field
Chlorothiazide	+	II		
Gases				
Carbon dioxide			yellow	
Ganglionic blockers				
Hexamethonium		III		
Heavy Metals				
Arsenicals	+	II		
Cyanide		II		
Lead		II		
Thallium		II		
Hormones				
Oral contraceptives		II	halo, blue	
Nitrofurane deriv.				
Furaltodone		I, II ?		
Nalidixic Acid	+			
MAO inhibitors		II		
Metal antagonists				
Disulfiram		II	red green	
Phenothiazine deriv.				
Thioridazine	+	I		
Tuberculostatics				
Dihydrostreptomycin		II		
Ethambutol		II, III		For 3-6 months , defect persists
Isoniazide		II		
PAS		II		
Rifampin	+	II		
Streptomycin	+	II	yellow	
Miscellaneous				
Strychnine	+			
Cannabis indica	+			
Tobacco (amblyopia)		II, III +		
Sildenafil citrate	+	II, III	blue, blue-green, yellow, pink	flashing lights, photophobia

Acquired color vision deficits have been categorized by means of a system devised by Verriest (1963). They are shown in the column labeled Deficit Type. Although not designed for that purpose, the system is often used to characterize color vision errors due to drug effects. The system is repeated here for convenience in viewing the table that follows.

TYPE I – a red-green deficit characteristic of retinal pathology in the posterior pole macula, where there are only "red" and "green" cones. There is an accompanying loss of visual acuity. The disease may progress to total color blindness and a nearly complete loss of visual acuity.

TYPE II – a red-green deficit with an accompanying milder loss of blue-yellow sensation. This problem is seen when there is optic nerve involvement as is seen in optic neuritis, retrobulbar neuritis, optic atrophy, optic nerve intoxication, or in tumors of the optic nerve or chiasm.

TYPE III – a blue-yellow deficit which is, by far, the most common acquired color vision defect. It occurs in choroidal, pigment epithelial, retinal and neural disorders including nuclear cataract, chorioretinal inflammations and degenerations, vascular disorders, glaucoma and many others.

Chromatopsia is a visual defect in which colorless objects appear to be tinged with color.

TABLE 2: Possible Adverse Pulmonary Reactions

Drug	**Possible Pulmonary Reaction**
Amiodarone	Acute pneumonitis, fibrosis,
ASA	Bronchospasm, NSAID sensitivity
ACE inhibitors	Cough
Beta-blockers	Bronchospasm
Betamethasone (inhaled)	Cough
Bromocriptine	Pleuritis, fibrosis
Carbamazepine	Hypersensitivity pneumonitis
Cromolyn (inhaled)	Cough
Dantrolene	Pleuritis, pneumonitis
Hydrochlorothiazide	Edema
Isoniazid	Pulmonary infiltrates
Nitrofurantoin	Hypersensitivity pneumonitis, fibrosis, pleurisy and effusion
NSAIDs	Bronchospasm, hypersensitivity pneumonitis, edema, fibrosis
p-aminosalicylic acid	Pulmonary infiltrates
Penicillin	Pulmonary infiltrates
Penicillamine	Bronchiolitis obliterans, hypersensitivity pneumonitis, fibrosis
Phenytoin	Hypersensitivity pneumonitis
Pilocarpine	Bronchospasm
Propafenone	Bronchospasm
Psyllium (inhaled)	Bronchospasm
Pyrimethamine compounds e.g., Daraclor, Maloprim, Fansidar	Hypersensitivity pneumonitis
Salicylates	Bronchospasm
Sulfasalazine	Hypersensitivity pneumonitis, bronchiolitis obliterans, fibrosis
Sulfonamides	Pulmonary infiltrates
Terbutaline	Edema
Tryptophan	Pneumonitis

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Losartan Potassium : A Review of Its Suitability for Use in Military Aircrew

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The renin-angiotensin system (RAS) plays a central role in the control of blood pressure, and in particular it is felt to play a crucial role in neurogenic hypertension. The RAS appears to act through two mechanisms, affecting the acute control of blood pressure through the pressor action of angiotensin II, and the long-term regulation of cardiovascular remodeling through the growth factor properties of angiotensin II.

