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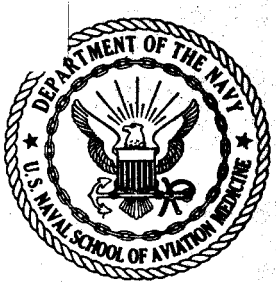
JOINT REPORT



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U. S. NAVAL SCHOOL OF AVIATION MEDICINE
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SUMMARY PAGE

THE PROBLEM

To investigate any possible increase in effectiveness provided by increased doses of some antimotion sickness drugs previously tested on the Pensacola Slow Rotation Room.

FINDINGS

The most effective preparation in this study was hyoscine (1.2 mg) and d-amphetamine (20 mg). The total number of tolerated head movements, while on the Slow Rotation Room, exceeded the sum of that with these drugs when they were tested alone. The next most effective drug was hyoscine (1.2 mg) followed by d-amphetamine (20 mg) and meclizine (150 mg) in that order. The remaining drugs which included thiethylperazine (Torecan 30 mg), trimethobenzamide (Tigan 750 mg), and prochlorperazine (Compazine 15 mg) were less effective than in a previous study when the recommended doses were used.

INTRODUCTION

The antimotion sickness drugs have been studied under a wide variety of conditions (3). The difficulty of maintaining a standardized test situation under field conditions indicates the need for a reliable laboratory method for testing these drugs (9). The Slow Rotation Room (SRR), which is a laboratory mounted on a human centrifuge at the U. S. Naval School of Aviation Medicine, provided such a standardized test situation for an earlier study of the antimotion sickness drugs (13). Some of the drugs which are reported in the literature (14) to be effective failed to reduce susceptibility to motion sickness in that study. In the present investigation the dose of these drugs was increased to investigate the possibility that this might increase their level of effectiveness.

PROCEDURE

The subjects for this experiment were ten healthy young Navy enlisted men. Two of these subjects were rejected due to their having an exceptionally high resistance to motion sickness. The remaining subjects were subjected to vestibular caloric studies and all had normal responses.

On test days the subjects were given a light breakfast of milk, cereal, and juice. The drugs were administered in matched oral capsules, one and one-half to two hours before the experiment. Double blind and placebo procedures were used throughout the study. A rest period of from 48 to 72 hours was allowed between administration of each drug. All subjects were tested with each of the drugs used. A total of 112 separate experiments were performed using six different drugs, one of which was given in two amounts and was also combined with another. The results were compared with the previous study which involved fifteen subjects and utilized the recommended dose of these same drugs.

The drugs and the doses used were as follows:

Meclizine	Bonamine	150 mg
Hyoscine	Scopolamine	0.06 mg
Hyoscine	Scopolamine	1.2 mg
d-Amphetamine	Dexadrine	20 mg
Thiethylperazine	Torecon	30 mg
Trimethobenzamide	Tigan	750 mg
Prochlorperazine	Compazine	15 mg
Placebo	Lactose	750 mg

A combination of 1.2 mg hyoscine and 20 mg of d-amphetamine was also used.

The subjects were given questionnaires which were filled out prior to the test procedure to record the side effects produced by the drugs. Medical surveillance was maintained for eight hours following administration of the drugs. Blood pressures and pulse rates were recorded periodically.

To avoid conditioning the subjects against the experiments a scale of signs and symptoms of motion sickness was adopted from previous research (6,10). This enabled a definite diagnosis of motion sickness to be made short of emesis.

The subjects were required to continually set a sequence of five dials to numbers given at four-second intervals by a tape recorder (Figure 1, reference 7). The dials were arranged in such a manner as to require head movements which approximated the stimulation received by the vestibular receptors from the roll, pitch, yaw, and heave of a surface vessel or aircraft. The subjects were spun at increasing RPM in the SRR until they developed the malaise III (Table I) (6) condition of motion sickness in 50 head movements or less. This was considered to be the subject's basal susceptibility to motion sickness. Two control runs and a placebo run were then taken for each subject to confirm this baseline before administration of the drugs. Placebo runs were given periodically throughout and at the end of the experiment to determine any adaptation of the subjects to the stimulus. If a subject completed 300 head movements without developing malaise III, the test was halted.

The subjects were isolated in the SRR during the test periods except for a television monitor and a trained observor who recorded signs and symptoms of motion sickness.

RESULTS

The therapeutic effect was enhanced by the increased dose with only two of the antimotion sickness preparations used in this project. An increased effectiveness was seen with d-amphetamine (20 mg) and with the combination of d-amphetamine (20 mg) and hyoscine (1.2 mg). In a previous study 10 mg of d-amphetamine increased the tolerance to motion by 80 per cent or an average increase of 44 head movements over the placebo level. In this study the dose of 20 mg of d-amphetamine increased this protection to a level of 170 per cent or an average of 92 head movements over the placebo level (Figure 2).

