

**EVALUATING CREW PERFORMANCE AFTER ANTI-EMETICS:
A SCREEN FOR ASSESSING MILITARILY RELEVANT MEDICATIONS**

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SUMMARY

Prophylactic, pharmaceutical countermeasures hold the potential to protect aircrew from a wide variety of threats during contingency operations, ranging from fatigue to radiation exposure. In order to assess the impact of these potential countermeasures on cognitive abilities, a 2-phase drug screen was developed. A battery of cognitive, affective and physiological measures was utilized in Phase I of testing to rapidly evaluate the performance liability of militarily relevant compounds. The carefully controlled Phase I lab study incorporated diurnal and nocturnal performance trials to assess potential drug interactions with circadian and sleep deprivation effects. During Phase II, flight performance was tested in a high fidelity aircraft simulator using embedded operational tasks, expert evaluation and subjective metrics. The Phase I screen evaluated two novel anti-emetic compounds, granisetron (2 mg) and ondansetron (8 mg), compared to placebo and a positive control, prochlorperizine (10 mg), in a double blind, crossover study of 24 subjects. Performance was assessed hourly from 1800 until 0200. All Phase I metrics were degraded during nocturnal performance trials for all drug conditions, presumably due to circadian and sleep deprivation effects. The positive control was identified by the divided attention task in terms of accuracy ($p < 0.05$) and reaction time ($p < 0.05$) and by the mean lambda for the tracking task ($p < 0.05$), but only during a time when blood levels of prochlorperizine were elevated. None of the affective state questionnaires were able to identify the positive control, suggesting that the dose was low enough that the participants were unable to discern it. None of the target anti-emetic compounds differed from placebo suggesting that they were not likely to affect sensitive performance. Phase II also revealed no differences between target anti-emetic compounds and placebo in any of the segments of an F-16 defensive counter-air mission flown by 9 pilots. Based on these tests, the target compounds were considered safe to use prophylactically, with respect to cognitive ability, for crews in danger of radiation exposure. The utility of the drug screen as a rapid and thorough means to assess the cognitive impact of militarily relevant compounds was established.

1 INTRODUCTION

There are many pharmaceutical agents of interest to the armed forces because they may improve human effectiveness during physiological stress imposed from a range of threats like hazardous environments or during long duty days. For example, compounds such as anti-malarials or anti-histamines or anti-nerve agents are important for symptomatic treatment and as prophylactics against entities that might degrade military preparedness. There are other classes of compounds that can extend the range of human effectiveness for short durations such as the stimulants and sedatives. Often these drugs are approved for field use purely on the basis of their clinical profile. However, pharmaceutical houses are not equipped to study the compounds in militarily relevant settings. For example, it is rare that a new compound will be tested throughout the nycthemeron, thereby ignoring any chronopharmacodynamic effects (1). It is conceivable that compounds may not have any deleterious effects in normal populations but during

acceleration or at high altitude, such effects might be present. The Sustained Operations Branch at Brooks Air Force Base was interested in developing a series of drug screens for militarily relevant compounds that would test for potential chronopharmacological cognitive effects using aeromedically relevant tests. Protocols for phased testing of compounds were established. In addition to a standard series of computer generated cognitive tests developed by the US military (2), if warranted, a compound of interest could be tested for performance effects during high Gz acceleration, hypobaric and hyperbaric altitude chambers as well as in a series of high fidelity flight simulators, ranging from long duration bombers to combat sorties in fighter aircraft.

The opportunity to test militarily relevant compounds came about at the request of NATO Project Group 29. They were interested in discovering any cognitive performance effects from two novel anti-emetic drug that might be useful as prophylaxis against radiation induced emesis for military as well as emergency personnel. The two compounds of interest

were granisetron (Kytril; Smith-Kline Company) and ondansetron (Zofran; Glaxo-Wellcome Company), both selective serotonergic antagonists (3,4). Both granisetron (GSN) and ondansetron (ODN) were considered to have similar clinical profiles (5) and since both were being considered for NATO use, both were transitioned through two phases of the drug screen. Both drugs have about a 5-hour plasma half-life availability. In Phase I, a carefully controlled laboratory study was conducted that incorporated chronopharmacological testing for cognitive effects, mood effects and physiological effects (see Table 1). In Phase II, complex cognitive effects associated with a high fidelity fighter aircraft simulated mission were tested. The fighter aircraft mission was selected because it was considered most similar to a NATO-type scenario for these compounds. No other screening phases available, such as spatial disorientation, acceleration or altitude effects were considered essential since no indication in the literature suggested such effects.