While all known actions of the RAS are mediated through angiotensin II alone, it is important to review the metabolic process leading to its production, since it is possible to intervene at several points along the pathway. Renin is released by the kidney in response to a number of stimuli, including decreased renal perfusion, circulating blood volume and/or sodium load to the kidney, and increased sympathetic nervous system activity. Renin cleaves four amino acids from angiotensinogen, a fourteen amino acid glycoprotein derived predominantly from the liver. The resulting decapeptide angiotensin I is converted to the octapeptide angiotensin II primarily by the action of angiotensin-converting enzyme (ACE), which circulates in the plasma. This is not a particularly specific system; angiotensin I can also be converted by other enzymes, such as cardiac chymase and tonin, while ACE itself plays another role as kininase, inactivating circulating bradykinin. Although the RAS has previously been viewed as a circulating neuroendocrine system, recent studies have shown evidence of angiotensin producing systems within tissues. Tissue renin-angiotensin systems appear to be responsible for angiotensin II-induced hypertrophy in myocardium and vascular smooth muscle.[1] Furthermore, since angiotensin II, as an octapeptide, is unable to penetrate most of the blood-brain barrier, the majority of the angiotensin receptors in the central nervous system probably respond to locally generated angiotensin.

There are several points along the renin-angiotensin cascade which are susceptible to intervention. Renin release can be inhibited by the use of beta blockers. Inhibition of the second step, the cleavage of angiotensinogen by renin, would appear to be particularly attractive since it is rate-limiting, but compounds currently known to inhibit that reaction have low bioavailability and a short duration of action.[2] The most widely used approach has been the inhibition of ACE. ACE inhibitors have been very successful antihypertensives because of efficacy at lowering blood pressure and favorable side effect profiles. While studies evaluating their efficacy in actually reducing hypertensive morbidity and mortality are only now being completed, they have clearly been effective in reducing morbidity and mortality in heart failure and diabetic nephropathy. Besides blocking the conversion of angiotensin I, ACE inhibitors also prevent the degradation of bradykinin and prostacyclin. It is not clear whether the latter effect is beneficial or not, since the resulting elevated levels of these vasodilators may be at least partially responsible for some of the clinical effects of ACE inhibitors. However, it is likely that elevated bradykinin levels are to blame for the dry cough that occurs in 5-10% of patients taking ACE inhibitors.

The fourth method of inhibiting the renin-angiotensin system consists of blockade of the angiotensin II receptor. In addition to avoiding interference with kinin metabolism, antagonizing the angiotensin II receptor is theoretically more effective than ACE inhibition, since other enzymes are capable of generating angiotensin II. The concept is not new; saralasin, an octapeptide analogue of angiotensin II, was first studied nearly three decades ago. However, saralasin proved useful only in research applications, since it could only be given by constant intravenous infusion, and showed partial agonist activity. It was the development of losartan potassium, an imidazole with good

enteral availability, a long duration of action, and no agonist activity, that allowed the first clinical application of angiotensin receptor antagonism.

ANGIOTENSIN II RECEPTORS

Two principal angiotensin receptors have been identified on the basis of binding studies, and have been labeled AT_1 and AT_2.[3] All known cardiovascular effects of angiotensin II, including vasoconstriction, beta-adrenergic stimulation, and aldosterone release, appear to be mediated by the AT_1 receptor, of which losartan is a specific inhibitor. While the function of the AT_2 receptor is uncertain, it appears to inhibit angiogenesis, and is postulated to play a significant role in fetal development. In the adult, AT_2 receptors are most widespread in the central nervous system.[4] In addition, AT_3 and AT_4 receptors have been recently described, but have yet to be characterized. Losartan therapy results in a rise in renin and angiotensin II; although the effect of increased stimulation of AT_2 receptors by elevated angiotensin II levels has been an area of concern, to date no deleterious effects have been identified.

PHARMACOKINETICS OF LOSARTAN

Losartan is readily absorbed, and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via the cytochrome P-450 system. Absorption is not affected by food. Times to peak concentration are 1 hour for losartan, and 3.5 hours for the active metabolite. The peak effect on blood pressure occurs 6 hours after the dose. Mean elimination half-lives average 2.1 hours for losartan, and 6.3 hours for EXP-3174; at 24 hours after acute or chronic dosing, only the metabolite is still detectable in plasma.[5] EXP-3174 is a noncompetitive antagonist of the AT_1 receptor, with a potency 10-40 times that of the parent compound. It is probably for this reason that 63-74% of the peak antihypertensive effect is maintained at the 24 hour trough.[6] Blood pressure effects have been found to more closely parallel levels of the metabolite rather than of losartan.[7] Fewer than 1% of subjects fail to metabolize losartan to EXP-3174; in those individuals, the AT_1 receptor is blocked by losartan alone, and even though the half-life of the parent compound is prolonged in that situation, the drug appears to be less efficacious.

