Strategies to Improve Alertness during Extended Deployments

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ABSTRACT

During extended deployments there are a number of strategies available to increase alertness. The initial approach is to optimise work rest patterns and the tool being developed at QinetiQ will make this process simpler for commanders. The judicious use of naps is the second approach recommended. The choice of nap duration should take into account the problem of sleep inertia and allow sufficient time for recovery. Should these two approaches be insufficient then the use of drugs may be considered. Depending on the time available for sleep, hypnotics such as temazepam (for sleep periods of 6h or more) or zaleplon (for shorter sleep periods) have been shown to be effective, although particular care should be taken in the choice of hypnotic for females. As far as stimulants are concerned, none are currently approved for use in the UK military. Caffeine is effective and it may also lessen sleep inertia. Modafinil has a slower onset of activity and is long acting, although it may impair subsequent sleep. A handbook for commanders or medical officers on the use of these strategies could be a significant aid in the management of alertness during extended deployments.

1.0 INTRODUCTION

During extended deployments reduced alertness is an inevitable consequence of working for long periods that include duty overnight. Over a number of years QinetiQ has been involved in programmes for the Ministry of Defence and other customers investigating potential strategies to improve alertness. There is also a substantial body of work in this area from universities and military organisations in Europe, North America and Australia. There is, however, no real consensus on the relative merits of the various strategies or a road map to aid military commanders in their implementation. This conference is particularly apposite in this context as modern military operations may involve joint teams from different nations with the inevitable differences in the management of fatigue. A collaborative approach to this problem could maximise performance and reduce accidents and other incidents. In this paper we will outline interventions that we believe lead to improved alertness and also report progress in a programme to improve alertness by optimising military work patterns.

1.1 Hypnotics

The careful management of the timing and duration of work and rest periods may go some way to avoid performance decrements. However, after a few days it may be impossible to sustain sleep of acceptable quality. This may be due to a variety of reasons or to combinations of disturbing factors. For example, the time available for sleep may coincide with the peak in circadian alertness. Sleep may be disturbed by poor sleeping conditions, by environmental factors associated with the mission such as noise, heat, cold, uncomfortable posture, or by the overall stress and anxiety associated with the mission. In these circumstances the use of hypnotic drugs to aid sleep may be considered. Some individuals appear to be

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able to sleep well in almost any situation but others may be unable to gain any benefit from the time available for sleep. Adequate sleep is essential to the maintenance of alertness during continuous and sustained operations, and sleep-promoting substances or hypnotics have been used successfully in support of demanding scenarios extending over many weeks.

The majority of studies into the potential use of hypnotics in military operations have been carried out in research establishments or universities which have been supported by the military. This research not only tells us about the drugs considered by the military, but also the circumstances and scenarios for their administration. Hypnotics are used for critical sleep periods and some studies have combined a stimulant with a hypnotic.

1.1.1 Short acting hypnotics (temazepam and zolpidem)

Early studies on the efficacy and residual effects of hypnotics were carried out at one of the UK military establishments, which was partially subsumed into QinetiQ. A number of hypnotic drugs were studied and temazepam was selected as the drug of choice for aircrew. A rapidly-absorbed formulation at a dose of 10 or 20 mg has been shown to provide useful hypnotic activity without residual effects on performance or mood. It was also useful at inducing sleep during the day and for these reasons it has been used by both military and civil aircrew in the United Kingdom for the last 20 years. In particular it has been used in support of intensive air operations [1], [2].

The Royal Australian Army Medical Corps has also carried out studies on the effects of temazepam (20mg) in relation to travel across time zones [3]. They reported a beneficial effect on sleep and alertness after transmeridian travel without adverse effects on performance. However, the rate of adjustment to the new time zone was not increased. The Italian Air Force has also carried out studies on temazepam (20mg) in individuals who were subjected to a rapid shift of their sleep / wake cycle [4]. The drug was effective at inducing and maintaining sleep during the day and was not associated with any carry over effects.

