HUMAN BIOASSAY OF ANTIMOTION SICKNESS DRUGS

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13. ABSTRACT

Three experiments were conducted with the main object of improving a procedure for evaluation of antimotion sickness drugs in human subjects. In previous experiments, a constant level of stressful stimuli was generated by requiring subjects to execute standardized head movements at a predetermined angular velocity in a rotating room. The ceiling on the test (300 head movements) was often reached before the motion sickness endpoint. A second handicap in past experiments stemmed from the need to measure the effectiveness of a drug in terms of departures from a placebo baseline. Drugs and placebos were administered using a 10-unit Latin-square design and, although the placebo baseline was accurate for the group (10 subjects), the number and distribution of the placebos prevented drawing adequate placebo baselines for individual members of the group. In the experiments now reported an incremental increase in stressful stimuli was used, thereby reducing the number of failures to reach the motion sickness endpoint. By increasing the number of placebos (involving a modification of the Latin-square design) the accuracy of drawing placebo baselines was increased. Only drugs known to have antimotion sickness effectiveness were tested and the cardinal findings can be briefly summarized.

1. Great individual differences in response to antimotion sickness drugs administered in usual doses were revealed. In one experiment (involving 11 subjects and 7 drugs) the single best therapeutic response implicated all seven drugs tested (three single drugs and four fixed-dose combinations).

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2. In terms of percentage of subjects demonstrating a substantial beneficial antimotion sickness drug effect, administration of a fixed-dose combination of promethazine hydrochloride and ephedrine sulfate (25 mg each) proved to be outstanding; this combination of homergic drugs clearly exhibited a suprasummation effect.

3. A few tests were conducted using larger than usual doses and the results support previous findings that for a maximal beneficial effect in response to a single dose, individuals may vary both with regard to the choice of drug and the amount administered.

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SUMMARY PAGE

THE PROBLEM

Previous reports from this laboratory dealing with the assessment of antimotion sickness remedies in man employed a 10-unit Latin-square design under a double-blind condition; susceptibility to motion sickness was measured in a rotating room using a stressful stimulus of constant intensity. Employing this procedure, two limitations were revealed: 1) the ceiling on the test (30 rpm) was sometimes reached before the motion sickness endpoint, and 2) the findings had validity for a group but not for every individual in the group. The main object of the present experiments was to overcome these limitations.

FINDINGS

1. The substitution of an incremental increase in the intensity of the stressful stimuli for stimuli of constant intensity and the systematic use of placebos instead of a random distribution within a Latin-square design, yielded findings valid both for a group and for all individuals within the group and, at the same time, demonstrated substantial individual differences in response within the group.

2. Only drugs known to have antimotion sickness effectiveness were tested and the cardinal findings can be briefly summarized.

Great individual differences were revealed both in the general effectiveness of antimotion sickness drugs and in the effectiveness of a particular drug in a particular dose.

The overall beneficial effects of a combination, promethazine hydrochloride (25 mg) and ephedrine sulfate (25 mg), that had not been tested previously, were outstanding and ranked first among 15 drugs tested alone or in combination. Singly, promethazine (25 mg) was in a tie for ninth place and ephedrine (25 mg) ranked last. In other words, these two homergic drugs demonstrated, to a striking degree, supra-summation effects.

Ephedrine sulfate in combination with either promethazine or scopolamine occupied the first three places in the rankings for overall effectiveness, implying that it has a greater role to play in the identification of antimotion sickness remedies than was formerly thought to be the case.

Single drugs and drug combinations not outstanding in terms of overall effectiveness nevertheless were often the single most effective antimotion sickness remedy. Our meager findings suggest the need for a systematic evaluation (dose-response relationships) of representative antimotion sickness drugs.

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INTRODUCTION

The fact that antimotion sickness drugs are effective in any motion environment implies that their effectiveness may be evaluated in any motion environment but it must be kept in mind that persons may differ in their susceptibility to motion sickness under different stimulus conditions. We have exploited the advantages of a slow rotation room (SRR) in a laboratory setting for assessing antimotion sickness drugs (1). In a SRR the stressor effect is trivial unless a person moves his head out of the plane of the room's rotation, hence the experimenter can remain symptom-free while observing the subject who is required to execute head movements in a standardized manner. Susceptibility to motion sickness was measured as a function of length of exposure using a stimulus of constant intensity, i.e., by executing standardized head movements while rotating at a predetermined angular velocity. Subjects were given the drugs (usually seven) and placebos (three, regarded as drugs) according to a 10-unit Latin-square design using a double-blind technique. When the data from experiments on 60 subjects were summarized (1, 2), ranking the drugs in terms of their antimotion sickness effectiveness tended to place them in classes according to their pharmacological activity, an observation that supported the validity of the procedure used. Moreover, there was a clear indication that beneficial effects were related to central parasympatholytic and sympathomimetic actions.