The pharmacokinetics of both losartan and its active metabolite are linear, and not affected by repetitive dosing. Although clearance is both by hepatic and renal mechanisms, only hepatic impairment appears to affect plasma half-life. In rats, losartan crossed the blood-brain barrier after a single intravenous dose of 3 mg/kg, but not after a single oral dose of 10 mg/kg or 3 consecutive daily doses of 3 mg/kg.[8] However, chronically administered losartan does appear to cross into the CNS, since administering losartan in the drinking water modifies the dipsogenesis induced by angiotensin II.[9]

DRUG EFFECTS

Experimentally and clinically, AT_1 receptor blockers, in the presence of an activated renin-angiotensin system, decrease systemic vascular resistance without significantly affecting cardiac output or heart rate. The lack of reflex tachycardia may reflect the blockade of AT_1 receptors on postganglionic sympathetic neurons, which decreases norepinephrine (noradrenaline) secretion. Wood et al. found that in normotensive, salt-replete animals, intravenous losartan had no effect, although the pressor response to angiotensin II was blocked, whereas in animals pretreated with furosemide, blood pressure was reduced.[10] Results in normotensive humans have been similar. While up to 120 mg of losartan has little measurable effect in salt-replete individuals, the systemic pressor response to angiotensin II is blocked, from a threshold effect at 10-20 mg to a maximal effect at 80-120 mg.[5] In normals who were salt-depleted by a low sodium diet plus furosemide, losartan induced a dose-related fall in systolic and diastolic blood pressure.[11]

The response of the renin-angiotensin system to losartan in normals is mirrored by its effectiveness in hypertensive individuals. One randomized, double-blind, multicenter study evaluated 491 patients with mild to moderate essential hypertension on varying doses of losartan (10–150 mg) compared with placebo, extending over 8 weeks. Losartan 50 mg resulted in significant reductions of systolic and diastolic blood pressure at 24 hours after dosing. Maximal reduction occurred between 4 and 6 weeks, and was maintained throughout the study; approximately 70% of the maximal reduction had occurred by one week of therapy.[12] Several studies have examined increasing the dose of losartan from 50 mg to 100 mg daily; there appears to be a small additional benefit.[5] As one would suspect from studies in normals, and from similar studies with ACE inhibitors, the addition of hydrochlorothiazide enhances the antihypertensive efficacy of losartan.[13,14]

Whether losartan will have a beneficial effect on left ventricular hypertrophy (LVH) similar to that seen with ACE inhibitors is still to be determined. In rats, losartan does reduce LVH, even at doses too low to control blood pressure.[15] Losartan is natriuretic in the volume-depleted state, without altering glomerular filtration rate in normals or hypertensives. It is also uricosuric, and causes a modest decrease in serum uric acid concentrations. Interestingly, this effect does not appear to be mediated by the AT_1 receptor, since neither EXP-3174 nor other AT_1 antagonists such as irbesartan have exhibited this effect.

Plasma renin and angiotensin II levels rise with losartan therapy. In healthy subjects, losartan doses of 100 mg daily or higher result in increases of renin and angiotensin II up to ten times baseline.[7] The rise in renin is exaggerated in the volume-depleted state.[11] Although there has been concern that rebound hypertension would occur upon withdrawal from the drug, this has not been observed, perhaps because of the gradual decline of plasma levels of EXP-3174. It may also be due to the fact that, compared with normotensives, hypertensives have a diminished rise in renin activity when placed on losartan, due to less feedback inhibition in the untreated state.[16] The presumed lack of effect of losartan on bradykinin metabolism is supported by physiologic data. In a study of human forearm blood flow, both 20 and 100 mg doses of losartan blocked reductions in blood flow associated with arterial infusions of angiotensin I and angiotensin II, while not affecting bradykinin–induced vasodilation. By comparison, enalapril in the same study inhibited the response to angiotensin I, did not affect the response to angiotensin II, and enhanced vasodilation from bradykinin.[17]

SAFETY

General

In Phase II and Phase III trials, approximately 2900 subjects received losartan, about 2000 of those as a single drug, the rest in combination with a diuretic. Sixteen trials were double-blind, while four were open, with a duration of 8-12 weeks. Clinically, dizziness was the only side effect noted significantly more often with losartan that with placebo, occurring in 4.1% versus 2.4% respectively. Cough occurred in 3.1% of losartan-treated patients, compared with 2.6% of placebo-treated subjects. Laboratory adverse events occurred with equal frequency between the two groups.[18] In long-term use, losartan has tended to cause a rise in serum potassium levels, although no patient needed to discontinue the drug due to hyperkalemia.[5]

