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Summary

Intramuscular (i.m.) injections of promethazine in 25 mg or 50 mg dosages are commonly used to treat space motion sickness in astronauts. The present study examined the effects of i.m. injections of promethazine on neuropsychological performance, mood states, and motion sickness tolerance in humans. Twelve men, mean age 36 ± 3.1, participated in one training (no injections) and three treatment conditions: a 25 mg injection of promethazine, a 50 mg injection of promethazine, and a placebo injection of sterile saline. Each condition, spaced at 7 day intervals, required an 8–10 hr session in which subjects were given four repetitions of 12 performance tasks, and one rotating chair motion sickness test. On the training day subjects were trained on each task to establish stability and proficiency. On treatment days, the order in which the drug or placebo was assigned to subjects was counterbalanced and a double-blind technique was used. Statistically significant decrements in performance were observed on 10 of 12 tasks when subjects were given 25 mg or 50 mg of promethazine as compared to the placebo. Performance decrements were associated with mean blood alcohol dose equivalency levels of 0.085% for 25 mg and 0.137% for 50 mg dosages. The mood scale results showed significant changes in individual subjective experiences with maximum deterioration in the arousal state and fatigue level. When compared to placebo significant increases in motion sickness tolerance were found for both dosages of promethazine. These data suggest that effective dosages of promethazine currently used to counteract motion sickness in astronauts may significantly impair task components of their operational performance.

Introduction

The consequences of spaceflight are both physiological and psychological and may lead to operationally significant medical and behavioral problems. In recent years, the drug promethazine has been administered to crew members early in the space mission as a prophylactic treatment for space motion sickness. Concern that anti-motion sickness medications cause side effects that impair operational performance has provided impetus to study drug effects on both human physiology and performance.

Observations that intramuscular (i.m.) injections of promethazine are effective in attenuating motion sickness have been evaluated during both ground-based and space studies. I.m. injections of promethazine were first used during a shuttle flight in March 1989 and have been used on 14 other occasions since (ref. 1). Promethazine and its efficacy in the treatment of space motion sickness were evaluated using standardized questions administered during post flight debriefings. Results showed that 25% of crewmembers treated with i.m. injections of promethazine were "sick" on flight day 2, compared to 50% of crew members who did not receive promethazine (ref. 1). The efficacy of i.m. injections of promethazine as a countermeasure for motion sickness was also evaluated on subjects who experienced symptoms during parabolic flight. Within 10 min of 50 mg i.m. injection of promethazine, 78% of individuals experienced symptom relief, whereas 25 mg of promethazine was not effective (ref. 2). I.m. injections (25 mg) of promethazine increased motion sickness tolerance by 78% during exposure to cross-coupled angular accelerations (ref. 3). In the latter study, i.m. injections were administered 30 min before a rotating chair test, and the criterion for improvements was the number of head movements subjects could tolerate as compared to the number of head movements when they received a placebo.

The Physician's Desk Reference (1995, p. 2711) cautions under Information for Patients that ". . . Phenergran (promethazine) may cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery." Ground-based studies have shown that significant decrements in performance scores, psychomotor function, information processing, and alertness may occur with both oral and

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i.m. injections of promethazine. For an oral dose of promethazine (12.5 mg and 25 mg), maximal effects may be seen on information processing and psychomotor performance tested at 2 hr intervals, within 3–4 hr after ingestion, with a return to baseline after 8–9 hr (ref. 4). In another study, impaired dynamic tracking performance and reduced ability to maintain visual fixation were observed following oral ingestion of 25 mg of promethazine (ref. 5).

The assessment of performance in space on small samples of subjects necessitates the use of within-subjects, repeated-measures designs. The time restrictions also require the use of performance measures that demonstrate rapid stability and reproducibility for brief testing periods. The Automated Performance Test System (APTS) is an assessment tool for human performance and cognition (ref. 6). The APTS was developed with emphasis on within-subjects, repeated-measures designs, and has been proven both reliable and valid in a number of investigations; administration of the APTS takes approximately 15 min (refs. 7–11).

Jeanneret (ref. 12) reported that a high percentage of attributes associated with successful job performance in various NASA mission specialist tasks are measured by the APTS. Six key cognitive abilities were identified by this study that are required of individuals performing any of the 14 mission specialty functions. These are: (1) intelligence; (2) verbal comprehension; (3) numerical computation; (4) arithmetic reasoning; (5) convergent thinking; and (6) short term memory. Three perceptual aptitudes were found to be the most essential requirements across mission specialty functions: (1) spatial visualization; (2) visual form perception; and (3) perceptual speed. There were two psychomotor abilities found to be especially important job requirements: (1) eye-hand coordination and (2) simple reaction time.

The APTS has been used extensively to study the effects of environmental and chemical stressors on human performance. These include hypobaric hypoxia (ref. 13), 30 days of bed rest (ref. 14), head-down tilt (ref. 15), scopolamine and amphetamine (ref. 10), promethazine, blood alcohol content (ref. 13), sleep deprivation (ref. 16), and a variety of other conditions (ref. 17). In addition, performance on APTS tests are predictive of performances in a flight simulator, and on tank gunnery simulators (ref. 18). The results of all of these studies are concordant in that the APTS is a sensitive metric for detecting changes in performance.

Jeanneret (ref. 12) demonstrated that one psychomotor skill which was most important to the job requirements of astronauts was "eye-hand coordination." This skill is reliably tested by pursuit tracking tasks , i.e., vigilant observation of a moving visual target with coordinated hand-movements. During typical tracking tasks, the subject is required to maintain contact with the target using a hand-held stylus, hence directly testing "eye-hand coordination." The APTS version used in this study contained the Air Combat Maneuver (ACM) tracking task. However, in an early study by Kennedy (ref. 13), it was shown that mean performance on this task failed to stabilize on 10 trials.

Because the ACM task was not reliable, a critical tracking task (CTT) was used in the present study. The CTT was developed as a simple method of evaluating a subject's eye-hand-coordination or manual control ability (ref. 19). It has been used extensively as a means of evaluating the effects of alcohol and/or drugs on a person's skill in performing a manual task (refs. 20 and 21). Since the 1950s the CTT has been used by the U.S. Air Force to investigate pilot's abilities to perform inflight (refs. 22 and 23). NASA has used this test to assess the impact of environmental stressors (e.g., isolation and noise-levels) on an astronaut's ability to carry out mission duties (ref. 24) and the U.S. Navy has used it to study the effects of rough water operations on crew performance (ref. 25).

Lastly, a mood and sleep quality scale (ref. 14) was included in this study as a means of assessing some of the side effects of promethazine on mood state changes in arousal, fatigue, concentration, psychological tension, and physical discomfort. This scale provides fast and reliable mood assessment (ref. 26), with a high degree of mood state resolution and less chance of subject non-compliance, response stereotyping or remembered responses (ref. 27). The test included eight mood scales, two sleep questions extracted from the St. Mary's sleep questionnaire (ref. 28) to document sleep latency and disturbance, and a self-rated estimate of overall change in performance proficiency between tests.

The general aim of the present study was to examine the effects of promethazine on motion sickness tolerance, performance and subjective mood states. The specific objectives were: (1) to determine if promethazine, given in both 25 and 50 mg fixed dosages, increases motion sickness tolerance; (2) to determine if performance decrements are greater with the higher dosage of promethazine; and (3) to determine if performance decrements found during both drug treatment conditions are associated with specific changes in mood states (e.g., decreased arousal or motivation).

Methods

Subjects

Twelve men, mean age 36 ± 3.1 (ranging between 30 and 40 years old), weighing between 68 and 82 kg, and who were right-handed, participated in this study. All subjects were certified to be in good physical health by a medical examination, and had no history of cardio-pulmonary disease nor requirement for chronic medication. As part of the medical examination, all subjects were screened for HIV. Their voluntary participation was solicited after all procedures and risks associated with experiment had been explained to them, and they were informed of the requirement that they refrain from using medications (e.g., antihistamines for colds or allergies) during the course of the study. The research was reviewed and approved by the NASA Ames Research Center Human Research Evaluation Review Board.

Experimental Protocol

Each subject participated in one training condition (no injection) and three treatment conditions: a 25 mg i.m. injection of promethazine, a 50 mg i.m. injection of promethazine, and a placebo i.m. injection of sterile saline. Each condition, spaced at 7 day intervals, required an 8–10 hr session in which subjects were given four repetitions of 12 performance tasks, and one rotating chair motion sickness test. The order in which the drug or placebo was assigned to subjects was counterbalanced and a double-blind procedure was used to administer the injections. The promethazine used in this study was manufactured by Wyeth-Ayerst Laboratories. The duration of action of injectable promethazine is generally between 4 and 6 hr.

Table 1 shows the test schedule used during the training and treatment days of this study. On the first day, the training condition, subjects were given four repetitions of CTT and SMD tasks, five repetitions of the APTS task, and a motion sickness test. Each task was repeated once more following the motion sickness test. Blood and saliva samples were collected before drug or placebo injections and at 15 min, 30 min, 1 hr, 2 hr, and 4 hr post-injection. Samples were also collected following motion sickness tests. On treatment days, following a baseline of each performance task, subjects were given an i.m. injection of promethazine (25 mg or 50 mg) or a placebo injection. Each performance task was repeated twice before the motion sickness test and once following the test.