Since no cognitive effects had ever been reported for these compounds already in use clinically, the need for a positive control was critical to demonstrate that if the target compounds had an effect on cognition or mood, the screens would discern it. Prochlorperazine (Compazine; Smith-Kline Company) was selected because it met three criteria for an appropriate positive control to determine if the tests would be sensitive enough to ascertain an effect if one were there. First, prochlorperazine (PRP) has a similar mechanism of action to the 5-HT anti-emetics (6). Although it is primarily active at dopaminergic sites, prochlorperazine can influence 5-HT₃ receptor sites. Indeed, the effectiveness of dopaminergic compounds, such as prochlorperazine, as anti-emetics may relate to their effectiveness as 5-HT₃ antagonists. Second, PRP is also used for the same purpose medically as the target drugs, an established anti-emetic (7). Finally, as a major tranquilizer (8), although at higher doses than used for anti-emesis, PRP was expected to produce an effect on the cognitive and mood tests.

The purpose of Phase I of the experiment was to establish the impact on cognition, mood and physiology of the target compounds, GSN and ODN. No effects were expected. Additionally, the positive control, PRP, was expected to have an impact on the test batteries. The purpose of Phase II was to demonstrate the absence of an effect in a complex cognitive task associated with an operationally relevant fighter aircraft simulator mission.

2 METHODS

All tests in both phases of the experiment were double blind to dose condition and a utilized repeated measures design. Dose administration was counter-balanced using a modified latin square to control for order effects. All doses were orally administered at the manufacturer's recommended anti-

emetic dose; GSN (2 mg), ODN (8 mg) and PRP (10 mg).

PHASE I

Training and testing occurred in a large performance habitat (Lt 54.7 ft x Wt 8.6 ft x Ht 10.1 ft) that was configured to test 8 subjects at a time in individual computer stations in sound attenuated booths at the performance end of the habitat. A complete phlebotomy facility was at the opposite end of the habitat. Lighting was kept to below 100 lux in the performance section. Subjects were assigned to individual computers for the duration of the study. The subjects were 24 active duty military personnel (20 males, 4 females; 19 enlisted, 5 officers) between 19-31 years old and 125-210 pounds. All had recently passed a standard military physical. They were financially reimbursed for their participation. The requirements of the study minimized social interactions.

Each group of 8 subjects was tested over 1 week in 4 exposures with one evening for each of the 4 drug conditions followed by a 40 hour drug washout period. Each subject got either a test compounds (GSN, ODN, PRP) or placebo during each of the exposures sessions. During the week before the first drug exposure, all subjects were trained on the cognitive tasks for 2 hours every day after work at 1700 hours for 4 consecutive days before testing began. This allowed for 4 cycles of the 12-minute cognitive test battery and 3 cycles of a complex cognitive task (Table 1) daily. On each exposure session, subjects reported to the testing facility at 1700. Pre-dose symptoms were assessed by a survey and compared to a post dose symptom survey administered 2 hours after dosing to isolate drug effects from pre-existing symptoms. Symptoms for all drugs were compiled from the Physicians Desk Reference (1995) and included in a pre and post mission symptom survey.

The test batteries in Phase I required about 55 minutes to complete the cognitive and physiological tests. Blood samples were taken every hour beginning at 1940 until 2140 and then again at 0140. Profile of Mood Surveys (POMS) were given every hour through first 4 hours and again during the 8th hour.

The grammatical reasoning, continuous recognition, pattern recognition (matrix) and critical tracking test required 2 minutes each to complete. Continuous recognition and matrix were used to test short term memory function. Critical tracking is a psychomotor skills test. These were taken from a standard test battery developed for tri-service use (9).