Shortcomings in the method were also revealed, attributable in part to the necessity of having subjects serve as their own controls, in part to a low ceiling on the test (nonmotion sickness endpoint) and in part to the fact that the results, while valid for the group of subjects, varied in their validity for individuals within the group. This report describes three experiments directed at overcoming these handicaps which also provided new information on representative antimotion sickness drugs.

EXPERIMENT I

PROCEDURE

SUBJECTS

Fourteen men 21 to 28 years of age were selected for participation as paid volunteers. All were college students and selected from among a larger number on the basis of a comprehensive medical evaluation and the absence of vestibular defects based on specific tests of canalicular, otolithic, and combined vestibular functions. Persons with exceptionally high or low susceptibility to motion sickness were not accepted.

METHOD

The Stress Profile

Stressful types of accelerative stimuli were generated by the active rotation of the subject's head (and body) out of the plane of the room's rotation (always counterclockwise).

The head movements were executed while the subject (each subject was tested individually) was seated in a specially designed chair (Figure 1) that had adjustable pads (front, back, left and right) acting as "stops" limiting the head movements in the four quadrants to 90 degrees. Head movements "over" and "back" in the four cardinal directions were randomized, and a taped recording set the cadence at one movement every 2 seconds (3). Forty head movements were executed at 1 rpm and were repeated at 1-rpm increments in angular velocity (standardized at 40 seconds) until either the ceiling on the test, 30 rpm, or the motion sickness endpoint (defined below) was reached. If the motion sickness endpoint was reached prior to the execution of 40 head movements, it presented a minor problem in scoring; sometimes it was convenient (more accurate) to deal with the number of head movements rather than rpm but usually the score was measured in 0.1 rpm's (four head movements) and added to the completed rpm score.

Scoring the Severity of Motion Sickness

The observer, in collaboration with the subject, estimated the levels of severity of the symptoms after every set of 40 head movements; the 40-second intervals during change in rpm were for this purpose. The levels of severity of motion sickness were given numerical scores according to the diagnostic criteria in Table I (4). In Experiment I the motion sickness endpoint was either slight nausea or 12 points, whichever came first. Subject rarely gave the signal to stop a test before a motion sickness endpoint was reached; this only occurred at high rpm.

Drugs and Their Administration

The following drugs were chosen for evaluation based mainly on previous findings demonstrating their efficacy:

1. l-scopolamine hydrobromide (0.6 mg)
2. dimenhydrinate (50 mg)
3. d-amphetamine sulfate (10 mg)
4. l-scopolamine (0.3 mg) + d-amphetamine sulfate (5 mg)
5. l-scopolamine (0.6 mg) + d-amphetamine sulfate (10 mg)
6. dimenhydrinate (50 mg) + ephedrine sulfate (50 mg)
7. promethazine hydrochloride (25 mg) + ephedrine sulfate (50 mg)

Ten of the 14 subjects were fitted into a 10-unit Latin-square design that was typical except that two extra placebos were added as tests number 1 and number 12. When these additions resulted in a series of three placebos the opportunity was taken to substitute a drug for a placebo. The four "extra" subjects were treated as Subjects 1-4 in a second 10-unit Latin-square design.

Figure 1

Subject Seated on a Specially Designed Chair in a Slow Rotation Room. The Hand Holds Facilitate the Execution of Head Movements and the Adjusrable Stops Ensure Control Over the Arc of Rotation

Table I

Diagnostic Categorization Of Different Levels Of Severity Of Acute Motion Sickness

Category	Pathognomonic 16 points	Major 8 points	Minor 4 points	Minimal 2 points	AQS* 1 point
Nausea syndrome	Nausea III,† retching or vomiting	Nausea II	Nausea I	Epigastric discomfort	Epigastric awareness
Skin		Pallor III	Pallor II	Pallor I	Flushing/Subjective warmth ≥II
Cold sweating		III	II	I	
Increased salivation		III	II	I	
Drowsiness		III	II	I	
Pain					Headache (persistent) ≥II
Central nervous system					Dizziness (persistent)
					Eyes closed ≥II
					Eyes open III