Table 1. Subject test schedule for training and treatment days

time	training day 1	treatment days 2, 3, 4
7:45	baseline blood and saliva	baseline blood and saliva
8:00	APTS	APTS
8:15	CTT	CTT
8:30	SMD	SMD
8:45	no injection	injection
9:00	15 min blood and saliva	15 min blood and saliva
9:15	30 min blood and saliva	30 min blood and saliva
9:30	APTS	APTS
9:45	1 hr blood and saliva	1 hr blood and saliva
10:00	SMD and CTT	SMD and CTT
10:15	APTS	
10:45	2 hr blood and saliva	2 hr blood and saliva
11:00	lunch	lunch
11:45	APTS	
12:00	SMD and CTT	
12:15	APTS	APTS
12:30	CTT and SMD	CTT and SMD
12:45	4 hr blood and saliva	4 hr blood and saliva
1:15	motion sickness test	motion sickness test
2:00	post-test blood and saliva	post-test blood and saliva
2:45	APTS	APTS
3:00	CTT	CTT
3:15	SMD	SMD

Motion Sickness Test

The initial symptoms of motion sickness were induced in subjects using clockwise rotating chair tests (i.e., cross-coupled angular acceleration). Tests were conducted in a Stille-Werner rotating chair located in a sound attenuated room which was temperature controlled (70 ± 2° F). Padded head rests were mounted on the left, right, front and back of the chair allowing subjects to make head movements at 45 degree angles from an upright position. Subjects were blindfolded and were seated in the rotating chair with the center of rotation through their own vertical axis (spine). The rotating chair tests were conducted by initiating rotation at 6 rpm (0.628 rad/s) and incrementing by 2 rpm (0.209 rad/s) every five minutes, with a maximum velocity of 30 rpm (3.142 rad/s). During each five minute period of rotation, subjects were instructed to make head movements (front, back, left, and right) in random order at two second intervals. A tape-recorded voice presented through an overhead speaker provided instruction for direction of head movements. At the end of five minutes, rotation continued but the subject was instructed to stop making head movements and to hold his head in the upright position. During the next 30 seconds the subject was asked to describe his symptoms to the experimenter. The Graybiel diagnostic scale was used to evaluate the symptom levels (ref. 29). Tests were terminated and rotation stopped when any of the following occurred: (a) the subject requested termination, (b) the subject reached malaise level III (8 or more diagnostic points), or (c) the experimenter felt, from observation of the subject, that the test should be terminated.

Blood and saliva samples were collected to measure circulating levels of promethazine, (individual dose response curves), and comparisons of these levels relative to changes in performance and mood states were made. Saliva samples were taken by having the subject chew on a small piece of parafilm to induce salivation, and then expectorate into a glass collection vial. Blood samples were obtained through an indwelling catheter (20 g, 3.2 cm) inserted into a vein on the dorsal surface of the left hand (and/or through venipuncture of the anticubital vein of the left arm), into heparinized containers. The total amount of blood drawn in this study did not exceed 80 cc (2.7 ounces). Samples were then separated and frozen by the Central Clinical Laboratory at NASA Ames Research Center. The drug/dose levels of each sample were calculated in ng/ml, and were obtained by gas chromatographic analysis performed by an outside contractor, National Medical Services, Inc.

Automated Performance Test System (APTS)– Most of the performance testing was conducted using the APTS (Essex Corp., Orlando FL), a standardized task battery that required 15 to 18 min to complete. The APTS software was implemented on a NEC 8201 microcomputer. This system was selected for portability, reliability, test automation capability, and utility for short-duration testing (ref. 30). The present study used ten performance tests (ref. 8) from the 30 recommended tests in earlier research (ref. 30). Below is a description of the 10 APTS subtests used in this experiment.

REACT4: Four-choice reaction time (60 seconds or 15 trials). The this test involved the presentation of a visual stimulus and measurement of a response latency (in msec) to the stimulus. The subject's task was to respond as quickly as possible with a key press to a simple visual stimulus. On this test, four "outlined" boxes were displayed and one of the four boxes was "filled." A short tone preceded the filling a of box to signal that a "change" in the status of a box was about to occur. The box changed from "outlined" to "filled." The subject observed the boxes for the change and then pressed the numeric key corresponding to the box that changed.

CODSUB: Code substitution (75 seconds). This task was a mixed associative memory and perceptual speed task. The computer displayed nine characters across the top of the screen. Beneath them, the numbers one through nine were displayed within parentheses. The subject's task was to associate the number with the character above it. This was called the subject's "code." Under the code were two rows of characters with empty parentheses beneath them. The subject responded by pressing the number associated with the character from the code above. When the subject has completed a row, the bottom row moved to the top and a new row appeared below. This is a cognitive and perceptual test with visual search encoding/decoding and incorporates memory recall and perceptual speed.

PATRNC: Pattern comparison (75 seconds). This test measured spatial ability. The task involved comparing two patterns of asterisks that were displayed on the screen simultaneously. The subject's task was to determine if the patterns were the same or different and responded by pressing "S" or "D" key.

STERNB: Sternberg short term memory (75 seconds). This test involved the presentation of a target set of four random numbers for one second (positive set), followed by a series of single numbers presented for two seconds (probe numbers). The subject's task was to determine if any of the probe letters were contained in the positive set. The subject responded by pressing "T" (true) or "F" (false) on the keyboard.

This is a cognitive item recognition task which reflects short term scanning rate.

ACM: Air combat maneuvering (2 minutes). This was a two-dimensional pursuit tracking task in which an animated "spacecraft" moved slowly from left to right across the top of the screen. The subject's task was to launch missiles by pressing the space bar, and "hit" the spacecraft. The position of the "missile launchers" was controlled by the left and right arrow keys. The subject was scored on the number of "hits" made within the allotted time.

PHTAP: Preferred hand tapping (10 seconds, 2 trials each). The tapping tests measured manual motor skill and coordination. The subject was required to press the indicated keys as fast as possible with the fingers from the preferred hand (PHTAP), the nonpreferred hand (NPTAP), or one finger from each hand (TFTAP). Correct responses are based on the number of alternate key presses made in the allotted time.

NPTAP: Non-preferred hand tapping (10 seconds, 2 trials each).

TFTAP: Two finger tapping (10 seconds, 2 trials each).

REASON: Grammatical reasoning (90 seconds). This test was designed to measure logical reasoning ability. Stimulus items were sentences of varying syntactic structure (e.g., A precedes B) accompanied by a set of letters (e.g., AB). The sentences were generated from possible combinations of five conditions: (1) active versus passive wording, (2) positive versus negative wording, (3) key words such as "follows" and "precedes," (4) order of appearance of the two symbols within the sentence, and (5) order of the letters in the simultaneously presented symbol set. The subject's task was to determine (i.e., read and comprehend) whether the sentence correctly described the sequence of the symbols in the symbolic set which appears to the right of the sentence. The subject responded by pressing the "T" (true) or "F" (false) keys.

MANKIN: Mankin spatial transformation (60 seconds). This test measured the ability to spatially transform mental images and determine the orientation of a given stimulus. A figure of a sailor is presented on the screen with a box below his feet and a box in each hand. A pattern (XXX or 000) appeared in the box below which matched the pattern in the box in one of his hands. The figure stands either facing away or toward the subject. The objective of this task was to determine which hand (right or left) matched the objects that appeared in the box on which the sailor is standing. The subject responded by pressing one of the two arrow keys, (i.e., to indicate left or right hand).

Mood Test– A visual analog scale mood test (refs. 14 and 31) was incorporated into the APTS performance software. The mood test initiated the APTS test battery to avoid possible modulation of mood responses by the performance tests. This test provided 21 levels of mood state resolution on a 10-cm scale which was displayed on a computer monitor. For example, when reporting his perceived state of arousal, the subject moved the cursor (with arrow keys) along the scale which ranged between SLEEPY (score = 0) to ALERT (score = 10).

The mood scales were allocated four each into two composite dimensions (ref. 27). The global "Affective Mood Dimension" included four measures of feelings or affective states and incorporated physical discomfort (very high (0) to very low (10)), elation, (sad (0) to happy (10)), psychological tension (tense (0) to relaxed (10)), and contentedness (unpleasant (0) to pleasant (10)). The global vigor or "Activation Mood Dimension" incorporated four measures of activation including fatigue level (weary (0) to energetic (10)), arousal state (sleepy (0) to alert (10)), motivation to perform (bored (0) to interested (10)), and ease of concentration (very low (0) to very high (10)). The physical discomfort scale indicated the state of physical uneasiness or the extent of mild aches and pains (very high (0) to very low (10)).