The attention switching test was developed separately and measured dual processing task skills (10). The dual tests consisted of the maniken test of spatial recognition and an addition test and the display screen for this representative test is shown in Figure 1. This test was the most affected by the

positive control and is shown as an example of the cognitive test battery screens. The maniken test is on the left hand side of the figure. It stands on a pedestal with the target object, and facing away or towards the viewer or right side up oriented towards or away from the viewer. The math tests consists of the addition problem shown on the right of the figure. If the numbers add to more than 5 one key is touched, if less than 5, another key is touched. The small icon in the bottom center of the figure instructs the subject to do either the maniken or the math test. In this figure, it is pointing to the maniken test. The attention switching test required 4 minutes to complete and a new screen was put forward after every subject input or would time out after a few seconds if no keys were pressed. For all of the cognitive tests, three measures were extracted; response time, overall accuracy and throughput (responses per minute). The Defensive Systems Officer (DSO) analog task was intended to represent the decision skills required of a DSO on a B-1B bomber and required 20 minutes. The results of this task are still being considered.

The tracking test was also sensitive to PRP and consisted of a computer mouse controlled cursor which would attempt to

either a ball or a rectangle; in this case a rectangle. The subject must decide in which hand the maniken figure holds the target symbol. The maniken can be oriented upside down move from the vicinity of the center of the screen to the right or left borders. The speed with which it would move was not set and would increase in speed as the subject improved. Thus, the test got more and more difficult within each 2 minute test trial.

The critical flicker fusion test is considered a measure of visual information processing that is reported to be sensitive to fatigue. This test consisted of adjusting a knob on a binocular viewing visor until a flashing light stopped flashing. It was administered three times and generally took about 2 minutes to complete. Oral temperatures were collected every hour and recorded on log sheets along with a School of Aerospace Medicine (SAM) fatigue score. This procedure required about 2 minutes. The POMS is a standard survey for assessing drug effects and took about 3 minutes to complete. Finally, Air Traffic Control (TRACON) commercially available software was used to complete the remainder of each hour. Previous experience with these tests indicated that fatigue effects should be seen.

Performance Switching Task-Manikin and Mathematical Processing:

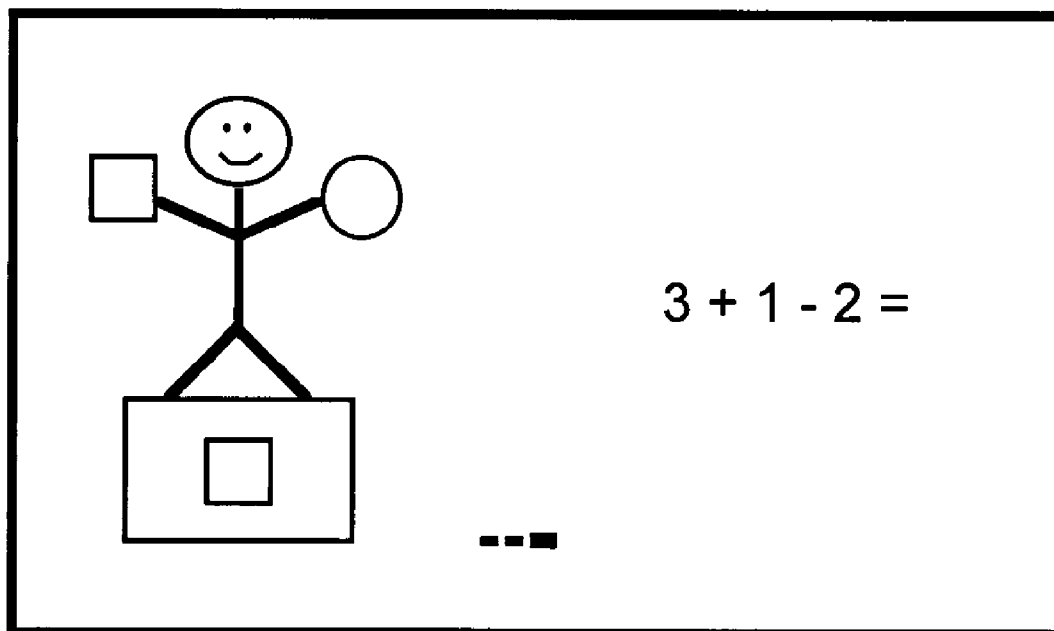


Figure 1. The computer screen from one of the tests, a divided attention task called Switching, used in the Phase I tests. See text for details.

