NAMI-983

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JOINT REPORT

NAVAL AEROSPACE MEDICAL INSTITUTE
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

August 1968

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Bureau of Medicine and Surgery
MR005.04-0021.139

NASA Order R-93

Released by

Captain J. W. Weaver, MC USN
Commanding Officer

7 August 1968

*This research was conducted under the sponsorship of the Office of Advanced Research and Technology, National Aeronautics and Space Administration.

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SUMMARY PAGE

THE PROBLEM

Fifty subjects were exposed to stress on 500 occasions in a slow rotation room (SRR) to determine the effectiveness of 16 representative drugs in reducing susceptibility to acute motion sickness.

FINDINGS

Only the drugs with a sympathomimetic or parasympatholytic action and some of the antihistamines were notably effective. The summation effect of dextroamphetamine sulfate and l-scopolamine hydrobromide provided far better protection than any single drug. Other classes of drugs had either a slightly favorable or slightly unfavorable action.

INTRODUCTION

Bard, in a review of the status of the motion sickness problem, which appeared in 1948, wrote as follows:

> "In respect to drug therapy, both prophylactic and curative, it can be be said that no claim of the effectiveness of any pharmacologic agent or combination of agents made before the war was convincing. Most of these claims were based on the impressions of physicians who had, from time to time, treated small numbers of seasick patients, most of whom doubtless represented the most susceptible group in the general population. Scarcely any tests were controlled by the giving of placebos, and one looks in vain for data that could meet the most rudimentary statistical requirements (1, p. 279). . . .
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> . . . "The first indisputable evidence that prophylactic drug medication was effective ... came as the result of carefully controlled experiments carried out during amphibious training operations, in a few longer sea trials, in aviation training programs, and in swing tests. The agreement is general that hyoscine, in a dose of 0.6-0.8 mg., protects from 50 to 60 per cent of susceptibles over a period of at least eight hours . . . . It now seems fairly certain that benzedrine, prostigmine compounds, thiamine, nicotinic acid and pyridozine do not give protection (1, p. 285)." *

The identification of dimenhydrinate as an agent effective in blocking the action of histamine (13) and the demonstration by Gay and Carliner (8) that it was effective in preventing motion sickness led to a great exploitation of the antihistaminic drugs and, to some extent, an unwarranted neglect of hyoscine. Many additional antihistaminic preparations were identified, and their value in the prevention of motion sickness has been extensively and authoritatively reviewed (3,6).

Another important development involved the elucidation of the neural mechanisms underlying emesis (2,23,24) and the identification of emetic and antiemetic drugs (reviewed by Wang, ref. 22). This brings up the question of the relationship between emesis and motion sickness. Wang (22) classified motion sickness under "emetic syndromes" and emphasized studies in which "vomiting" was used as the diagnostic criterion for the presence of motion sickness. Actually, the "nausea syndrome" is only part of the widespread symptomatology of motion sickness and emesis only one of its manifestations. In the prevention of motion sickness the drugs of choice seem not to be those whose principal action is on the chemoceptive trigger zone and emetic center.

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* Note: Representative reports of these controlled experiments are listed in the bibliography.

The high "cost" and great difficulties in conducting rigorous empirical testing of antimotion sickness drugs under field conditions led to the exploitation of a slow rotation room (SRR) where the stressful Coriolis accelerations were under quantitative control (9) and the experimenter and subject could collaborate in determining when a specified "end point" had been reached (10). This report summarizes our published (7,25,26) and unpublished data regarding the study of 16 drugs with eight variations in dosage and three different combinations of drugs; selection was based on the reported effectiveness of drugs in different categories as revealed by a review of the relevant literature (27).