The lack of effect of losartan on cough frequency has been confirmed by two studies which evaluated patients who had previously experienced cough on ACE inhibitors. Both studies found that losartan was not associated with cough any more frequently than was hydrochlorothiazide, while both were associated with cough much less frequently than was lisinopril.[19,20]

Post-marketing surveillance has uncovered a small number of serious complications. Those that have been confirmed by rechallenge include migraine, Henoch-Schönlein purpura, hepatitis, pancreatitis, and psychosis.[21-25] Although bradykinin has been presumed to cause the angioedema that is occasionally seen with ACE inhibitors, cases of angioedema have already been associated with losartan.[26,27] In the case reported by Sharma and Yium, the patient had had an earlier episode of angioedema shortly after receiving intravenous enalapril.

The fetotoxicity seen with ACE inhibitors appears to be shared by losartan. In animal studies, losartan appeared to have no effect on fetal development in the first half of gestation. However, when given in the last half of pregnancy, it was associated with serious fetal toxicity.[5]

Specific Organ Systems

The central nervous system is of particular interest in angiotensin research. Angiotensin II is known to centrally stimulate drinking and salt appetite, and to modulate release of pituitary hormones. The CNS is heavily populated with angiotensin II receptors in the hypothalamus, circumventricular organs, and autonomic control centers of the medulla. In the mammalian brain, there is a strong association between angiotensin II immunoreactivity and catecholamine cell bodies and terminals. Angiotensin II appears to stimulate release of both norepinephrine and dopamine.[9] Available studies of cognitive effects of losartan are sketchy. Losartan has been shown to reduce the performance impairment due to alcohol, while losartan alone appeared to be no different from control.[28] In a preliminary report, Braszko noted that, in the rat, angiotensin II increased passive behavior recall seven-fold, and doubled the amount of time spent exploring new objects, effects that were abolished by losartan, and to a lesser extent by an AT_2 blocker.[29] On the other hand, Shepherd et al,

studying rodents in two models of anxiety and two models of working memory, found no effect of losartan or an AT_2 blocker.[30]

There is essentially no data on other organ systems of interest to aviation. The significant increase in dizziness seen in Phase II and III trials likely represents the usual adjustment in cerebral perfusion that occurs when any hypertensive therapy is initiated; nonetheless, it should be noted that no information on vestibular testing is available. No data is available concerning ocular effects, or effects of losartan on the QT_c interval. Although cardiovascular effects of losartan through the RAS have been widely explored, no data exists concerning acceleration.

CONCLUSION

Losartan potassium, 50-100 mg/day, seems to be a reasonable medication to consider for the control of hypertension in aviators. Although it may affect release of catecholamines, it seems to leave autonomic responses intact. The side effect profile appears to be favorable, and generally equal to placebo, and for the 5-10% of patients who experience cough on ACE inhibitors it could be a particularly useful drug. Further testing is certainly indicated before the drug is employed in aircrew; for most organ systems of interest to aviation medicine there is no data, while in the central nervous system there exists some evidence of potential interaction.

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Losartan Potassium: Evaluating the Treated Aviator for Medical Waiver

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Literature Review

A review of the literature concerning losartan has shown it to be a potential candidate for use in aircrew. Based on clinical studies and post-marketing surveillance, no side effects have been uncovered that would preclude aviator use *a priori*. However, a number of questions remain to be addressed before deciding whether losartan is suitable for use in military aviation. For example, data is either lacking or scant concerning cognitive, vestibular, and acceleration effects, to name a few.

Acceptable Candidates for Losartan

Candidates suitable for losartan therapy are those aviators with sustained hypertension who have not responded to nonpharmacologic methods of blood pressure control. Compared to ACE inhibitors, the mode of action of losartan involves a different step along the same renin-angiotensin pathway; since there is more experience with ACE inhibitors in aircrew, the use of losartan should primarily be reserved for those who are unable to tolerate the older medications, such as drug-induced cough. It should be noted that, since angioedema has also been associated with losartan, including in one case after a previous episode of enalapril-induced angioedema, losartan is not recommended if there is a history of angioedema following treatment with ACE inhibitors.

Aviators considered for waiver of losartan therapy must show successful control of hypertension on the drug, in the standard dosage range of 50 to 100 milligrams per day, without unacceptable side effects.

Evaluation Process

Since the pharmacokinetic half lives of losartan and its active metabolite, EXP-3174, are 2.1 hours and 6.3 hours, respectively, the standard washout time (5 half lives) for the metabolite would be 31.5 hours. However, because the latter is a noncompetitive antagonist at the AT_1 receptor, 63 to 74% of the hypertensive effect is maintained by 4 half lives. Furthermore, there is some data suggesting a diastolic antihypertensive effect lingering for as long as a week after therapy.