The tests were conducted from 1800-0200 to determine if sleep deprivation induced fatigue might enhance any

cognitive impairment produced by the drugs. By comparing early evening results with early morning results, any chronopharmacological effects of the drug might be

ascertained. Phase I was conducted from November 1994 – March 1995

Table 1. Cognitive, mood, symptom and physiological assessment techniques used in the Phase I laboratory study.		
<u>COGNITIVE</u>	<u>PHYSIOLOGICAL</u>	<u>MOOD and SYMPTOMS</u>
Grammatical Reasoning	Critical Flicker Fusion	Profile of Mood
Continuous Recognition	Serum Samples	Pre-test symptoms
Pattern Recognition	Oral Temperature	Post dose symptoms
Attention Switching		SAM fatigue
Critical Tracking		
<u>COMPLEX COGNITIVE</u>	<u>OTHER</u>	
TRACON	Actigraphy pre and post test sleep	
DSO Analog	Sleep survey pre and post test nights	

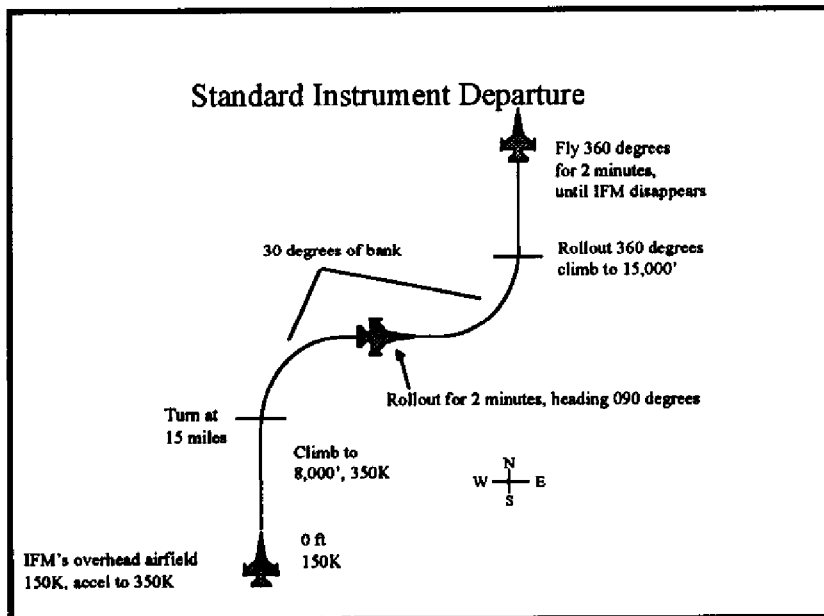


Figure 2. Flight requirements for one of the embedded tasks in Phase II of the screen. See text for details.

PHASE II

A total of 9 active duty US Air Force Reserve pilots, participated in groups of two, one flying lead and one wingman, during August - September 1995. A simulator operator assisted as wingman but did not receive any drug during one week when only one pilot was available. The high fidelity F-16 simulator facilities at Williams-Gateway airport were used. No positive control was used since results were

clearly seen in Phase I and it was considered unlikely that F-16 crews would take prochlorperazine while flying.

The pilots arrived on Monday and were given an orientation flight on the simulator and the conditions of the test between 0900 and 1100. The first mission/dose condition was given in the early afternoon. Day 2 was a drug washout day. Mission 2 was conducted on the third day afternoon and day 4

was a drug washout day. The last mission was given on the afternoon of Day 5. Pilots were given either GSN, ODN or placebo during each of the missions. All doses were given 2 hours pre-mission. Prior to each mission the crews were given pre-mission symptom surveys. Immediately after each mission, crews were given POMS and a post mission symptom questionnaire identical to that used in Phase I.