PROCEDURE

Fifty Navy enlisted men 17 to 23 years of age were volunteer subjects. A comprehensive medical evaluation revealed that all were in good health. With regard to the sensory organs of the inner ear, none had any significant loss of: 1) hearing as revealed by audiometry, 2) otolith function as revealed by ocular counterrolling (16), or 3) canal function as revealed by the threshold caloric test (14). The Coriolis accelerations were generated by requiring the subject, while seated, to flex his head and upper part of the body out of the plane of the room's rotation. These "head movements" were standardized (9) by requiring the subject to set the needle of five dials to different locations according to taped instructions; the sequential order of the dial settings was varied in a random fashion. A series of five head movements followed by a pause was termed a "sequence" and required 30 seconds. Thus, the duration of stress in minutes was equivalent to ten head movements, or two sequences, and the severity of the stress increased as a function of the room's angular velocity.

By individualizing the level of stress, persons with varying susceptibility to motion sickness could serve as their own controls in an experiment. As part of the initial workup, subjects were "calibrated" in terms of the number of head movements at a given rpm necessary to produce a level of motion sickness termed "Severe Malaise" (M III). This end point has been precisely defined (10), and suffice it here to describe it as mild motion sickness to which subjects do not object. Independent estimates of the M III end point indicated close agreement among experimenters with previously shared experiences.

The double blind technique was used. Drugs and placebo (lactose) were in matched oral capsules and administered using a Latin square design. In each of five experiments, seven drugs and three placebos (four placebos on one occasion) were given to ten subjects, each participating in ten experimental trials. In all, the 50 subjects were exposed to stress on 500 occasions.

The capsules were given one to two hours prior to exposure in the SRR. Only one subject was exposed at a time. The number of head movements was recorded when the M III end point was reached and then the room brought to a stop. Habituation was taken into account by establishing the mean placebo level of susceptibility which was

used as the baseline in measuring the effects of the drugs. It should be emphasized that the procedure made it possible to demonstrate increased as well as decreased susceptibility.

RESULTS

The results are summarized in Figure 1 where the drugs and combination of drugs are ranked according to their effectiveness in reducing susceptibility to acute SRR sickness.

Among drugs with either a sympatholytic action or a tranquilizing effect, some caused a slight decrease and others an increase in susceptibility to SRR sickness. Phenoxybenzamine HCl and thiethylperazine maleate in the usual doses, as well as a triple dose of the latter, were found to reduce the subjects' tolerance to the stressful Coriolis accelerations. Trimethobenzamide HCl in a triple dose and meprobamate ranked just below the placebo level, while a single dose of the former was effective just above that level. A new drug known as Experimental 999 was the most effective although its level of effectiveness was below that of all antihistaminic drugs tested with the exception of meclizine in the usual dose. When 2 $\frac{1}{2}$ times the usual dose of Exp. 999 was administered, its effectiveness decreased.

All six of the antihistaminic agents tested caused a decrease in susceptibility to SRR sickness although the difference between the least and most effective was large. The effectiveness of meclizine was not increased when given in combination with dextroamphetamine sulfate.

The effectiveness of the sympathomimetic drugs was a chance finding and is thus explained: amphetamine was given to counter the drowsiness caused by l-scopolamine hydrobromide and then administered alone for purposes of experimental control. In a 10-mg dose it was found to rank in effectiveness near the middle of the antihistamine group. It was unique among drugs tested in that a larger than the "recommended" dose increased its effectiveness, but the side effect (nervousness) contraindicated this dose for routine use.

Scopolamine with a parasympatholytic action was the single most effective drug. When the usual dose of 0.6 mg was doubled, its effectiveness was not increased, the actual number of head movements decreasing slightly. Drowsiness and "dry mouth" were prominent side effects.

The combination of the sympathomimetic drugs and scopolamine, a parasympatholytic drug, was additive in case of ephedrine and synergistic in the case of amphetamine 20 mg plus scopolamine 1.2 mg. The only troublesome side effect was "dry mouth." The same combination in half the doses was nearly as effective.