The Sleep Quality Scale– This scale rated whether or not subjects had experienced trouble falling asleep. Scores were rated on a scale of "much worse" (score = 0) to "much better" (score = 10). This scale also required the subject to report the number of previous night waking episodes, which was scored on a total episode (score = 0 to 6) scale. The subjects rated their overall performance relative to the previous test battery from "much worse" (score = 0) to "much better" (score = 10).

Critical Tracking Task (CTT)– The CTT is available commercially as the FACTOR 1000$_{TM}$ (manufactured by Performance Factors, Inc., Alameda, CA). This pursuit tracking task was performed by a subject seated at a desk with a PC computer. To the side of the keyboard was a small knob which could be operated with one hand. On the computer screen, a horizontal line was displayed with a perpendicular "cross-hair" line at the center. As a trial began, the perpendicular line (or "target") gradually moved off center (to the left or right). The subject's task was to keep this target as close to center as he could by turning the knob. As the trial continued, this became increasingly difficult because the target moved faster and faster, until maintaining control became impossible, and the target moved completely off the screen, marking the end of a trial. Hence, this task required the operator to

actively stabilize, by continuously correcting displayed errors, an otherwise divergently unstable control element. The performance measure was the "critical instability" level (i.e., the rate of divergence of the pointer) at the point when control was lost. The score for each trial was displayed at the bottom of the screen. Typically, a trial lasted 10 to 15 sec, with 30 sec being an extremely long trial. During a CTT session, subjects performed twenty-five trials in five blocks of five trials with a short rest between blocks. The first set of five trials was considered practice and were not included in the analysis.

Symptom Monitoring Device (SMD)– The SMD, developed at NASA, contained a battery operated 8051-derivative CMOS microcomputer with 32-Kbyte memory and a seven-key computer keypad (three for the thumb and four for each of the remaining fingers of the right hand) (ref. 32). Data were independently stored on the microcomputer itself (autonomous mode), or were captured and transmitted to another PC computer via a built-in serial port (tethered mode). When in tethered mode, text was typed into the keypad while a program read the data. Specific combinations of key-presses were displayed as alphanumeric characters on the PC's monitor. Within the SMD, the microprocessor was enclosed in a durable polycarbonate case with separate mounting for the key-pad, and this device was attached to the right arm rest of the rotating chair. Table 2 shows the combination of key strokes each subject was expected to learn. Figure 1 shows a top-down view of the 7-key SMD keypad as operated by the subject's right hand.

On the first day of the study (training day), subjects were given five sessions prior to the rotating chair test. During each session, subjects were verbally instructed to enter specific symptoms using the keypad, in random order. During the first session, subjects learned the key presses that represented eight alphabetic characters (A, E, D, S, N, T, H, and Z). During the second session, emphasis was placed on teaching subjects which combination of alphabetic characters represented specific motion sickness symptoms. Each subject was read 100 symptoms (nine different symptoms in random order). Throughout both the first and second sessions, subjects viewed a computer screen which displayed each entry, thereby providing feedback on correct or incorrect typing. During the third, fourth and fifth sessions, subjects were not allowed to view the computer screen and an experimenter recorded subjects' responses. Each subject had reached a training plateau by the fifth session on training day one. The criterion for learning was no more than 15 errors out of 100 symptoms entered with the key-pad. A sixth training session followed the rotating chair test. On the subsequent days of the study, each subject participated in four SMD sessions, where again, their task was to enter 100 key-stroke combinations in response to a random ordered list of symptoms read by the experimenter.

Table 2. Symptom key-stroke list

Symptom	Letter	Key*
temperature	t	2 + 4
dizziness	d	1a + 2 + 3
headache	h	1 + 5
drowsiness	z	1a + 3 + 5
sweating	s	4
salivation	sa	4, 2 + 3
nausea	n	3 + 4
epigastric awareness	ea	2, 2 + 3
epigastric discomfort	ed	2, 1a + 2 + 3
Symptom level	**Number**	
mild	1	1c
moderate	2	1c + 2
severe	3	1c + 3

* The + indicates that these keys were pressed simultaneously.

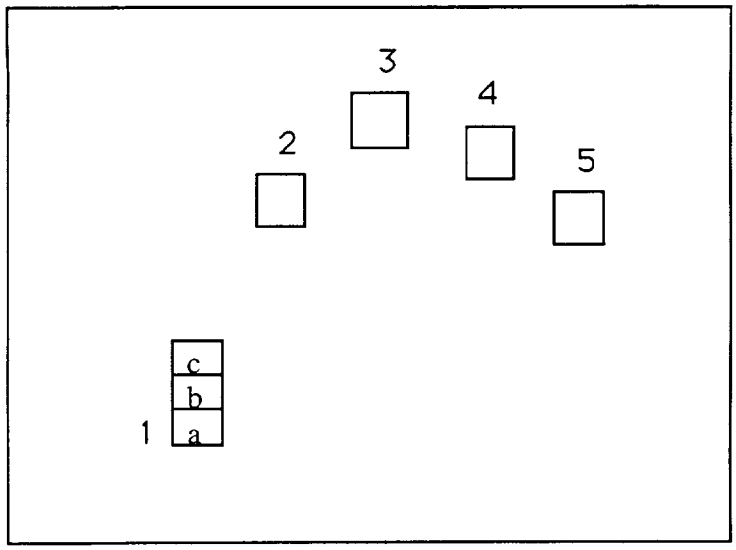

Figure 1. Top-down view of the 7-key SMD key-pad. The subject used his right hand to enter the different combinations of key strokes representing specific motion sickness symptoms (refer to table 2). The keys were numbered as follows: 1a, 1b, and 1c entered with thumb, 2 entered with index finger, 3 entered with middle finger, 4 entered with ring finger, and 5 entered with the little finger.

Statistical Analysis

Statistical analyses of the results were performed by ANOVA and MANOVA to examine performance changes across treatment conditions and sessions (repeated trials). The Greenhouse-Geisser formula (ref. 33) was used to adjust the P-values for those tests involving repeated measures.

The APTS performance tests which were scored on accuracy (number correct responses minus the number of errors), and mid-mean latency in msec included: CODSUB, PATRNC, STERNB, REASON and MANKIN. The test of reaction time (REACT4) was scored only on mid-mean latency. Tests of manual dexterity (PHTAP, NPTAP, TFTAP) were scored by counting the number of alternate presses. The tracking task ACM was scored on number of hits subjects made on the targets.

A MANOVA was performed to determine differences in APTS subtest scores as related to drug condition (25 mg, 50 mg, and placebo), and sessions. There were three sessions: a baseline prior to injections, 1-hr and 4-hr post-injection. Comparisons of drug conditions across sessions controlled for the possible effects of diurnal variations on performance which are magnified by antihistaminic drugs (ref. 34) and practice effects between successive tests. Task data were obtained within 30 min of the baseline, 1 hr, and 4 hr blood and saliva samples. Data collected on the first day were not included in the analyses because this day was used to train subjects on each task and to establish a performance plateau (task proficiency and stability). The number of sessions required for APTS performance test means and variances to stabilize was determined by Bittner's methods (ref. 35).

The performance metric used for the CTT tracking task is referred to as a critical instability level (ref. 19). The SMD task was scored by the number of incorrect responses out of 100 key-pad entries of symptoms. Separate ANOVAs were performed for CTT and SMD scores (3 experimental conditions by 3 sessions).

Drug dosage-associated performance decrements were evaluated for potential operational significance by establishing blood alcohol level dose equivalency (BAL). A study of APTS subtest performance changes associated with different fixed BAL (0.0, 0.05, 0.10, 0.15%) provided conversion tables (ref. 20). This study employed a subject group (21–42 year old males) comparable to the subject group in the present study. Test scores from the BAL study were converted from the number of correct responses to net accuracy scores for the appropriate subtests. Linear regression of performance decrement against BAL% was done. The BAL dose equivalency was considered valid for a subtest where $R^2 > 0.81$ ($P < 0.05$, 1-tail test).

Mood test and sleep quality data were ordinal and therefore separately analyzed by nonparametric methods, Friedman's ANOVA with Wilcoxon's paired comparisons for repeated measures.

Motion sickness tolerance was measured as the accumulated number of rotations tolerated by each subject during rotating chair motion sickness tests. An ANOVA was performed to examine differences in motion sickness tolerance across the training condition and three treatment conditions (25 mg of promethazine, 50 mg of promethazine, and placebo).

In a supplementary analysis, data of the present study were compared to archived data on motion sickness tolerance of subjects given Autogenic Feedback Training (AFT) (refs. 36 and 37), a physiological training method, and a no-treatment control group. From this archive, it was possible to "select" 12 men who had been given AFTE as part of earlier studies and 12 men who had participated as controls (no treatment). These subjects were matched to the promethazine study subjects for age, sex, and susceptibility to motion sickness based on the duration of their first rotating chair test. The rotating chair motion sickness tests given to all subjects were identical and had the same interval between tests (one week).