All missions were identical. The two-plane formation took off singly and followed an intelligent flight model according

to the design shown in Figure 2. Deviations from expected altitude, heading and airspeed as well as expert evaluations from the sim operators were used to assess the results of each drug/mission combination. A tactical scenario provided the combat engagement phase of the mission. An air-refueling task, shown in Figure 3, was also used to assess piloting skills. Finally, the crews proceeded to an Instrument Landing System (ILS) approach for touchdown after the mission according to the diagram. The entire mission lasted about 1 hour.

Table 2. Complex performance assessment techniques used in Phase II F-16 simulator study

Flight following during take-off, instrument landing system approach to landing,
Metrics : Heading, altitude, airspeed at critical stages of flight; RMS error

COMBAT ENGAGEMENT

Number of kills
Wingman protection

AIR REFUELING

Amount of gas received
Time on boom
Number of disconnects

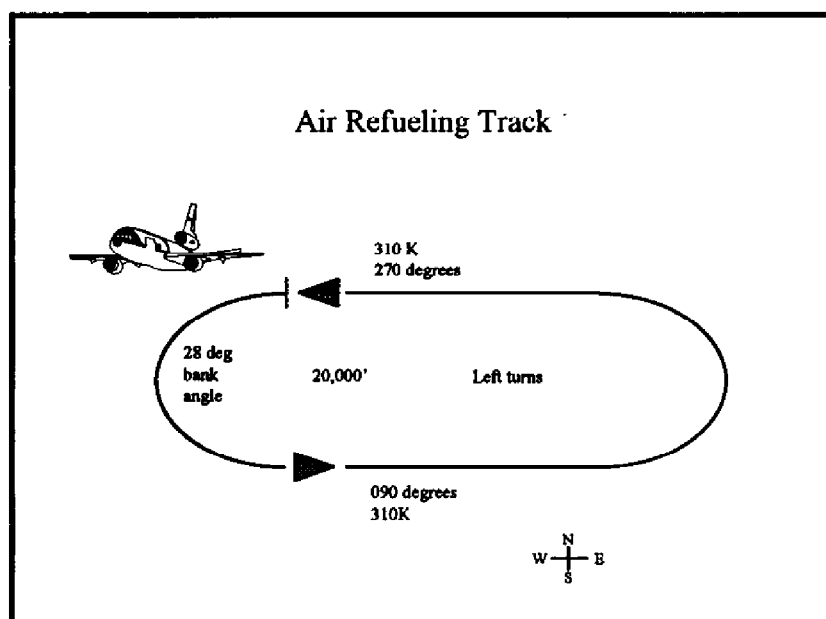


Figure 3. One of the embedded tasks required of Phase II subjects in the screen. See text for details.

3 RESULTS

None of the tests registered any performance or mood degradation as a result of the target drugs. Both the laboratory study in Phase I results and the flight performance results from Phase II agreed that the target compounds were free of debilitating side effects. No chronopharmacological effects of the target compounds were found and no compounding of normal fatigue effects on these tests were noticed. Either of the target compounds, based on these tests, could be used prophylactically as a counter measure to radiation induced emesis. In contrast, Phase I tests revealed that the positive control drug, PRP, was identified by 2 of the 5 cognitive tests and 7 of the 23 possible dependent measures.

All of the cognitive tests demonstrated a fatigue effect in that performance declined in the last half of the test session compared to the first half for 21 of the 23 dependent measures.

Phase I

Two examples are shown in the figures to follow, from the two tests that were the most sensitive to the positive control; Switching and Tracking. In Figure 4, the average throughput score for the maniken section of the Switching test is shown. Figure 5 is the average throughput score for the math section of this divided attention task.