Temazepam has therefore been proved to be a useful drug for those attempting to sleep at phases of the circadian cycle when sleep is difficult, and also under difficult environmental conditions. Unfortunately, in the United Kingdom at least, temazepam has become a drug of abuse, and for this reason its use is controlled. In spite of changes in formulation some abusers still use temazepam, and an alternative drug free of medico-legal constraints is desirable. In this context, zolpidem would appear to be a useful drug. Studies in the United Kingdom have shown that in male subjects it is free of residual effects on performance and is also effective at promoting and maintaining sleep during the day [5]. This has been confirmed by studies carried out in France into the residual effects of zolpidem (10mg) on daytime alertness in naval fighter pilots [6]. It was concluded that, in the absence of such effects, zolpidem could be considered for operational use.

On the other hand, other data suggest that zolpidem may have residual effects on performance after short sleep periods, at least in females. In our study of the use of 10mg zolpidem to ensure adequate sleep during an afternoon rest period, three out of nine female subjects were incapacitated 6h after ingestion and the other subjects showed performance decrements [7]. The use of zolpidem (10mg) to aid napping has been studied by the US Army Aeromedical Research Laboratory, Fort Rucker [8]. It was concluded that post nap impairments could compromise performance under operational conditions.

However, in a recent review of US military approved pharmacological countermeasures [9] it was suggested that zolpidem would be a better choice than temazepam for short sleep periods. Nevertheless, we would consider that temazepam is a suitable hypnotic even though its half-life is longer than that of zolpidem. It has a relatively short duration of action due to the decrease in plasma levels when the drug is distributed from the central to the peripheral compartment. However, in the formulation used in the US, temazepam is more slowly absorbed and therefore has a longer duration of action than the formulation used in the UK. Therefore, the choice of hypnotic also depends on the formulation available.

1.1.2 Ultra short-acting hypnotics (zaleplon)

Whereas benzodiazepines such as temazepam and related drugs such as zolpidem are suitable for use as sleep inducers in sustained and continuous operations, they are only suitable if at least six hours intervene between ingestion and the requirement to be alert. Further, as suggested above, a longer interval of time may be required if females were to use zolpidem. When periods shorter than 6 hours are available for sleep, drugs such as temazepam are not suitable as their use would be associated with impaired performance. Zaleplon (Sonata'®), is a pyrazolopyrimidine compound, unrelated to barbiturates, benzodiazepines and other hypnotic drugs, that binds selectively to the γ-aminobutyric acid $(GABA)_A$ receptor complex [10], [11]. It is rapidly absorbed, with peak plasma concentrations at around 1 hour, and rapidly eliminated, with a plasma elimination half-life of approximately 1 hour [12], [13]. Zaleplon therefore has a rapid onset of action and a rapid elimination half-life.

Zaleplon has been shown to have useful hypnotic effects in patients with insomnia [14], [15], [16], [17], [18], [19]. These effects have included reduction in sleep onset latency, unassociated with rebound insomnia on withdrawal or with any other withdrawal symptoms. In addition, no tolerance during therapy has been reported. Hence zaleplon can be used as a treatment for sleep onset insomnia or indeed for those with situational insomnia which manifests itself in problems falling asleep. In a study carried out in the United Kingdom, situational insomnia was induced in the middle of the night using a sound stimulus [20]. No residual effects of zaleplon (10 and 20 mg) were found on psychomotor performance, memory, or subjectively assessed sedation. On the other hand, the active control (zopiclone 7.5mg) impaired several measures of performance. Both doses of zaleplon reduced the latency to persistent sleep and the duration of stage 1 (drowsy) sleep was reduced by the 20 mg dose.

In the review by Caldwell and Caldwell [9], it was suggested that zaleplon may be the best choice for initiating very short naps. It has also been reported by a US team [21] that zaleplon improved the quality of a 3.5 h nap without adversely altering performance. However, we would suggest that at least 4h after ingestion is required for recovery from performance decrements, at least in females (Turner et al., unpublished data).