Seven days prior to the initial evaluation, the aviator should discontinue therapy with losartan to allow washout prior to baseline tests. Frequent blood pressure checks should be performed over that week to rule out significant rebound hypertension off medication, although this has not been recognized with losartan. (While some degree of hypertension will undoubtedly recrudesce during this period, a few days off drug should have no significant impact, except perhaps in cases of severe hypertension. Since consistent availability of medications cannot be ensured under wartime conditions, disease of that severity should raise questions as to the member's fitness for continued military aviation.) After the washout period, baseline testing will be performed. The drug will then be restarted at the prior dosage. After 72 hours on the drug, those tests which need to be repeated will be performed. In addition, high performance aviators will undergo acceleration testing according to the proficiency profile of their air frame.

Tests to be Performed

These are outlined under the "Gold Standards" chapter. Acceleration testing would only be performed in high performance aviators. If results of testing showed no unacceptable drug effects, return to flying status would be favorably considered.

Follow-up

The aviator should be reevaluated in 6-12 months. Organ systems which may typically develop delayed drug side effects, such as the eye, will be reevaluated at that time. If the results of such testing are acceptable, subsequent follow-up will be according to usual policy.

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Section V: Conclusions

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Current Use of Medications In NATO Military Aircrew

The collection of data from NATO nations regarding use of medications for aircrew contains some interesting information and is a tool of great potential utility to NATO flight surgeons. In our survey of therapeutic medications use, we concentrated on medications used for long-term or sustained therapy for medical conditions. We did not survey nations on short-term therapeutic agents such as antibiotics.

As we stated in the introduction, there is a growing requirement to expand the range of medications available for use in aircrew. Allow me to repeat the list of factors driving these requirements:

- Rapid expansion of the number of new drugs available for clinical indications, offering enhanced disease management
- Diminished funding for research making it difficult for any single nation to completely evaluate aeromedical issues for one or more drugs
- Sustained round-the-clock operations and rapid deployment across multiple time zones
- Increased emphasis on mitigating the risk of chronic disease development through early intervention and improved disease management to reduce risk of disease complications
- Focus on population-based medicine leading to the understanding that consistently sound disease management, often involving newer pharmacologic agents, will maintain higher qualification rates in the aviation force
- Emphasis on force protection and emerging infectious disease threats increases demand for effective pharmacologic prophylaxis
- Absence of information on aeromedically significant effects of drugs from initial research required for licensure

Flight surgeons, particularly those serving in smaller nations, generally do not have access to the data to address aeromedical issues for newer medications. This makes decisions on aeromedical policy difficult. Access to experience and research from other nations can enable a sound aeromedical policy decision. The data set we have presented gives the flight surgeon the knowledge of which nations have information of potential use regarding a particular medication or class of medication. The potential advantages to the military service conducting air operations and to the individual aircrew member are considerable. As flight surgeons, we must strive to expand our options for use of medication in order to improve performance in the air operations we support and to give our aircrew the full benefit of the existing standard of care. Expansion of our options must, however, follow adequate evaluation of significant aeromedical issues. That is not to say that every potential aeromedical issue must be studied for every new medication considered—targeted evaluation based on risk assessment for a particular drug is a reasonable approach requiring aeromedical judgement.

Some NATO nations chose not to provide data for this database. Perhaps this reflects the sensitivity in some nations regarding use of medications by aircrew and the fear of generating the perception of chemically affected aircrew. Generally this sensitivity is more pronounced for operational medications. However, use of medications in military aircrew tends to be more restricted than that by civil aircrew and our Working Group has noted that occasional public interest in this topic abates with explanations of experience with the

medications in question. We believe more open sharing of this information between NATO nations will be to the benefit of the air forces and their aircrew. We also believe the benefits will outweigh the risks of public misperception.

The data on use of agents for treatment of asthma in aircrew indicates there is considerable interest in keeping aircrew with mild asthma flying within the countries surveyed. Beta agonist therapy has long raised aeromedical concerns but they data does show considerable use of salbutamol in aircrew. Dr. Gray points out in his paper that expanded options in antiinflammatory therapy for asthma, including inhaled steroids, disosium cromoglycate, and leukotriene inhibitors, appear to hold some promise for control of mild asthma in aircrew.