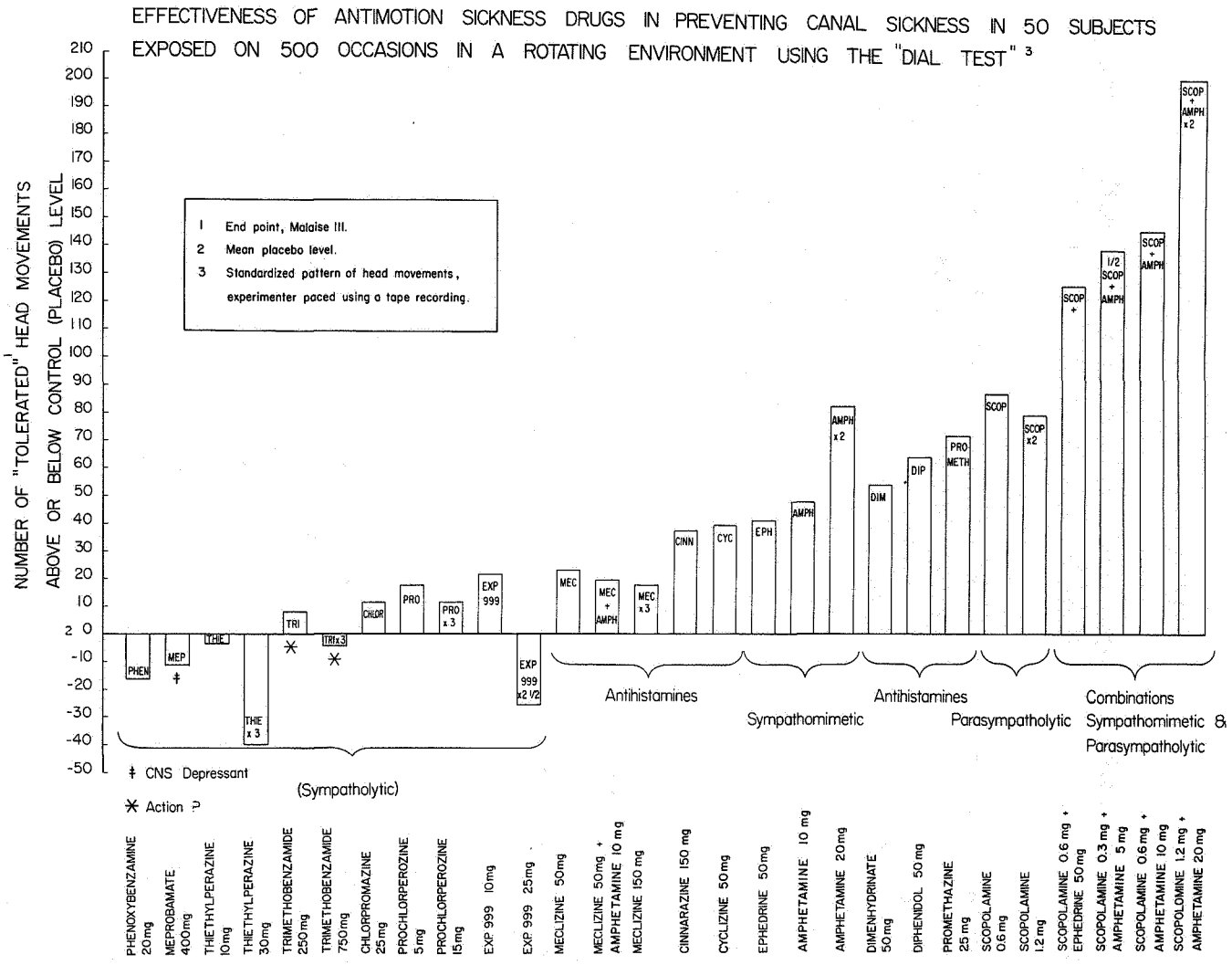

Figure 1

Drugs and Combination of Drugs Ranked According to Their Effectiveness

DISCUSSION

The fact that the act of ranking the antimotion sickness drugs in terms of effectiveness also tended to place them in classes according to their principal pharmacological action is proof both of the reliability and validity of the method used in the Slow Rotation Room.