The combination of hyoscine and d-amphetamine was the most effective preparation in both studies. Earlier 0.6 mg of hyoscine with 10 mg of d-amphetamine increased the tolerated head movements by an average of 133 movements or by 240 per cent. A dose of 20 mg d-amphetamine with 1.2 mg hyoscine increased this to an average of 206 movements or by 375 per cent over the corresponding placebo level.

Hyoscine (0.6 mg) increased the tolerated head movements by an average of 88 or by 160 per cent in the first study. Doubling the dose of hyoscine (1.2 mg) in the present research failed to produce an increase in resistance to motion sickness. This failure to increase therapeutic effectiveness with increased dosage was also seen with all other drugs used in this study with the two exceptions which were mentioned above. A decrease in effectiveness was seen with increased doses of prochlorperazine (Compazine) 15 mg, trimethobenzamide (Tigan) 750 mg, and meclizine (Bonamine) 150 mg. Thiethylperazine (Torecan) 30 mg showed the most marked drop in effectiveness as the number of tolerated head movements fell from an average of 4 less than the placebo to an average of 40 less with the increased dose.

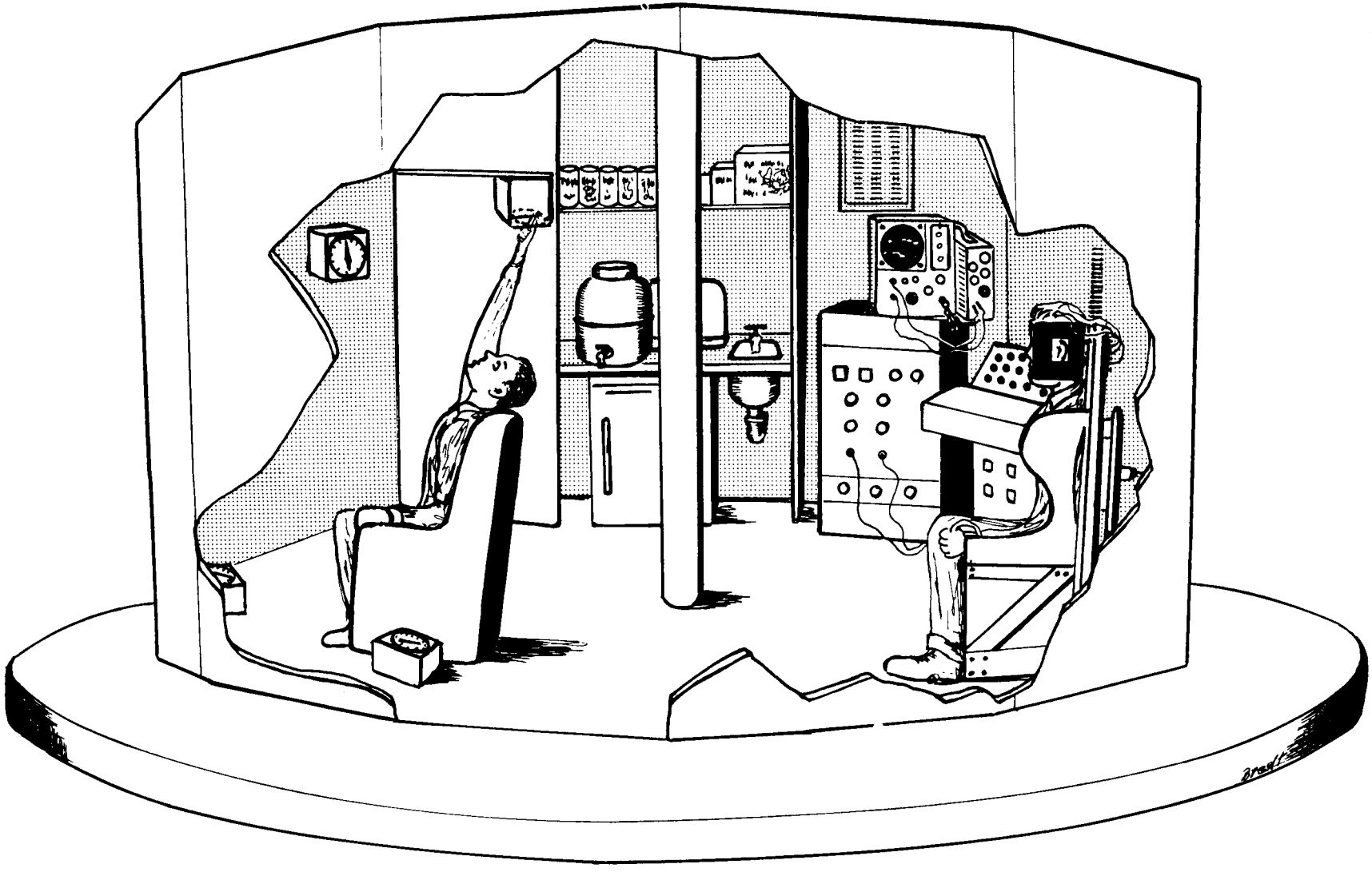

Figure 1

Subject Performing Dial Test in Pensacola
Slow Rotation Room (reference 7)

Table I

IMPORTANT VESTIBULAR SYMPTOMS* USED IN DIAGNOSTIC CATEGORIZATION

PATHOGNOMONIC	MAJOR	MINOR	DIAGNOSTIC TERMS
VOMITING	RETCHING		VESTIBULAR SICKNESS:
	NAUSEA III OR II	NAUSEA I	VOMITING OR TWO MAJOR SYM. OR ONE MAJOR & TWO MINOR
	INC. SALIV. III OR II	INC. SALIV. I	MALAISE III:
	PALLOR III	PALLOR II	ONE MAJOR OR TWO MINOR OR ONE MINOR & TWO OTHER
	COLD SWEAT III	COLD SWEAT II	MALAISE I:
	DROWSINESS III	DROWSINESS II	ANY SUBJ. SYM. OR ANY SIGN USUALLY ASSOC. WITH SUBJ. SYM.
			MALAISE II:
			ALL OTHER

* IN RARE INSTANCES OTHER SYMPTOMS QUALIFY

(Graybiel, A., reference 6)

Figure 2

Average Number of Tolerated Head Movements for Each of Drugs Tested. Arrows Indicate Effectiveness of Recommended Dose of These Drugs in Previous Study.

The results of the questionnaire on side effects are in Table II and are reported in percentages to correspond with other side effect studies. The dose of 1.2 mg of hyoscine produced marked drowsiness, blurring of vision, fatigue, and nervousness. Hyoscine in the 0.6 mg dose produced a slightly less severe state of drowsiness, but a greater incidence of vertigo was reported. The combination of hyoscine (1.2 mg) and d-amphetamine (20 mg) caused the largest number of