Allergic rhinitis is a very common condition generally compatible with military aircrew duties while under treatment. The data collected shows widespread use of inhaled steroids in military aircrew. Most interest has focused on the use of H1 antihistamines for this condition in aircrew because of their superior therapeutic response. The data shows that several nations have forbidden the use of terfenadine and astemizole in aircrew, while several nations are using loratadine. The paper by Dr. Davidson et al points out that loratadine and fexofenadine appear to hold the most promise for treating military aircrew for allergic rhinitis, although full data is not yet available on cognitive effects.

Among digestive disorders, reflux esophagitis and dyspepsia are the two conditions most often requiring sustained therapy in aircrew. Our survey did not include antibiotic therapy for peptic ulcer disease since that therapy is used for a finite, relatively short course of treatment. The data shows that side effect concerns have led several nations to specifically forbid the use of metoclopramide and cisapride. Antacids, omeprazole, and ranitidine are the most widely used agents for dyspeptic and reflux symptoms in military aircrew among the nations surveyed. Considerable aeromedical experience appears to be accumulating for these agents. The common use of mesalamine and sufasalazine in aircrew most likely reflects good experience with keeping aircrew with mild or limited inflammatory bowel disease in flying duties.

The treatment of hypertensive aircrew primarily is carried out to prevent long-term rather than near-term health complications. For many years, treatment options available to flight surgeons were limited to thiazides, leading to marginal or inadequate control in many aircrew, whose only other option was grounding. The data now reflects considerable use of angiotensin converting enzyme inhibitors, particularly enalapril and lisinopril, and considerable use of the beta blocker, atenolol, in aircrew. Dr. Pickard's paper shows us the continuing need for more options in treating hypertensive aircrew. The 20% incidence of cough with ACE inhibitors and the side effects from beta blockers (particularly in high performance aircraft) make these agents unsatisfactory for too many military aircrew. Dr. Pickard points out that angiotensin II converting enzyme inhibitors, such as losartan, appear to hold promise for use in aircrew and would be a significant addition to treatment options available to military flight surgeons. Dr. Pickard's paper proposing a study protocol for further evaluating the aeromedical suitability of losartan led our group to designate losartan as a drug in need of immediate study.

Evidence is mounting favoring treatment of moderate LDL cholesterol elevations as primary prevention of coronary artery disease. The advent of the HMG CoA reductase inhibitors (statins) gave us lipid-lowering drugs with side effect profiles compatible with use in military aircrew. So great was the interest around 1990 in this therapy for primary prevention, we saw nations proceeding with use of lovastatin prior to availability of good studies on cognitive performance effects. Dr. Eliopoulos reviewed aeromedical issues in lipid lowering therapy in his paper, including the fact that we now know lovastatin penetrates the blood-brain barrier and has measurable effects on sleep and cognitive performance (as do other lipophilic statins). Despite this, there have been no reports of aircraft incidents or accidents attributable to aircrew on lovastatin therapy. The data collected in our survey now shows widespread use of pravastatin and simvastatin in military aircrew. Dr. Eliopoulos makes the point that pravastatin is the only hydrophilic statin and thus has no significant penetration of the blood-brain barrier. This, along with the measured effects on sleep and performance in the lipophilic statins, makes pravastatin the optimum choice for treatment of LDL cholesterol elevations in military aircrew.

Our survey did not include medications for psychiatric disorders, but in discussions since conducting our survey we recognized that the use of selective serotonin/norepinephrine reuptake inhibitors has become quite common in treatment of depression and anxiety disorders. Informal surveys indicate that military air forces are keeping aircrew grounded while on these medications, but the significant incidence of these conditions and the need to encourage aircrew to seek treatment warrants consideration of the suitability of these medications for use while performing flying duties. Some significant aeromedical issues, such as sleep disturbance, need to be carefully evaluated before their use is considered in military air operations.

The continuing emergence of drug resistance in *Plamodium falciparum* around the world raises signficant concern about chemoprophylaxis in military aircrew. Our data shows that chloroquine and doxycycline are the most commonly used agents. Due to chloroquine resistance in many locations, doxycycline has become the primary means of protecting aircrew from malaria. Recent emergence of doxycycline resistance is has generated interest in the possibilities of using mefloquine in aircrew. Dr. Paris' paper includes a review of the available information on mefloquine side effects, which is a fascinating topic. Reports of serious psychiatric side effects and anecdotal reports of CNS side effects have led most nations to prohibit use of mefloquine in military aircrew. However, some nations do use mefloquine and their experience with it has been favorable. In fact, Dr. Paris summarizes several studies showing superior compliance and lower side effect rates among military members taking mefloquine in comparison to those taking chloroquine or doxycycline. Also, Dr. Paris point out that more recent studies suggest that the incidence of CNS side effects with mefloquine have been much lower than reported in earlier studies. Even so, CNS side effects, particularly those involving psychosis, generate much caution about their use in military aircrew. The evolving need for an alternative to doxycycline and the controversy about the side effects of mefloquine led our group to designate mefloquine as a drug in need of immediate aeromedical study. Ideally, a breakthrough in preventive measures for malaria will eliminate the need for chemoprophylaxis—but until that occurs, more options for prophylaxis are needed.