Results

Table 3 shows the latin-square design used to counter-balance the order of presentation of drug and placebo conditions. This latin square design was compromised when two subjects were excluded from the study, and when subject 8 was mistakenly given the protocol for subject 14. Subject 5 reported extreme discomfort from this medication and subject 7 began taking another medication, fluoxetine, for reasons unrelated to this study. Subject 6 participated in all experiment sessions but was found to be labyrinth-defective (i.e., not susceptible to motion sickness), and therefore his data are not included in the analysis on motion sickness tolerance. Since practice effects in APTS subtests are commonly observed even after subject training (ref. 14), further analysis of practice effects in this study was necessary to distinguish performance test changes in response to the experimental protocol from those due to practice effects resulting from an unbalanced order of presentation between successive experimental trials.

Linear regressions were performed on baseline sessions of the placebo, 25 mg and 50 mg conditions in order of presentation for each APTS subtest. There were seven sessions (repetitions of task batteries) between the first and last baseline session on the treatment days for each subject. Although all tests showed improvement between sessions 1 and session 9, significant practice effects were found only for the CODSUB ($t\ 34 = 2.39$, $p < 0.022$, +3.1%/session), MANKIN ($t\ 34 = 2.08$, $p < 0.045$, +3.0%/session) subtests and for composite performance

Table 3. Order of presentation for treatment conditions

Subject	Placebo	25 mg	50 mg
1	3	4	2
2	4	3	2
3	2	3	4
4	2	4	3
5*	-	2	–
6*	4	2	3
7*	–	–	2
8	4	3	2
9	2	3	4
10	2	4	3
11	3	2	4
12	4	2	3
13	3	2	4
14	4	2	3
15	4	2	3

* Subjects 5 and 7 were excluded from the experiment. Subject 6 was found to be labyrinth-defective and his motion sickness data were not included in analyses of drug effects on motion tolerance.

(z-scores, $t\ 34 = 5.65$, $p < 0.002$). Composite scores are computed from a mean of subtests which were common to our performance battery and an earlier study by Kennedy (ref. 21). This index excluded the ACM and TFTAP scores. Paired t-tests were then done on these three tests for the placebo/25 mg, placebo/50 mg and 25 mg/50 mg baseline sessions to determine if the unbalanced order of presentation for each combination was associated with significant practice effects. Out of 9 combinations (3 tests × 3 paired sessions), only MANKIN (25 mg vs. 50 mg conditions, +9.7%, $t\ 11 = -2.27$, was suggestive of a protocol practice effect, which given the Bonferroni correction for 9 paired sessions (alpha = 0.05/9 = 0.006), was not statistically significant.

Figure 2 shows the group means (± S.E.M.) for blood serum and saliva concentrations of promethazine taken throughout test days.

Baseline blood and saliva samples were taken before injections were administered. Concentration of the drug in each subsequent sample and the time from injection when the sample was taken are shown. Note that less data is available on serum levels because of procedural difficulties in obtaining the blood. The last samples were taken immediately following rotating chair tests, which occurred between 5 hr and 6 hr following injections

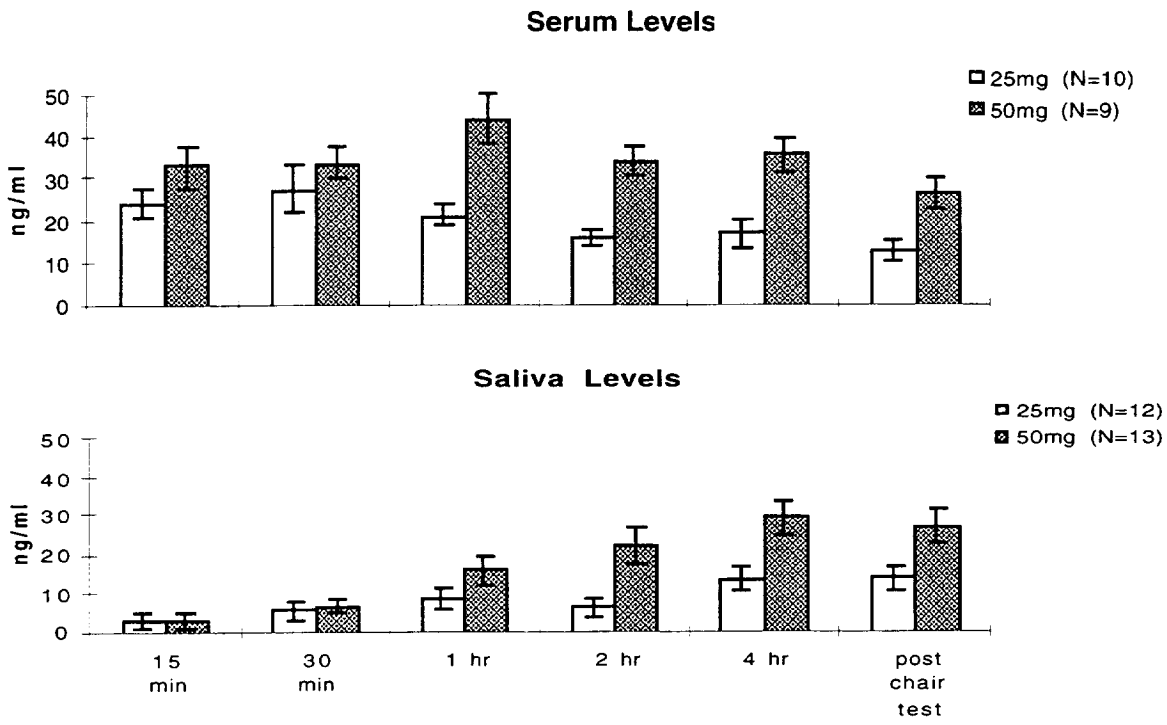

Figure 2. Promethazine concentration in serum and saliva. The data represent the mean (± S.E.M.) serum and saliva concentrations of promethazine (25 mg and 50 mg dosages). The x-axis labels represent post-injection times.

(dependent upon the duration of time that subjects could tolerate the motion sickness tests). Group means for serum levels show promethazine peaking at 1 hr post injection for the 50 mg dose, with the peak time at 30 min for the 25 mg dose. As expected, during all sample periods the levels were higher for the 50 mg than the 25 mg dose. Group means for saliva concentrations show that the 50 mg dose peaks at 4 hr, rather than 1 hr. As measured in saliva, circulating levels increased more slowly than in blood serum which is already high by 15 min and remains fairly stable over a 5–6 hr period.

Linear regressions were performed on circulating levels of promethazine (25 mg and 50 mg doses) in both serum and saliva samples obtained at 1 hr, 2 hr, 4 hr, and following rotating chair motion sickness tests (approximately 6 hr) against blood alcohol level equivalency scores from the corresponding time periods. Significant positive correlations between serum levels and BAL scores were found for the 25 mg dose during the period following the rotating chair test, ($n = 8$, $r = 0.88$, $p < 0.004$), while the 50 mg dose was significant at 4 hr post-injection ($n = 11$, $r = 0.65$. $p < 0.03$). Separate linear regressions for saliva concentration levels vs. BAL scores showed significant correlations at 1 hour post-injection for both the 25 mg dose ($n = 10$, $r = 0.77$, $p < 0.009$) and 50 mg dose ($n = 11$, $r = 0.65$, $p < 0.03$).

Dose Effects on Performance Tests

Performance test means and variances stabilized by a mean of 2.5 sessions out of a total of 6 training sessions presented during the training day. The MANOVA results of APTS scores revealed a significant overall interaction of treatment conditions by sessions, $F(80,116) = 1.5$, $p < 0.02$. Table 4 shows the specific subtests and their P values. Table 5 shows the probabilities of no difference for planned comparisons (separate one-way ANOVAs) which were performed to determine drug/placebo effects on performance at 1 hr and 4 hr. Figures 3 and 4 show the average scores of each subtest across sessions (baseline, 1-hr, 4-hr, and post-chair test).