subjects to report vertigo and stomach awareness. The drowsiness reported with this combination was milder than with hyoscine alone. When d-amphetamine (20 mg) was administered, some blurring of vision, vertigo, and nervousness were reported. One subject reported a headache which appeared to be due to an increase in blood pressure from 125/80 mm Hg to 140/90 mm Hg. This was the greatest alteration of blood pressure noted in the study and the only report of headache from this dose of d-amphetamine. The mildest drug as indicated by the questionnaire was meclizine in spite of the dose of 150 mg. One half of the subjects reported no side effects with this drug. Trimethobenzamide (Tigan) had only slightly more side effects reported than did meclizine. Thiethylperazine (Torecan) in the 30 mg dose produced considerable drowsiness and headache but no vertigo was reported. When the lactose placebo was given, one third of the subjects reported drowsiness and one sixth reported a headache.

DISCUSSION

The Slow Rotation Room appears to offer an excellent test situation for the antimotion sickness drugs. The standardized head movements and rate of spin permitted the same vestibular stimulus to be repeated for each subject through a series of experiments. This controlled test situation permits a more exact comparison of the effectiveness of each of a group of antimotion sickness drugs. Such an exact comparison is not possible under the uncontrolled conditions of field tests (9). The results of this study are in general agreement with the literature (14) in that the well-established drugs such as hyoscine and meclizine were most effective. Preparations which were ineffective in this research were those which have not had extensive testing as antimotion sickness drugs, such as thiethylperazine (Torecan) (12), trimethobenzamide (Tigan) (13), and prochlorperazine (Compazine) (1). The exception to this was d-amphetamine which has had only a few reports of effectiveness as an antimotion sickness remedy. Prior to World War II it was reported to have antimotion sickness activity by Hill (8). Blackham (2) shortly thereafter reported it to be one of the best drugs in his study. Since that time it has apparently not been used against motion sickness. In the present research it was the second most effective drug. In our previous study it also proved to be effective in the 10 mg dose. The fact that it has proven effective suggests that the sympathomimetics may be a promising area for future development of antimotion sickness drugs.