1.1.3 Melatonin

Melatonin is a naturally occurring substance with hypnotic properties that is secreted during the night. There have been a number of studies testing the activity of melatonin as an alternative to conventional hypnotics. Roth and Richardson [22] reviewed melatonin and emphasised that the majority of studies have evaluated only a single dose, or a limited dose range, and that there is a need for unambiguous information on its activity related to dose and to time of administration. Further, dose response data using electroencephalography are essential to an adequate understanding of its activity. Daytime ingestion of melatonin would appear to lead to reductions in sleep latencies [23], [24], [25], [26], but studies on its activity around the normal time of sleep have failed to establish a useful clinical effect, except possibly in elderly insomniacs[27], [28], [29].

It is in this context that we conducted a dose response study on the activity of melatonin when given in the early and late evening in healthy volunteers. The activity of melatonin was studied on nocturnal sleep (23:00-07:30) and on evening sleep (18:00-24:00), using electroencephalography, and was compared with temazepam (20 mg) [30].

No consistent effect of melatonin on nocturnal sleep across the dose range 0.1 to 10.0 mg was established. The only change observed was that 5 mg led to a reduction in stage 3 in the first 100 min of sleep. A reduction in stage 3 and 4 sleep with 5 mg melatonin has been reported previously in studies of a simulated 9h phase advance [31], but it is considered that the effect was small and has little, if any, clinical significance. In contrast, the active control, temazepam (20 mg), had beneficial effects on various sleep

parameters including reduced wakefulness and drowsy (stage 1) sleep and increased stage 2 sleep. On the other hand, we were able to establish an unequivocal effect of melatonin on early evening sleep across the dose range 0.5 to 10.0 mg. The effect was fully developed with the 0.5 mg dose, with no additional effect observed above this dose. Overall, the effect of melatonin was similar to that of 20 mg temazepam.

These studies suggest that melatonin is unlikely to possess useful hypnotic activity in healthy individuals when administered around the normal time of sleep, though the effect of melatonin on early evening as opposed to nocturnal sleep is comparable with that of a low dose of a benzodiazepine. Clearly, time of administration would appear to be a crucial factor in the appearance of the hypnotic activity of melatonin. In humans melatonin secretion occurs in the late evening [32]. It is, therefore, possible that in healthy young adults the limited hypnotic activity of melatonin is fully developed with the normal nocturnal endogenous secretion and that raising the plasma level of melatonin, at that time, by ingesting melatonin, may have little, if any, further effect. On the other hand, daytime doses, which raise plasma melatonin levels to within or beyond the normal nocturnal range, improve sleep [23], [24], [25], [26], [33], [34]. This response that varies with the time of day, together with the absence of a dose response over the range 0.5 to 10.0 mg, suggests that the effect of melatonin is fully developed at the natural endogenous plasma level.

The described study [31] has demonstrated that the hypnotic effect of melatonin is ineffective at certain times in the circadian cycle, and this, together with evidence that the ingestion of melatonin in certain circumstances may lead to sleep disruption [35], suggests that melatonin is only likely to be useful as a hypnotic at certain phases of the circadian cycle. It is not approved for use in the UK and has not been tested by UK forces, although it has been tested in Canadian Forces Air Transport operations supporting Canadian troops in Bosnia.

The first melatonin receptor agonist (ramelteon) has been approved for use by the US Federal Drug Administration as a treatment for insomnia and studies to determine its usefulness in a military context should be carried out before making recommendations.

Other drugs in development for the treatment of insomnia include compounds such as gaboxadol which enhance slow wave sleep and these should be also tested for use in military operations once they have been shown to be safe and effective in a clinical context.

2.1 Naps

Naps have been used to improve alertness in a number of contexts including during military operations. Provided that the environmental conditions are conducive to sleep, the quality of sleep taken as a nap is unlikely to be very different from that taken during the early part of a night [36]. However, other factors such as anxiety and apprehension can influence sleep quality. Apprehension, associated with being on-call, has been shown to reduce total sleep time, and reduce the amount of slow wave and rapid eye movement sleep [37]. There is likely to be anxiety induced by prolonged deployments.