Table 4. Results of APTS subtests

Test	Accuracy	Latency
REACT1	–	*
CODSUB	**	ns
PATRNC	*	*
STERNB	ns	*
ACM	ns	–
PHTAP [a]	ns	–
NPTAP [a]	***	–
TFTAP [a]	*	–
REASON	ns	*
MANKIN	***	*

[a] Scored on number of alternate presses.
* P < .05, ** P < .01, *** P < .001

Table 5. Secondary comparisons of APTS subtest scores

Accuracy

	Placebo/25 mg		Placebo/50 mg		25 mg/50 mg	
	1 hr	4 hr	1 hr	4 hr	1 hr	4 hr
REACT1	–	–	–	–	–	–
CODSUB	**	**	***	**	ns	ns
PATRNC	*	***	ns	**	ns	ns
STERNB	–	–	–	–	–	–
NPTAP[a]	*	***	***	***	**	ns
TFTAP[a]	**	ns	***	**	**	ns
REASON	***	**	***	**	ns	ns
MANKIN	***	**	***	**	ns	ns

Latency

	Placebo/25 mg		Placebo/50 mg		25 mg/50 mg	
	1 hr	4 hr	1 hr	4 hr	1 hr	4 hr
REACT1	**	**	**	***	ns	ns
CODSUB	–	–	–	–	–	–
PATRNC	ns	**	ns	ns	ns	ns
STERNB	*	ns	***	ns	ns	ns
NPTAP[a]	–	–	–	–	–	–
TFTAP[a]	–	–	–	–	–	–
REASON	ns	ns	**	ns	ns	ns
MANKIN	**	*	**	**	ns	ns

[a] Scored on number of alternate presses.
* P < .05, ** P < .01, *** P < .001

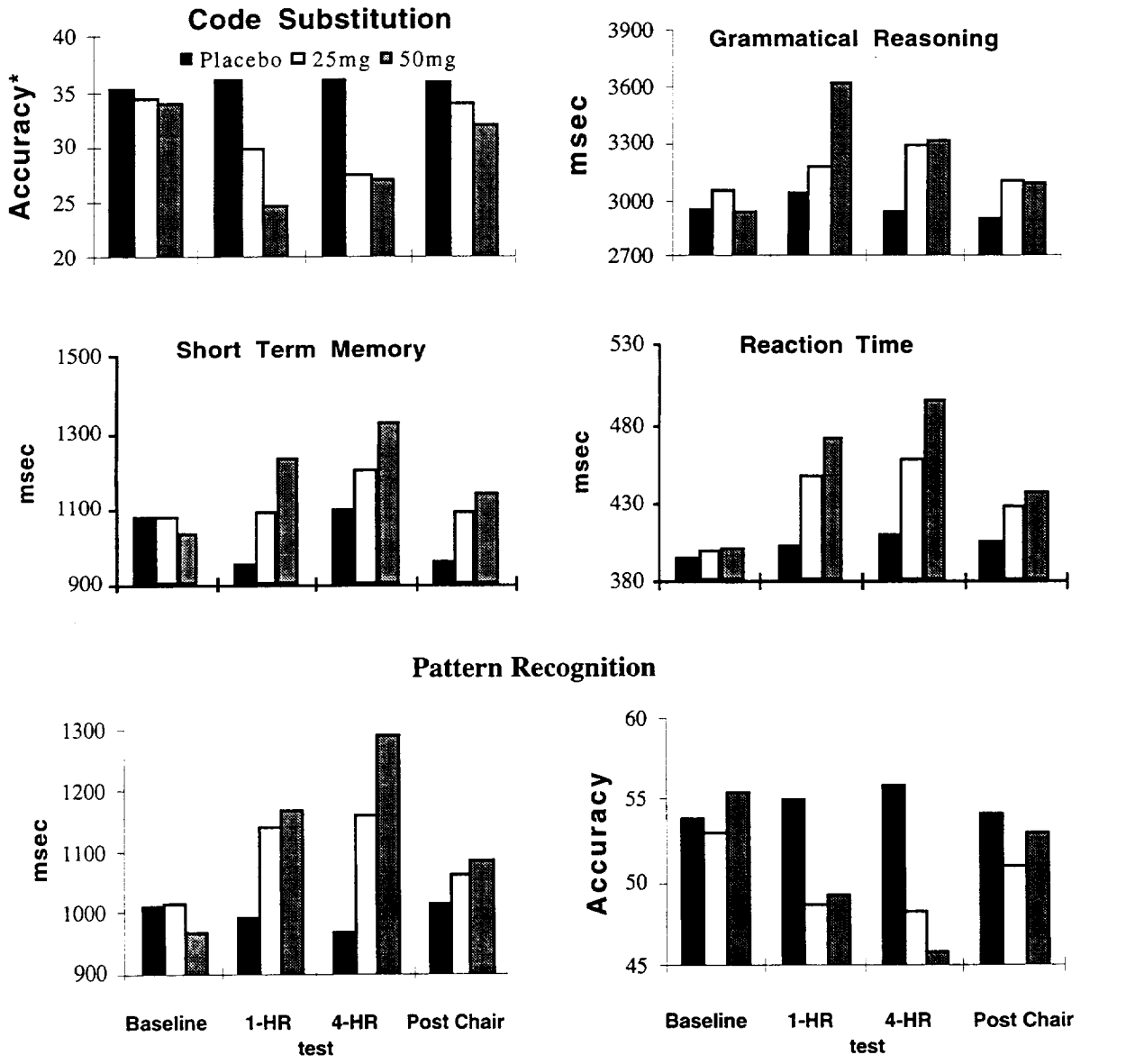

Figure 3. APTS subtest scores across treatment conditions. The data represent the mean (n = 13) accuracy (number of correct responses minus number of errors) and/or latency (msec) scores on code substitution, grammatical reasoning, pattern recognition, and spatial transformation tasks on the placebo day and on days when promethazine was given. The x-axis shows the times relative to injection when tasks were given. The baseline task preceded the injections.

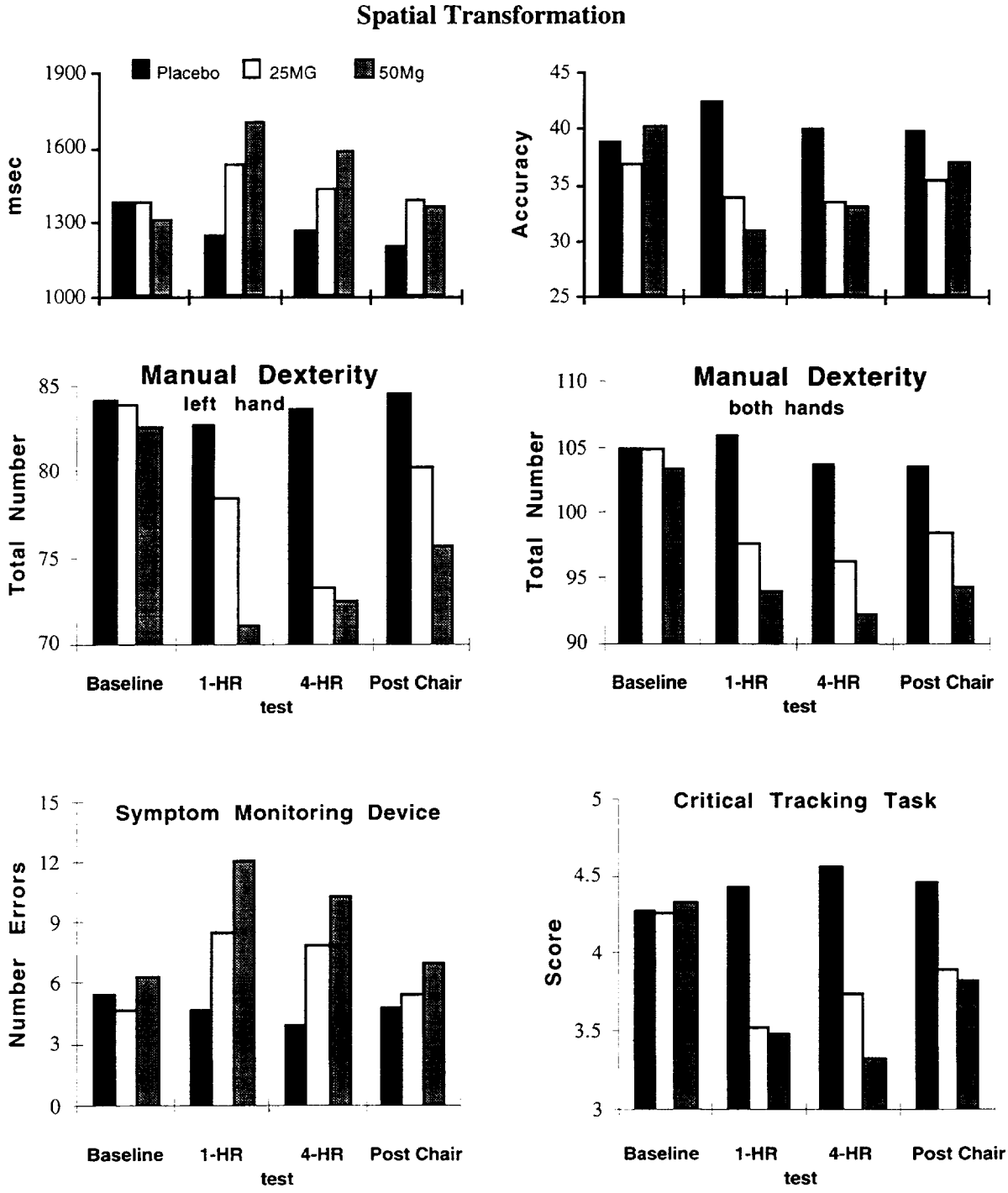

Figure 4. APTS, SMD and CTT task scores across treatment conditions. The data represent the mean (n = 12) latency (msec) on short-term memory and reaction time tasks, total number of finger taps (left hand and both hands) on the manual dexterity task, number of errors (incorrect key presses) on the symptom monitoring device, and score (rate of divergence of the pointer) on the critical tracking task. The x-axis shows the times relative to injection when tasks were given. The baseline task preceded the injections.