The advent of night air operations and rapid long-range deployment have increased interest in pharmacologic support of sustained operations. In particular, the use of stimulants to improve performance during prolonged periods without sleep is of greatest interest. Caffeine and dextroamphetamine are the stimulants with which certain nations have the most experience, but our data shows interest in finding improved alternatives. Although the operational experience with dextroamphetamine has been good, the potential for abuse and potential for side effects generate concern among flight surgeons. The dehydrating effects of caffeine limit its usefulness in physically demanding situations. As discussed in Dr. Nicholson's paper, this interest is focused now on modafanil, sustained release caffeine, and pemoline. Modafanil, a noradrenergic agent, and pemoline, a dopaminergic agent, hold promise as stimulants with less potential for side effects in comparison to dextroamphetamine. Several nations report studies underway on modafanil, but Dr. Nicholson's review indicates that pemoline is also a stimulant worthy of immediate study.

The Approach to Evaluating New Medications

Dr. Nicholson and Dr. Pickard have described and discussed the approach to evaluating medications to determine suitability for use by military aircrew. Evaluation of therapeutic and operational drugs shares several common characterisitics, but significant differences also exist.

Dr. Pickard explained the importance of first selecting a drug or class of drugs that will achieve the desired therapeutic end-point while posing minimal risk of aeromedically signficant side effects. The risk of such side effects has traditionally posed the most vexing question for flight surgeons. Dr. Pickard makes the point that military aviation is an occupation demanding high levels of performance and posing high levels of risk, making certain subtle side effects threatening to safety and the mission. These side effects, such as cognitive impairment or mild orhtostatic blood pressure changes, can be so subtle that prelicensure studies for the commercial market seldom address them, leaving the flight surgeon wanting for very important information. A medication with a long clinical track record adds some degree of comfort regarding side effects, but doesn't adequately address concerns about subtle, aeromedically significant side effects.

Operational medications often are directed at helping aircrew sustain performance over prolonged sleepless periods or deal with the effects of circadian desynchronization. Use of these medications to enhance performance in healthy individuals often falls beyond therapeutic experience with the drug, leaving a greater gulf between information needed by the flight surgeon and information available. Dr. Nicholson discusses the importance of verifying that the drug will reliably enhance performance in an operational setting. He stresses the importance of measuring relevant aspects of performance in ways that translate well into performance in the aircraft. He cautions against the common tendency to assume that simulator studies translate into operationally valid conclusions.

The approaches to evaluating new medications for aeromedical use described by Dr. Pickard and Dr. Nicholson are critically important to the aircrew and missions we support as flight surgeons. Recent history holds several examples of medications pressed into use in aircrew in a rush of enthusiasm (often propelled by commercial marketing) only to be withdrawn when aeromedically significant side effects come to light. Conversely, we do a disservice to all concerned if we rigidly adhere to protracted courses of evaluation over periods of years before considering a new medication. The right balance must embrace scientific evaluation of the most likely areas of aeromedical risk for a particular drug while accepting some degree of aeromedical risk for less likely side effects. Such a balance is most likely to enable us to be sufficiently responsive to those we support while fulfilling our duties to effectively use medication at minimal risk.

Ethical Issues

We must take care not to focus only on scientific facts when making decisions about operational or therapeutic use of medications in military aircrew. In this author's paper on ethics, the three spheres of influence when making such decisions were: 1) the law, 2) scientific facts, and 3) ethics. Experiences in the last decade, such as the controversy about Gulf War Illness, have reinforced the importance of considering all three spheres in our decisions.

Each nation has its laws governing the use of medications and sometimes these laws affect our ability to use medications for operational purposes. In some nations, documented informed consent is necessary. As part of a physician's duty to inform and obtain consent, the flight surgeon must ensure such consent is truly voluntary and ensure the aircrew are fully informed about the medication's effects and risks.

The flight surgeon has the duty to ensure disease in military aircrew is treated in accordance with the existing standard of care so that the long-term health of the aviator is not compromised. Likewise, the flight surgeon must ensure that mission enthusiasm does not lead to circumvention of the basic duty to communicate and manage risk.