Naps have a beneficial effect on performance and mood [36], [38], [39], and, after the use of careful scheduling, may be the most effective non-pharmacological countermeasure against fatigue. The performance benefits that may be gained from a nap will be dependent on several factors. These include the timing and duration of the nap and the length of the preceding period of sleep loss.

The main factor limiting the effectiveness of naps is Sleep Inertia (SI). SI is a transient period of impaired performance and alertness which occurs during the period after awakening and which may severely limit the individual's effectiveness and judgement if required to perform any duties immediately after waking.

Whilst much effort has been focused on this issue, it is still unclear how long SI may persist after waking and which factors are most important when determining its severity. It may be influenced by a number of

different factors including the amount of sleep loss prior to the nap, the time of day that the nap is taken, the depth of sleep and the duration of the nap.

In a recent study for the UK Civil Aviation Authority [40] we investigated the duration and extent both of any benefits conferred by a nap and of any performance impairments associated with sleep inertia. In this study, the nap was scheduled between 01:45 and 03:00, corresponding to a time of increased sleepiness on the circadian clock. Subjects reported to the sleep laboratory on 6 separate nights. On one night they remained awake throughout, while on the other nights they were allowed to sleep for 10, 20, 30, 40 or 60 minutes, in each case waking up at approximately 03:00. On average, subjects reached stage 2 sleep, after 15 minutes. In all napping conditions, they achieved some slow-wave sleep (SWS), which is thought to be associated with higher levels of sleep inertia. Amounts of SWS varied from less than a minute in a 10-minute nap to over 12 minutes in a 60-minute nap.

Some effects of sleep inertia were evident even after a 10-minute nap, but these were limited to the subjective assessments of fatigue and sleepiness. Performance decrements were only present after a nap of 30 minutes or longer. Two minutes after the end of a 60-minute nap, reaction times were increased by over 8% compared with the pre-nap value, to a level not reached for another 2.5 hours in the no-nap condition. There were significant long-term improvements in both performance and the subjective assessments of fatigue and sleepiness after naps lasting for 40 or 60 minutes.

From the results of this study it appears that major long-term benefits from napping cannot be achieved without a significant amount of sleep inertia lasting for a period of about 30 minutes immediately after waking. It may be that the sleep inertia is a price that has to be paid for the benefits, in terms of improved levels of alertness.

In these circumstances, a balance has to be struck between the long-term benefits and the risks associated with the removal of an individual from active duty for a significant period.

3.1 Compounds that enhance alertness

We have carried out a number of studies of stimulants including pemoline (now withdrawn), caffeine and modafinil. There are currently no stimulant drugs approved for use in the UK military and as far as we are aware they have not been used since World War II when amphetamine was used. In the US there has been a substantial programme investigating alertness-improving compounds and this has led to the use of amphetamines in operational scenarios.

In one of our studies we investigated the dose-related effects of modafinil on overnight performance from19:00 to 08:45 and recovery sleep from 09:15h to 15:15h in healthy subjects in a placebo controlled study with caffeine (300mg) as an active control. Modafinil ameliorated the circadian decrements in performance observed with placebo in a dose-dependent manner. With 100 mg modafinil performance was improved on two tasks. The 200, 300 and 400 mg doses improved performance on all tasks except choice reaction time, on which only 400 mg modafinil had a beneficial effect. Effects of the two highest doses were observed from around midnight onwards, while the activity of 100 and 200 mg was most apparent from 05:30h. Caffeine (300 mg) improved performance on digit and letter memory recall tasks, mathematical processing and all components of the MAT battery except tracking. Recovery sleep duration and efficiency were reduced by 300 and 400 mg modafinil, and the 400 mg dose also reduced rapid eye movement sleep. A dose of 200 mg improved performance overnight without adversely affecting recovery sleep the following morning. The study concluded that higher doses of the drug (300 and 400 mg) have an earlier onset and more prolonged duration of activity.