Dose Effects on Critical Tracking

Results on CTT scores showed a highly significant conditions by sessions interaction, $F(2.78,33.39) = 18.14$, $p < 0.00001$. Planned comparisons, one-way ANOVAs, were performed to determine drug/placebo effects on this tracking task at 1-hr and 4-hr post-injection. At 1 hr, the 25 mg and 50 mg conditions showed significantly lower scores (less time on target) when compared to the placebo condition, $F(1,12) = 32.1$, $p < 0.0001$ and $F(1,12) = 31.36$, $p < 0.0001$, respectively. At 4 hr, again both drug conditions showed significantly lower scores than the placebo, $F(1,12) = 17.40$, $p < 0.0013$; and $F(1,12) = 40.28$, $p < 0.00001$, respectively. Further, a comparison between the 50 mg and 25 mg conditions at 4 hr showed that tracking scores were significantly lower for 25 mg, $F(1,12) = 11.28$, $p < 0.0049$. Figure 4 shows the average CTT scores obtained during each condition.

Dose Effects on Symptom Monitoring

The analysis of SMD scores revealed a significant condition by session interaction, $F(2.1, 25.2) = 3.25$, $p < 0.05$. Planned comparisons, one-way ANOVAs, were performed to examine drug/placebo effects on this task at 1 hr and 4 hr. At 1 hr, both the 25 mg and 50 mg conditions when compared to the placebo condition showed significantly higher scores (more errors), $F(1,12) = 8.82$, $p < 0.012$ and $F(1,12) = 8.53$, $p < 0.013$, respectively. At 4 hr, again both drug conditions resulted in significantly more errors than the placebo condition, $F(1,12) = 11.89$, $p < 0.005$ and $F(1,12) = 10.01$, $p < 0.008$. Comparisons between the 25 mg and 50 mg conditions revealed no significant differences at either 1-hr or 4-hr post-injection. Figure 4 shows the average SMD scores across sessions for each condition.

Dose Effects on Sleep and Psychological Tension

Analyses on the two sleep scales by four conditions (training, placebo, 25 mg, and 50 mg) revealed no sleep quality changes for trouble falling asleep (SLEEP, X^2 (3) = 4.3, NS), or number of awakenings, (WAKE, X^2 (3) = 1.5, NS). Psychological tension showed no change across sessions (TENSE, X^2 (11) = 7.9, NS). These findings indicate that performance or mood changes observed in response to drug treatments were not attributable to changes in previous night's sleep quality, psychological tension or anxiety.

Dose Effects on Mood

Significant drug effects on the Activation Mood Dimension and its constituent scales were found, with maximum deterioration evident in the arousal state and fatigue level scales. These scales showed marked deterioration at 1-hr post-injection with 50 mg relative to the 25 mg dose. Changes in Activation Mood Dimension scales were significant across drug conditions, (X^2 (3) = 8.4, $p < 0.03$), and across sessions (X^2 (11) = 35.7, $p < 0.0005$). Only the arousal state scale had statistically significant changes between 25 mg and 50 mg doses.

The Affective Mood Dimension scales were relatively unaffected except for a progressive increase in physical discomfort following the 50 mg dosage (X^2 (11) = 22.7, $p < 0.02$).

Performance Impairment Index

Subject impairment was defined as six or more performance subtests out of ten total tests where performance decrements relative to control exceeded 5% (based on Turnage et al., ref. 38). The index number was the number of subjects meeting impairment criterion. There was a difference between the 25 mg dose (which induced impairment in 4 of the 12 subjects) and the 50 mg dose, (which induced impairment in 7 of the 12 subjects). These results indicate that although few significant changes in performance were found between the 25 mg and 50 mg dosages, the number of impaired subjects nearly doubled, thereby indicating that the higher dose may have undesirable operational implications for performance proficiency.

Dose Effects and BAL%

Individual subject BAL scores at 1 hr and 4 hr following injections of 25 mg and 50 mg of promethazine are shown in table 6. At 1-hr post-injections the BAL scores were highly variable, ranging from 0.000 to 0.243% for 25 mg and from 0.000 to 0.429% for 50 mg. BAL scores calculated 4 hr after injections ranged from 0.022 to 0.196 for 25 mg and from 0.017 to 0.418% for 50 mg. The subject group means exceeded the California state legal limit for BAL (0.080%) on all conditions reported.

Table 6. Individual blood alcohol equivalency percentages following promethazine injections

	25 mg		50 mg	
Subject	**1 hr**	**4 hr**	**1 hr**	**4 hr**
1	0.015	0.022	0.076	0.034
2	0.004	0.027	0.063	0.078
3	0.243	0.270	0.429	0.418
6	0.086	0.088	0.093	0.081
8	0.014	0.029	0.288	0.281
9	0.000	0.196	0.000	0.133
10	0.129	0.122	0.086	0.080
11	0.032	0.062	0.091	0.040
12	0.107	0.045	0.128	0.031
13	0.133	0.129	0.212	0.174
14	0.125	0.111	0.110	0.082
15	0.050	0.121	0.044	0.017
Mean =	0.085	0.105	0.137	0.128

Dose Effects on Motion Sickness

Figure 5 shows the group means for motion sickness tolerance across the four experimental conditions. The analysis of motion sickness data showed a significant effect for conditions ($F(3,33) = 6.70$, $p < 0.01$. Planned comparisons, one way ANOVAs, revealed no significant differences in motion sickness tolerance between training and placebo conditions and between the 25 mg and 50 mg conditions. However, motion sickness tolerance was significantly higher for the 25 mg dose than the placebo, $\underline{F}(1,11) = 14.44$, $\underline{p} < 0.003$; and was higher for the 50 mg dose than for placebo, $\underline{F}(1,11) = 6.19$, $\underline{p} < 0.03$.

Figure 6 shows the individual subjects' motion sickness tolerance across test conditions. Half of the subjects showed greater motion sickness tolerance with the 25 mg dose when compared to the 50 mg dose of promethazine.

AFT vs. Drug vs. Control Effects on Motion Sickness Tolerance

A two-way ANOVA was performed to examine differences between three groups (AFT, Control and Promethazine) over four motion sickness tests. Figure 7 shows the average number of rotations for each group during four rotating chair tests. The main effects for groups and tests were significant ($F(2,132) = 20.02$, $p < 0.0001$ and $F(3,132) = 10.33$, $p < 0.0001$, respectively), and the group by test interaction was also significant ($F(6,132) = 4.19$, $p < 0.0007$).

Comparisons of the baseline tests of the three groups (Bonferroni t-tests) showed no significant differences in motion sickness tolerance, indicating that the groups were matched for initial susceptibility. When 2 hr of AFTE was compared to 25 mg and 50 mg of promethazine, no significant differences were found. However, comparison of 4 hr of AFTE revealed that motion sickness tolerance was significantly higher than for subjects given 25 mg ($t = 1.33$, $df = 132$, $p < 0.005$) and 50 mg of promethazine ($t = 1.36$, $df = 132$, $p < 0.005$). Finally, 6 hr of AFTE was significantly higher than 25 mg ($t = 5.54$, $df = 132$, $p < 0.001$) as well as 50 mg ($t = 5.57$, $df = 132$, $p < 0.001$). Changes in motion sickness tolerance of individuals of each group are shown in figure 8. Four of the 12 subjects receiving AFTE had completely suppressed motion sickness symptoms after 6 hr of training. Of the subjects given promethazine, however, only one showed a large improvement in tolerance for both doses, while half of the subjects showed better tolerance after 25 mg than for 50 mg.

Discussion

Both dosages of promethazine were associated with significant decrements in performance on 8 of the 10 APTS subtests, as well as the CTT and SMD tasks. These findings are consistent with Wood (ref. 5) and Parrot and Wesnes (ref. 4), who observed performance decrements following oral ingestion of this medication. The studies using i.m. injections of 25 mg and 50 mg reported only on changes in motion sickness during parabolic flight (refs. 2 and 3), or space sickness (ref. 39) tolerance without measuring effects on performance.

The two tests which did not change significantly were PHTAP (preferred hand tapping), a test of manual dexterity, and the ACM (air combat maneuver) which measures eye-hand coordination. It is possible that a well learned manual dexterity task using the dominant hand is less likely to deteriorate in response to this medication. It is important to note, however, that the other two tests of manual dexterity (NPHTAP, non-preferred hand tapping and TFTAP, two-finger tapping) were significantly degraded by promethazine. The lack of a significant decrement in performance of ACM may be related to observations by Kennedy (ref. 8) that learning of this task was slow to stabilize and that it was not an optimal test of eye-hand coordination. This conclusion is further supported by our findings that the CTT, which has been widely used to test this performance dimension (refs. 38 and 40–43), showed significant decrements.