The most effective single drug in this study was hyoscine (0.6 mg). Doubling this dose failed to increase the therapeutic potency; however, in combination with d-amphetamine the increase in tolerance to motion exceeded the sum of the effect of these drugs when used separately. This separation would have shown an even greater effect except for the fact that five of the eight subjects on this drug completed the full three hundred head movements and were halted there. In two of the remaining subjects this drug combination produced the best therapeutic effect of the preparations tested.

Table II

Percentage of Incidence of Drug Side Effects as Recorded on Subjects' Questionnaires

Side Effects	Hyoscine & d-Amphetamine	Hyoscine 1.2 mg.	Hyoscine 0.6 mg.	d-Amphetamine	Meclizine	Torecan	Compazine	Tigan	Placebo
Fatigue	22%	56%	40%	10%	13%	42%	10%	13%	4%
Drowsiness	60%	86%	80%	10%	13%	56%	22%	13%	32%
Headache	0	28%	30%	10%	13%	28%	33%	13%	16%
Blurred vision	22%	56%	40%	33%	0	0	0	13%	0
Vertigo	55%	42%	50%	22%	13%	0	0	0	4%
Nervousness	10%	42%	0	33%	0	28%	10%	13%	8%
Dry mouth	10%	28%	30%	10%	0	0	10%	0	0
Nausea	33%	28%	30%	10%	13%	0	22%	0	4%
None	10%	0	0	22%	50%	0	33%	36%	36%

The signs and symptoms of motion sickness closely resemble the effect of overactivity of the parasympathetic nervous system. An overdose of neostigmine which protects acetylcholine, the mediator of the parasympathetics, produces similar reactions. The effective drugs discussed above included a parasympathetic blocking agent and a sympathomimetic; this with the aforementioned facts would suggest that part of the mechanism of action of these drugs could be the result of a shift of autonomic activity toward the sympathetics. Further support is lent to this contention by the report that dibenzoline, which blocks the sympathetics, increases susceptibility to motion sickness (4).

The increased dose of meclizine, thiethylperazine, trimethobenzamide, and prochlorperazine produced less of a therapeutic effect than did the recommended dose. This decrease in protection has also been observed in other studies on the antimotion sickness drugs (11). It is well established (3) that any factor that irritates the stomach lowers the tolerance for motion and this could be a factor with the large doses used here. Nausea is also a common side effect with overdose of various drugs. It was reported for six of the preparations on the side effects questionnaire which was completed by the subjects before entering the SRR. The decrease in potency with increased dose may have been related to these facts.

A review of the literature on antimotion sickness drugs indicated that hyoscine and meclizine should be of about equal potency. A very significant difference in favor of hyoscine was found in this and in our earlier study. The British investigators (5) have long held that hyoscine is the superior drug, while several U. S. reports favor the antihistamines as being the most effective (11). A difference in strength of stimulus in the various studies may be responsible for these divergent reports. Our results strongly support the view that hyoscine is the drug of choice for prevention of motion sickness.

Subjects with defective labyrinths have been studied and have been found to be resistant to motion sickness even under the most extreme conditions (6). The side effect of vertigo in this study was roughly correlated to potency of the drugs against motion sickness. These observations suggest that these drugs may act at the vestibular receptor sites by lowering their sensitivity. It is difficult, however, to visualize d-amphetamine as having this mechanism of action.

The scale of signs and symptoms used to determine motion sickness gave very good results with trained subjects and observers. It would most likely be difficult to apply it to untrained personnel under field conditions. The slight but steady rise in the basal (placebo) tolerance for motion indicated that little conditioning against the test occurred. This enabled each subject to be tested on all of the drugs used and also to serve as his own control.

The human centrifuge served as an excellent laboratory device for testing the antimotion sickness drugs. When the semicircular canals had stabilized to the constant rate of spin, no motion was perceived as long as the head remained stationary. With head movements the stimulation to the otoliths approximated that received from rough conditions in a plane or surface vessel.

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13. ABSTRACT In a previous study the recommended doses of some antimotion sickness drugs were tested on the Slow Rotation Room (human centrifuge). In the present study increased doses of these same drugs were used to investigate any possible increase in efficiency. Twice the dose of hyoscine (1.2 mg) failed to increase its effectiveness; however, when it was used in combination with d-amphetamine the total number of tolerated head movements exceeded the sum of that with these drugs when they were tested alone. A marked increase in effectiveness of d-amphetamine (20 mg) was noted over that in the earlier study in which a dose of 10 mg was used. Meclizine (Bonamine 150 mg), thiethylperazine (Torecan 30 mg), trimethobenzamide (Tigan 750 mg), and prochlorperazine (Compazine 15 mg) all were less effective than in the previous study when one third of these doses was used. The combination of hyoscine and d-amphetamine was the most effective drug, followed by hyoscine, d-amphetamine, and meclizine, in that order. Author

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