Levels of Severity Identified by Total Points Scored

Frank Sickness (FS)	Severe Malaise (M III)	Moderate Malaise A (M IIA)	Moderate Malaise B (M IIB)	Slight Malaise (M I)
≥16 points	8 – 15 points	5 – 7 points	3 – 4 points	1 – 2 points

*AQS – Additional qualifying symptoms

†III – severe or marked, II – moderate, I – slight

Measuring the Effect of a Drug on Motion Sickness Susceptibility

Taking account of variations in placebo responses always posed a problem, and the following criteria were used in establishing a placebo baseline or "level": 1) When the variations were similar and small, i.e., ≤ 2 rpm, a mean value level baseline was used, 2) When there was a rise or fall in placebo scores but the variation relatively small (≤ 3 rpm) the placebo level was indicated by one or more best-fit sloped baselines. When the variations in placebo scores were greater than 3 rpm the placebo level was estimated using the placebo score immediately preceding a particular test score, keeping in mind evidence of adaptation effects. First, the extremes of the placebo range were estimated and the mean placebo level or baseline identified. Next the range for "inconsequential" motion sickness response was defined as lying within limits representing twice the values of the placebo range. To qualify as a "beneficial" effect the difference between the placebo baseline score and the motion sickness endpoint score had to equal or exceed twice the difference (in rpm) between the placebo baseline and the score indicating the upper limit of the inconsequential range. When the motion sickness endpoint score equaled or exceeded twice the difference between the placebo baseline and the lower limit of the inconsequential range the therapeutic effect was termed "detrimental."

Plan

There was an initial period of familiarization that included provocative tests in the SRR designed to determine susceptibility to motion sickness. Subjects reported at 0730 hours (without breakfast) and were given four ounces of orange juice and a small package of crackers. Prior to each test the subject was interviewed with the aid of a "pre-experiment questionnaire" to ensure that he was fit for the test that day. At 60 minutes prior to testing the capsule containing the drug or placebo was given along with a tablespoon of applesauce if desired. At least 48 hours elapsed between tests; this period varied from 2 to 14 days and was usually 2-5 days. Much of the adaptation acquired in a brief test decays in a period of 2 days; at worst, variations in the intervals between tests only adds to the difficulty in drawing a placebo level or baseline.

RESULTS AND DISCUSSION

One subject failed to complete the experiment, one required an operation (unrelated to the study) and was forced to withdraw and another was dropped for lack of motivation. The findings on 11 subjects are presented in Table II. An estimate of the placebo level was impossible in two tests, and in three more instances the 30-rpm ceiling on the test was reached before the motion sickness endpoint. In these (and subsequent) instances the sign for "greater than," $>$, is used before the notation of "change" in rpm and "percent change in rpm." Note in Table II that the difference between the rpm's representing the drug and placebo scores is also expressed as a percent and that

Table II

Individual Responses to Seven Different Antimotion Sickness Drugs (Experiment I)

Subject	Drug 1. Scopolamine (0.6 mg)					Drug 2. Dimenhydrinate (50 mg)					Drug 3. Amphetamine (10 mg)					Drug 4. Scopolamine (0.3 mg) Amphetamine (5 mg)				
	Motion Sickness Endpoint		Column I minus Column II	% rpm Change	Significance of rpm Change[2]	Motion Sickness Endpoint		Column I minus Column II	% rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	% rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	% rpm Change	Significance of rpm Change
	I Drug rpm[1]	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%	
1	20.0					19.0	11.3	+7.7	+68	B	5					21.0	3			
2	22.0	12.2	+9.8	+80	B	17.0	11.0	+6.0	55	B	13.0	11.4	+ 1.6	+14	I	16.0	11.0	+5.0	+45	B
3	17.0	13.0	+4.0	+30	B	10.0	13.0	-3.0	-23	D	14.0	11.0	+ 3.0	+27	B	10.0	12.0	-2.0	-17	D
4	15.0	13.4	+1.6	+12	I	16.0	15.6	+0.4	+ 3	I	14.0	14.9	- 0.9	- 6	I	11.0	14.5	-3.5	-25	D
5	15.0	16.0	-1.0	- 6	I	16.0	18.6	-2.6	-14	I	30.0[6a]	19.5	>+10.5	>+54	B	21.0	13.2	+7.8	+59	B
6	27.0	22.7	+4.3	+19	B	25.0[4]	23.0				24.0[4]	20.0				21.0	22.4	-1.4	- 6	I
7	22.0	13.0	+9.0	+69	B	23.0	18.0	+5.0	+28	B	18.0	16.2	+ 1.8	+11	I	17.0	15.0	+2.0	+13	I
8	15.0	13.0	+2.0	+15	B	19.0	11.5	+7.5	+65	B	13.0	13.0	0	0	I	14.0	11.0	+3.0	+27	B
9	13.0	11.0	+2.0	+18	I	17.0	12.0	+5.0	+41	B	12.0	13.0	- 1.0	- 8	I	16.0	10.0	+6.0	+60	B
10	12.0	11.0	+1.0	+ 9	I	17.0	15.8	+1.2	+ 8	I	12.0	11.0	+ 1.0	+ 9	I	18.0	18.4	-0.4	- 2	I
11	11.0	11.0	0	0	I	8.0	11.0	-3.0	-27	D	13.0	11.0	+ 2.0	+18	B	11.0	11.0	0	0	I
	n = 10				B I D	n = 10				B I D	n = 9				B I D	n = 10				B I D
$\bar{X}$ =	16.9	13.6	+3.3	+24	50% 50% 0%	16.2	13.8	+2.4	+17	50% 30% 20%	15.4	13.4	+ 2.0	+15	33% 67% 0%	15.5	13.9	+1.6	+12	40% 40% 20%