Full consideration of the ethical sphere of influence is essential for future decisions about expansion of medications in use by military aircrew, both therapeutic and operational.

Gold Standards

The working group's paper on "gold standards" provides our conclusions about the most widely accepted means of assessing particular types of aeromedical risk. We believe use of such gold standards when studying medication for aeromedical risk is essential to producing valid answers useful to all nations with whom that data may be shared.

Of course, any list of scientifically accepted standards of evaluation will change over time with the advent of new knowledge and new technology. Agreement on such standards will be a cornerstone to any future cooperative research. Our paper on gold standards is an effort to publish standards as a starting point and source of information for cooperative research on aeromedical suitability of medications.

Need for Immediate Study of Certain Medications

After extensive study of operational requirements, aeromedical issues, and pharmacologic information, the working group has concluded there is a compelling need for immediate study of stimulants, antimalarials, angiotensin blocking agents, ultra short-acting hypnotics, and selective serotonin/norepinephrine reuptake inhibitors. Study of these types of drugs would be of

immediate benefit to NATO air forces and their aircrew.

Sustained operations in our air forces demand improved pharmacologic support to enhance safety and effectiveness for the aircrew. As pointed out in this publication's papers by Dr. Nicholson and the reprinted paper by Dr. LaGarde, pemoline and modafanil appear promising as safer stimulants for effective enhancement of performance during prolonged operations. Dr. Nicholson also proposes the ultra short-acting hypnotic agents as potential aids to brief napping to enhance performance.

The evolution of resistant strains of *Plamodium falciparum* and questions about the true incidence of side effects render mefloquine a prime candidate for immediate study.

The need to retain aircrew with mild to moderate hypertension, of which there are many, while protecting their future health leads us to urge the immediate study of angiotensin blocking agents, such as losartan.

Depression, anxiety disorders, and their treatment with selective serotonin/norepinephrine reuptake inhibitors are relatively common and, in many cases, the individual aircrew member does return to flying duties. The prolonged nature of the treatment, the need to retain trained aircrew, and the need to encourage identification of those in need of treatment all point to the importance of studying these medications immediately.

Dr. Pickard's description of a study protocol for evaluating the aeromedical suitability of losartan is an excellent example of the kind of road map that should guide such studies.

Working Group 26 Proposals

We believe the tables provide details on aeromedical usage of medication that has only previously been available anecdotally. Access to such information will be of significant value to NATO flight surgeons and the air forces they support. Not only will this information enable more expeditious policy changes about medication use in military aircrew, but it will help avoid duplication of research and encourage cooperative research between nations. Annual updates of this data and its continuing availability to NATO flight surgeons is essential to its utility. Our working group believes this data would best serve the mission as part of an official NATO publication subject to regular updates and expansion to include data from all NATO air forces.

We believe we have clearly established that our air forces and their aircrew require expansion of the range of medications known to be suitable for use in military aircrew. We believe we have also established that certain questions about aeromedical risk must be addressed before such expansion can occur. The primary constraints to expansion of available medications for military aircrew are funding and availability of particular types of aeromedical research capability. Our working group believes cooperative studies in which various nations contribute in their areas of research capability on a given medication would be most resource efficient and expedite the process considerably.

In particular, we believe consortia of NATO nations cooperating on the study of aeromedical questions pertaining to the medications we have identified for immediate study would be of great benefit. We strongly encourage prototype studies of some of these medications to demonstrate the feasibility and benefits of this cooperative international approach.

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14. Abstract

Working Group 26 evaluated issues pertaining to expanding the range of medications available for use in military aircrew. Working Group 26 completed its work under the auspices of the Human Factors and Medicine Panel of the NATO Research and Technology Agency. The group conducted a survey of medication use policies among NATO air forces and presents the data. The group also reviewed the current state of aeromedical issues for treatment of certain commonly encountered conditions in military aircrew. The working group also presents discussions of the general approaches to determining the suitability of medication for use in military aircrew for therapeutic indications and for operational indications. The ethics of such decisions in military aerospace medicine are also discussed. The best means for evaluating specific areas of aeromedical concern when studying medication are presented. Medications identified as candidates for immediate study for the benefit of military aircrew and their air forces are used for hypertension, lipid disorders, depression, anxiety disorders, malaria prevention, promotion of performance during prolonged sleepless periods, and promotion of sleep for short periods of time to support sustained operations. The working group provides recommendations to enhance knowledge between nations about aeromedical research on medications effects and aeromedical experience with medication. The group proposes use of cooperative research between nations to accelerate the process of answering questions about aeromedically significant side effects and expand the range of medications available for use in military aircrew.

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