The SMD was developed for this study and has not been previously validated as a research performance task in contrast to the APTS and the CTT. However, analyses showed that this task also was impaired by injections of promethazine and that the changes associated with the time course of medication and the dose (25 mg vs. 50 mg) was in fact very similar to the findings for the APTS and

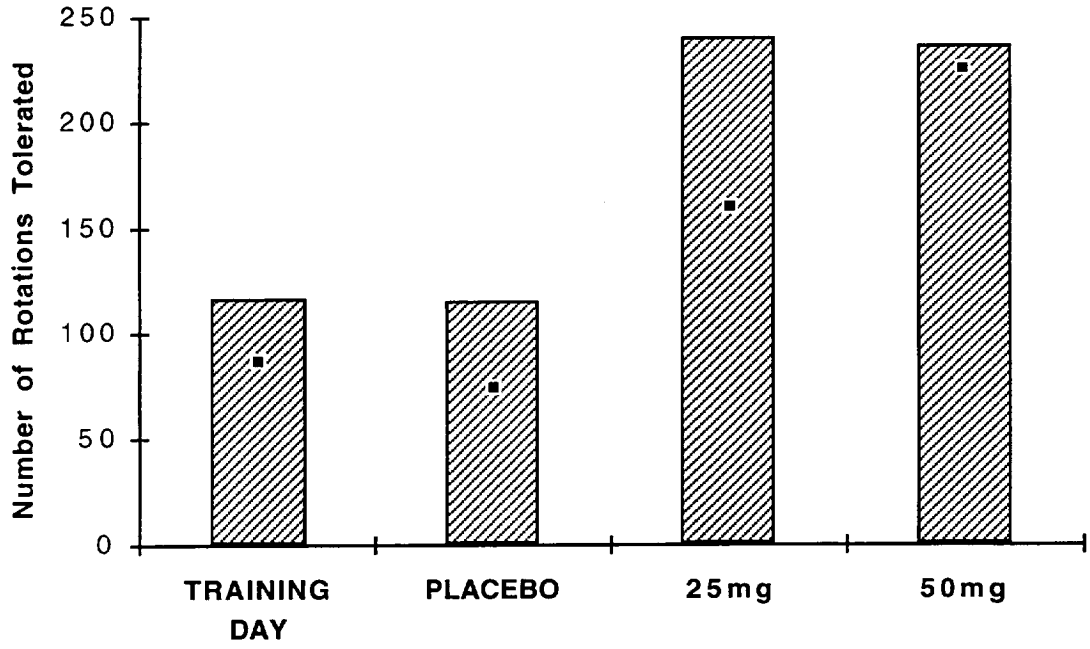

Figure 5. Motion sickness tolerance across treatment conditions. The data represent the mean (± S.E.M.) number of rotations tolerated on the training day (no injections), and on days when the placebo and promethazine (25 mg and 50 mg dosages) injections were given. Subjects could achieve a maximum of 1170 rotations (65 min of continuous rotation) during motion sickness tests.

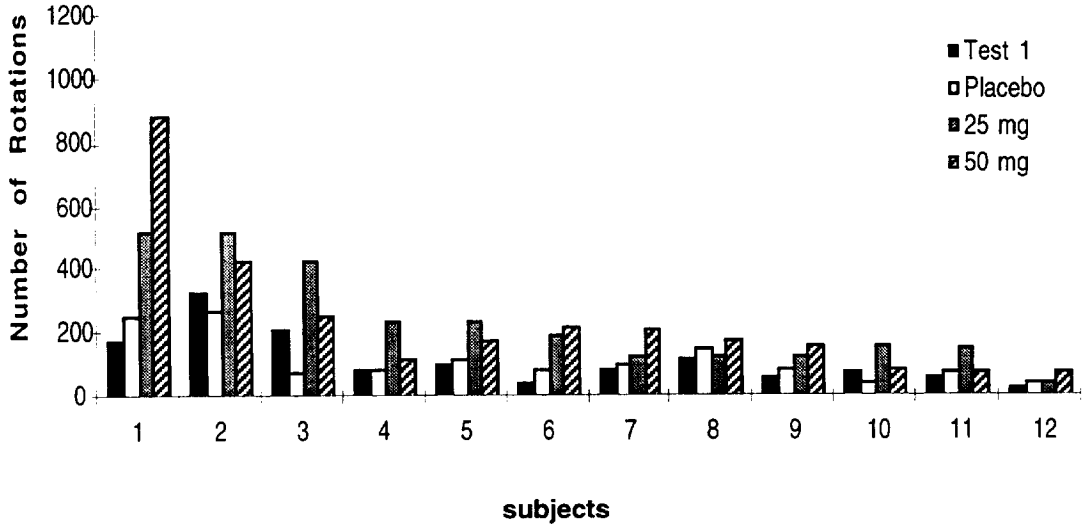

Figure 6. Motion sickness tolerance of individual subjects on the training day and on days when the placebo and promethazine injections were given. Subjects could achieve a maximum of 1170 rotations (65 min of continuous rotation) during motion sickness tests.

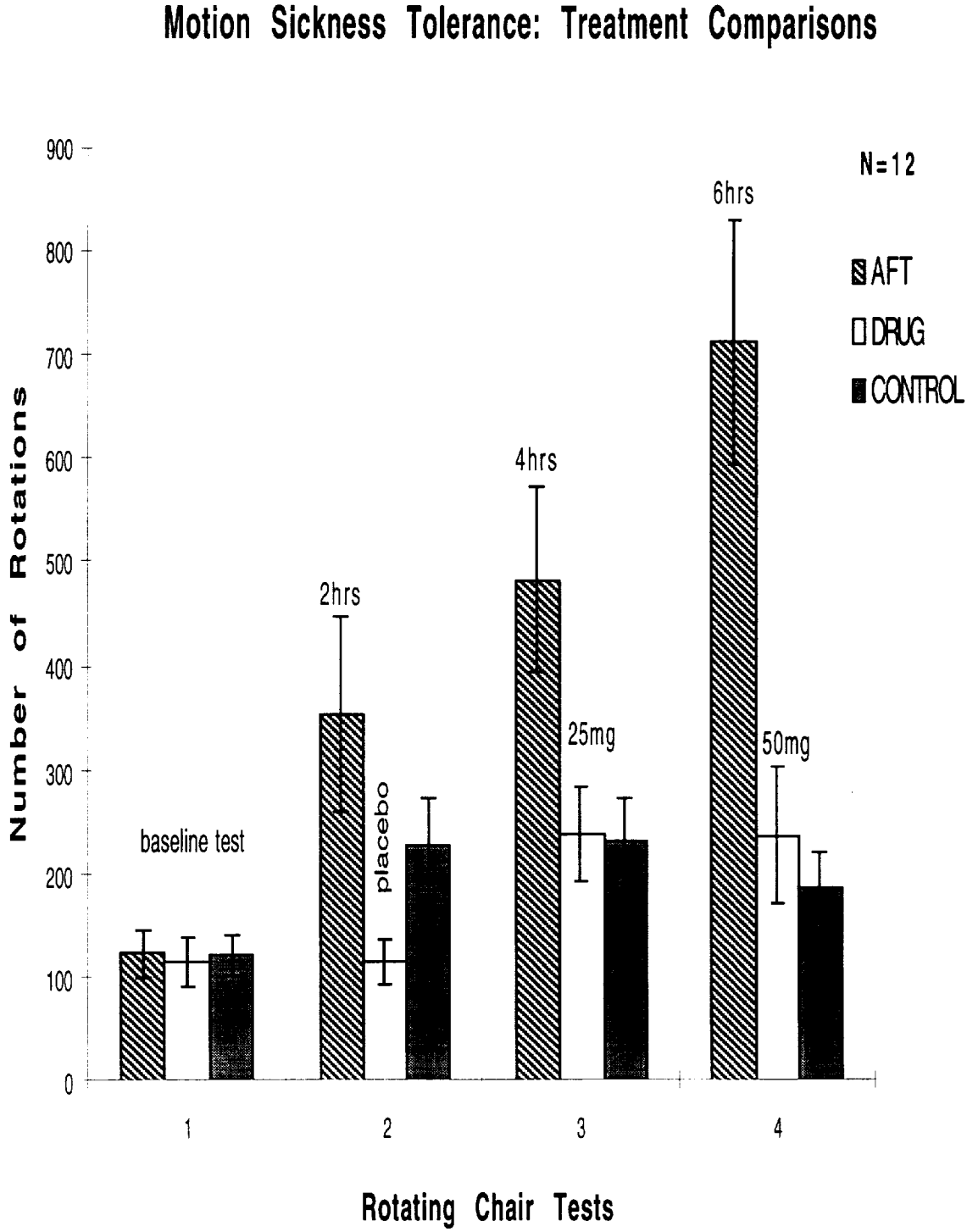

Figure 7. Rotating chair tests were separated by one week intervals. For the Drug group (given 25 mg, 50 mg of promethazine, and a placebo), treatment was counterbalanced over tests. AFTE and Control group tests were sequential. Treatment effectiveness is reflected by the number of rotations tolerated. After 6 hr of training, the AFTE subjects tolerated motion stress three times more effectively than the other groups.