Among the accounts (4,5,11,12,17-19) dealing with the value of sympathomimetic drugs in motion sickness, only two early reports (11,12) indicated that adrenergic drugs had prophylactic value, but these claims were lost among the welter of those (1,15,21) for other preparations with no value whatsoever. Our finding that ephedrine and amphetamine clearly decreased susceptibility to acute SRR sickness was bolstered by the fact that phenoxybenzamine, a sympatholytic drug, had an opposite effect. Indeed, when this drug is exhibited in proper dosage, the cardinal symptoms of motion sickness can be reproduced due to its central action.

Our findings with regard to scopolamine are fully in accord with those reported by other investigators using widely different force environments as indicated earlier.

There have been experimental trials with a combination of scopolamine and sympathomimetic drugs using swing tests (18,20), but the results were somewhat contradictory. Our findings demonstrating that the salutary effects of a combination of amphetamine and scopolamine summed or even reached a synergistic level could not be gainsaid. This combination also had a mutually advantageous behavioral effect in minimizing the individual side effects of overalertness and drowsiness.

The explanation for the differences in our results from those of other investigators with regard to the prophylactic value of sympathomimetic drugs is not clear. One possibility is that we were dealing with mild and not severe motion sickness, and another but less likely possibility is that the chief vestibular contribution to SRR sickness has its origin in the semicircular canals.

The absence of any benefit from drugs by virtue of their tranquilizing action in the SRR may be explained by the absence of anxiety under the circumstances. Drugs valued for their antiemetic action per se would not have had a proper trial when the end point was "severe malaise," a mild degree of motion sickness.

Although the procedural advantages mentioned above overcame handicaps which would be encountered under field conditions, they limit the validity of the results when applied to actual operational conditions. Some of the factors to be taken into account are: 1) the uniformity of our subjects, 2) the unique force environment, 3) the control over such secondary etiologic factors as anxiety and the visual environment, and 4) the fact that we were concerned only with the prevention of mild motion sickness.

Insofar as sympathomimetic and parasympatholytic preparations have prophylactic value, it would appear that they must counter the unusual vestibular inputs before these inputs have an opportunity to exert their influence in the genesis of symptoms. This is a fruitful line of investigation with regard to both the etiology and prevention of motion sickness.

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Unclassified
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
Naval Aerospace Medical Institute Pensacola, Florida 32512	UNCLASSIFIED
	2b. GROUP N/A

3. REPORT TITLE

EVALUATION OF SIXTEEN ANTIMOTION SICKNESS DRUGS UNDER CONTROLLED LABORATORY CONDITIONS

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*

N/A

5. AUTHOR(S) *(First name, middle initial, last name)*

Charles D. Wood and Ashton Graybiel

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
7 August 1968	11	27

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
NASA R-93	
b. PROJECT NO. MR005.04-0021	NAMI-983
c.	9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)*
d.	139

10. DISTRIBUTION STATEMENT

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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY

13. ABSTRACT

The effectiveness of a drug in reducing susceptibility to acute motion sickness is readily determined in a slow rotation room (SRR) where the stressful Coriolis accelerations are under quantitative control and the experimenter and subject can collaborate under laboratory conditions. Fifty subjects were used, each serving as his own control, in evaluating 16 representative antimotion sickness drugs. Only the drugs with a sympathomimetic or parasympatholytic action and some of the antihistamines were notably effective. The summation effect of dextroamphetamine sulfate and l-scopolamine hydrobromide provided far better protection than any single drug. Other classes of drugs had either a slightly favorable or slightly unfavorable action.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Acute motion sickness						
Susceptibility reduction						
Coriolis acceleration						
Antimotion sickness drugs						
Pharmacological action						