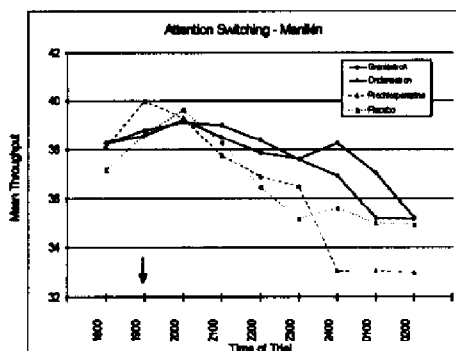


Figure 4. Correct responses / minute (throughput) Manikin test (Prochlorperazine (p<0.05))

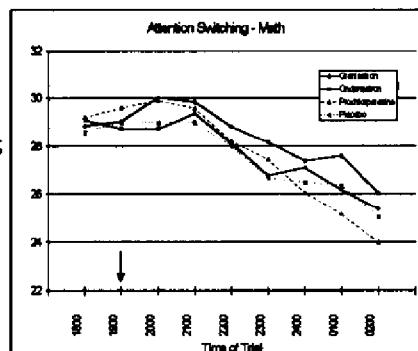


Figure 5. Correct responses / minute (throughput) for math test (Prochlorperazine (p<0.05))

The maximum lambda score is shown in Figure 6 for the tracking test. This was the highest lambda score achieved by each subject in a session. PRP degraded performance in a drug x trial interaction effect (p<0.05) for all of these effects. The subjects were able to identify when they had received the positive control drug at only chance levels. The complete results from Phase I of this study are available for review elsewhere (11).

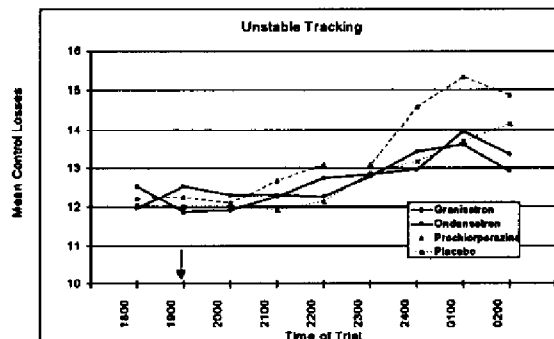


Figure 6. The number of control losses in the tracking test (Prochlorperazine p<0.05)

Phase II

No significant differences were found for either target drug

compared to placebo on any of the flying performance nor mood (POMS) measures. Neither could the expert evaluation of the crew's performance ascertain any target drug effects. Similarly, crews could not identify when they received target drug or placebo. Finally, there were no drug-related symptoms evident. The complete results of Phase II of this study are available for review elsewhere. (12)

Table 3. Summary of key results in Phase II screen with anti-emetic compounds.

No significant differences between the target drugs and placebo on any of the 7 objective

- flying performance measures.
- No differences in flight instructor evaluations
- No differences based on POMS results
- Pilots could not distinguish active drug from placebo
- No obvious drug related symptoms or side effects.

4 DISCUSSION

There were no effects of the target drugs on any of the tests used in both Phases of the experiment. This means that operational field tests might be the next place for these compounds to be tested in a Phase III study. The lack of effects for the target drugs is compared to the significant degradation produced by the positive control in Phase I. The fact that no one was able to discern the prochlorperazine suggests that the correct dose was used to demonstrate that some of the tests were sensitive to the tranquilizer/anti-emetic but the dose was not too high.

There is a need to test compounds beyond clinical efficacy for the extreme conditions in which they will be used in the aerospace environment. Many drugs were not studied under operational conditions but have been introduced into the operational military setting; amphetamines and Angiotensin Converting Enzyme (ACE) inhibitors like lisinopril are examples. Some times drugs are not studied thoroughly enough and admitted immediately into field operations because of expediency. Finally, compounds are not often tested at various times of day and night to determine if there is a chronopharmacological difference in their uptake and metabolism.

A drug screen is described which progresses from laboratory to operationally relevant simulator metrics. Two novel anti-emetic compounds, a positive control, and placebo were the first compounds tested in the laboratory screen. A second phase was used to assess operational questions about the two novel anti-emetic compounds and placebo. Other Phases could have been implemented if there were indications that

the compound would be affected by altitude or acceleration. Positive controls in the Phase I paradigm should, if possible, meet three criteria: have a similar mechanism of action to the target compounds, have similar medical uses and should be likely to produce an effect.

5 REFERENCES

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