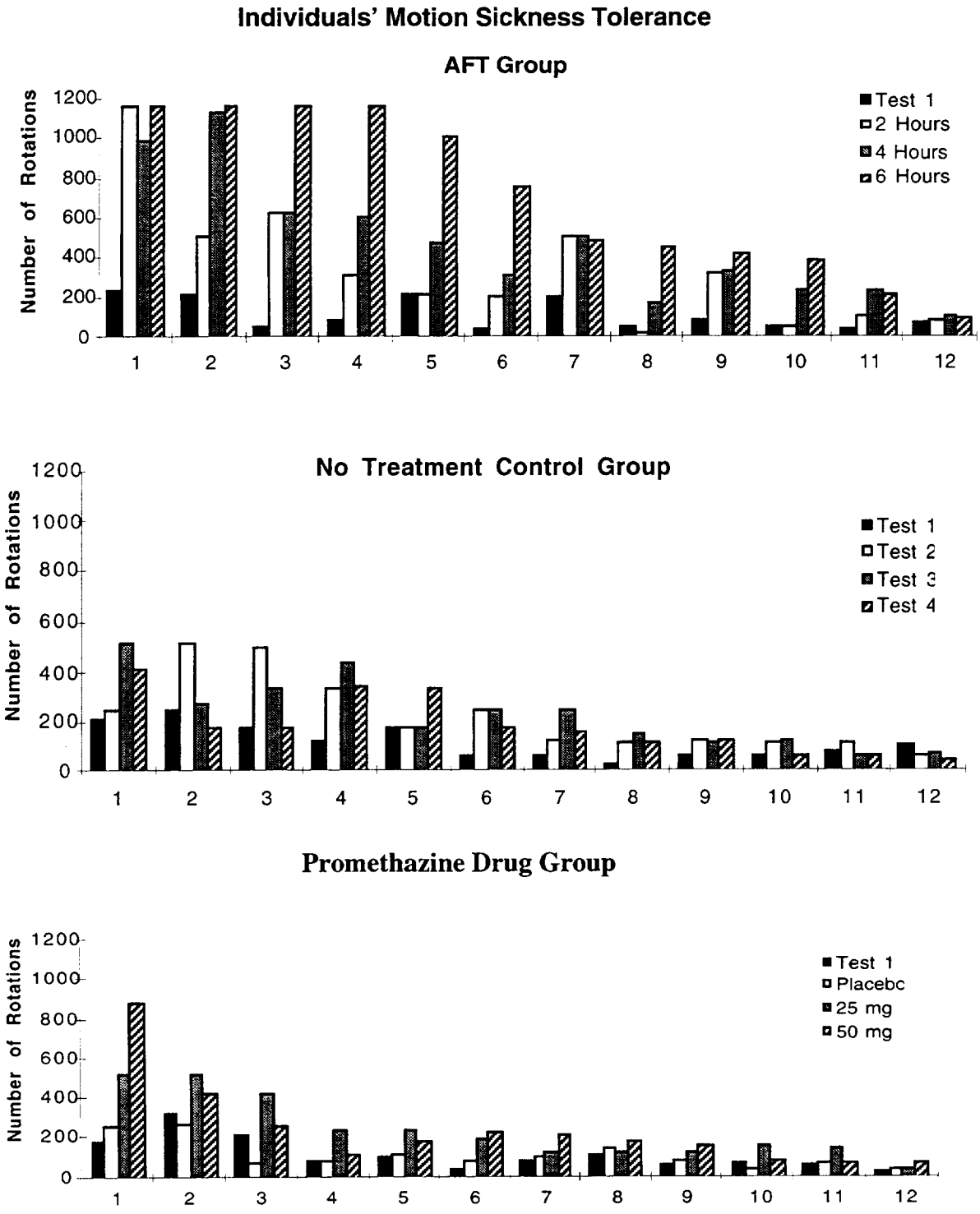

Figure 8. Five of the twelve AFTE subjects were able to completely suppress motion sickness symptoms after 6 hr of training. The drug and control groups do not differ significantly.

CTT. As the SMD was designed to "simulate" a payload activity which might be performed by crewmembers aboard shuttle, these results further serve to emphasize the impact of this antimotion sickness medication on imbedded task components of operational performance.

Significant performance decrements measured at 1-hr and 4-hr post-injection were associated with high serum levels of promethazine for both dosages. Although mean performance decrements were greater for 50 mg than for 25 mg, there were no significant differences between dosages on most of the tests measured at 1 hr and 4 hr. Although performance measures were obtained no earlier than 1 hr, it is possible that decrements may also be seen as early as 15 min post-injection. Concentration levels in saliva and corresponding decrements in performance are not as clear, as the circulating levels increase more gradually throughout the day. Therefore, dose response measures in saliva may be less accurate than serum for assessing performance changes over time.

Another objective of this study was to examine the possibility of any negative effects of this medication on individual subjective experience of malaise or "well being." To answer this question, subjective report scales on mood and sleep were added to this study. It was clear from these tests that decline in performance on days when promethazine was administered was not related to sleep disturbances (a significant potential intervening source of variance). The MOOD scale results showed significant changes in individual subjective experiences in response to medication, with the 50 mg dose having the greatest negative impact.

As a further measure of the effect of promethazine on subjective state, we calculated blood alcohol equivalency scores (BAL) for each subject. The establishment of alcohol dose equivalency levels for performance decrements provides a useful metric for evaluating the potential operational significance of drug treatment effects on performance because: (1) alcohol is known to be a global depressant with well documented impacts on performance and operational readiness; and (2) considerable research has been reported on the calibration of safe and unsafe alcohol dosages (ref. 20). These blood alcohol levels clearly exceed the legal limits for alcohol influenced driving impairment (0.08–0.10%) and are much larger than the 0.025% BAL which is sufficient to induce serious errors in pilots during B727 and B232 simulator performance tests (ref. 44). Therefore, the promethazine dosages used in this study induced blood alcohol equivalent levels of performance decrement which clearly exceed legal and operational thresholds for performance impairment (BAL = 0.085% for 25 mg injections and 0.137% for 50 mg).

These results indicate that a very wide range of individual responses to promethazine in terms of BAL dose equivalent performance decrements, with some individuals being severely impaired with respect to operational performance. Both the impairment index and the BAL dose equivalent data indicate that a higher proportion of individuals are performance impaired at the 50 mg dose than at the 25 mg dose.

Lastly, the results of this study showed that motion sickness tolerance was significantly increased with both dosages of promethazine when they were compared to the placebo or a no treatment baseline condition (training day). However, there was no statistical difference in motion sickness tolerance between 25 mg and 50 mg doses of promethazine. In fact, half of the subjects showed greater motion sickness tolerance with the 25 mg dose. And, only one subject clearly demonstrated an improvement in tolerance with both dosages of promethazine.

These data indicate that effective doses of promethazine used as a prophylactic treatment for motion sickness and space motion sickness may significantly impair most individuals with respect to their operational performance. Current policy involves giving a single 50 mg i.m. injection to sick crewmembers regardless of weight, gender, or symptom severity. Data from the present study strongly indicate that fixed doses of this medication are inappropriate and that even individually adjusted dosages may not lessen its degrading effects on performance. As mentioned, both doses increased motion sickness tolerance when compared to a placebo but this study does not demonstrate how this medication compares to other treatments or to habituation (i.e., repeated exposure to motion sickness tests, no treatment).

The analysis comparing data of the present study to archived data (AFT and a no-treatment control) revealed that neither 25 mg or 50 mg doses of promethazine resulted in increases in tolerance greater than the control group, and the AFT treatment provided significantly greater protection from symptoms. The question remains, is the relatively small degree of protection from symptoms achieved through either dose of promethazine "worth" the pervasive and long lasting decrements in performance observed? If these side effects are less pronounced in space as reported (ref. 1), it would be valuable to use a performance battery similar to the APTS to assess individual differences in response to this medication. Research in space should continue to evaluate this and other possible countermeasures with the goal of finding that treatment or combination of treatments most effective for individual crewmembers.

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Intramuscular (i.m.) injections of promethazine in 25 mg or 50 mg dosages are commonly used to treat space motion sickness in astronauts. The present study examined the effects of i.m. injections of promethazine on neuropsychological performance, mood states, and motion sickness tolerance in humans. Twelve men, mean age 36 ± 3.1, participated in one training (no injections) and three treatment conditions: a 25 mg injection of promethazine, a 50 mg injection of promethazine, and a placebo injection of sterile saline. Each condition, spaced at 7 day intervals, required an 8–10 hr session in which subjects were given four repetitions of 12 performance tasks, and one rotating chair motion sickness test. On the training day subjects were trained on each task to establish stability and proficiency. On treatment days, the order in which the drug or placebo was assigned to subjects was counterbalanced and a double-blind technique was used. Statistically significant decrements in performance were observed on 10 of 12 tasks when subjects were given 25 mg or 50 mg of promethazine as compared to the placebo. Performance decrements were associated with mean blood alcohol dose equivalency levels of 0.085% for 25 mg and 0.137% for 50 mg dosages. The mood scale results showed significant changes in individual subjective experiences with maximum deterioration in the arousal state and fatigue level. When compared to placebo significant increases in motion sickness tolerance were found for both dosages of promethazine. These data suggest that effective dosages of promethazine currently used to counteract motion sickness in astronauts may significantly impair task components of their operational performance.

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