In another study in collaboration with the University of Surrey [41] we investigated the effects of caffeine on sleep inertia. In view of the relatively rapid onset of activity of caffeine we tested whether caffeine

given immediately upon awakening would overcome, or at least, truncate sleep inertia. Twelve normal healthy subjects were studied. At 02:00h they had a one hour nap, they were woken at 03:00h by gentle shaking and the bed backs raised to support a sitting position and, three minutes later, they undertook their first performance session. Performance sessions commenced at 03:03h; 03:10h; 03:17h; 03:30h and then every 15 minutes until 09:00h. The four treatment conditions were 300mg caffeine taken on waking and 10mins of broad spectrum white light (10,000lux) 03:00-03:10h, caffeine and no bright light pulse (dim light), placebo and bright light, placebo and dim light.

Performance/alertness during the first half-hour (03:00-03:30h), first hour (03:00-04:00h) and 6 hour (03:00-09:00h) periods following treatment was analysed. Caffeine improved subjective ratings of alertness compared to placebo during the first half-hour after treatment, suggesting that it is useful to counteract sleep inertia. Caffeine also improved all performance/alertness measures compared to placebo during the six hours after treatment.

4.1 Optimisation of work patterns in military operations

A current programme at QinetiQ is leading to the development of a tool to optimise work patterns in military operations. The core element of the programme is the Centre for Human Sciences (CHS) Alertness Model [42]. This model, in its original form, was based on the results of a series of experimental studies of irregular patterns of work and rest [43], [44]. Since then, we have undertaken further development and various validation studies (e.g. [45]) so that the Model can be used in various civil applications. It forms the basis of a Fatigue Index, which was developed for the Health and Safety Executive [46] and is currently being updated, and of a computer program known as SAFE (System for Aircrew Fatigue Evaluation) that has been developed with the UK Civil Aviation Authority [47].

The purpose of the model is to provide an estimate of the level of alertness associated with any particular pattern of work and rest. It does not, at present, allow for differences between individuals. It provides an overall assessment of the impact of a duty schedule on a typical individual. As one of seven models that have been developed worldwide, it was presented at a recent modelling workshop held in the USA [48]. Like several of these models, it is based on a two- or three-process approach founded on the work of Daan *et al* [49]. However, the CHS model has a particular advantage since, although it was originally developed from laboratory-based trials, it has been applied and validated in a wide range of practical situations.

The aim of the new programme is to exploit the Alertness Model in a military environment by generating patterns of work that are the least fatiguing. The end product will be a computer-based device that can be used to provide guidance to those planning operations or to design duty rosters on the effective use of the manpower available.

The work completed to date has been mainly concerned with the identification of the main areas of applicability. This has involved discussions with interested parties to establish the range of factors that should be included in the prototype and there are clear areas of application in all three areas. There is particular interest in a tool that can be used in operational planning.

An initial version of the prototype device is being developed based on information relating to one particular operation. It will address the following issues:

- optimisation of the alertness of crews over a 30-day period;
- specified numbers of resources (vehicles, aircraft) and crews;
- allocation of crews to duty (at different levels of priority) and off-duty periods;
- work demands varying with time of day and/or time through the operation;
- work demands defined by fixed or random distributions.

To enhance its flexibility, the initial version will be generic and elements specific to a particular operation will be configured as optional features.

Summary

During extended deployments there are a number of strategies available to increase alertness. The initial approach is to optimise work rest patterns and the tool being developed at QinetiQ will make this process simpler for commanders. The judicious use of naps is the second approach recommended. The choice of nap duration should take into account the problem of sleep inertia and allow sufficient time for recovery. Should these two approaches be insufficient then the use of drugs may be considered. Depending on the time available for sleep, hypnotics such as temazepam (for sleep periods of 6h or more) or zaleplon (for shorter sleep periods) have been shown to be effective, although particular care should be taken in the choice of hypnotic for females. As far as stimulants are concerned, none are currently approved for use in the UK military. Caffeine is effective and it may also lessen sleep inertia. Modafinil has a slower onset of activity and is long acting, although it may impair subsequent sleep. A handbook for commanders or medical officers on the use of these strategies could be a significant aid in the management of alertness during extended deployments.

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