Subject	Drug 5. Scopolamine (0.6 mg) Amphetamine (10 mg)					Drug 6. Dimenhydrinate (50 mg) Ephedrine (50 mg)					Drug 7. Promethazine (25 mg) Ephedrine (50 mg)					B	I	D
1	12.0	11.3	+ 0.7	+ 6	I	15.0	11.3	+ 3.7	+33	B	17.0	11.3	+5.7	+50	B	3	1	0
2	13.0	10.0	+ 3.0	+30	B	12.0	13.0	- 1.0	- 8	I	15.0	10.7	+4.3	+40	B	5	2	0
3	13.0	13.0	0	0	I	13.0	10.0	+ 3.0	+30	B	20.0	13.0	+7.0	+54	B	4	1	2
4	16.0	14.7	+ 1.3	+ 9	I	15.0	15.3	- 0.3	- 2	I	19.0	12.0	+7.0	+58	B	1	5	1
5	30.0[6b]	17.2	+12.8	+74	B	12.0	14.6	- 2.6	-18	I	11.0	12.0	-1.0	- 8	I	3	4	0
6	26.0	22.8	+ 3.2	+14	B	27.0	22.5	+ 4.5	+20	B	25.0[4]	22.2				3	1	0
7	16.0	14.0	+ 2.0	+14	I	23.5	18.2	+ 5.3	+31	B	21.0	16.5	+4.5	+27	B	4	3	0
8	18.0	13.0	+ 5.0	+39	B	13.0	12.0	+ 1.0	+ 8	I	15.0	13.0	+2.0	+15	B	5	2	0
9	17.0	13.3	+ 3.7	+28	B	18.0	13.7	+ 4.3	+31	B	19.0	14.0	-5.0	+36	B	5	2	0
10	21.0	13.4	+ 7.6	+57	B	30.0	20.0	+10.0	+50	B	30.0[6c]	21.0	>+9.0	>+43	B	3	4	0
11	9.0	11.0	- 2.0	-18	D	11.0	11.0	0	0	I	9.0	11.0	-2.0	-18	D	1	3	3
	n = 11				B I D	n = 11				B I D	n = 10				B I D	n = 71		
$\bar{X}$ =	17.3	14.0	+ 3.4	+24	55% 36% 9%	17.2	14.7	+ 2.5	+17	55% 45% 0%	17.6	13.5	>+4.1	>+30	80% 10% 10%	B	I	D
																52%	39%	9%

1 rpm - revolutions per minute

2 B = beneficial; I = inconsequential; D = detrimental. See text.

3 No placebo baseline could be reasonably determined.

4 Subject did not reach endpoint because he complained of dizziness.

5 Subject did not receive this drug.

6 rpm ceiling. Motion sickness scores: 6a 10 points 6b 6 points 6c 9 points

= subject's best response. = detrimental response

the efficacy of the drug is categorized as beneficial (B), inconsequential (I) or detrimental (D). For each subject the drug demonstrating the highest efficacy is underlined and a square is used to indicate detrimental responses. The striking feature in Table II is the great intra- and interindividual differences in response to drugs generally regarded as effective in preventing motion sickness. Subject 11 manifested only one beneficial response (following the administration of amphetamine (10 mg)), and he accounted for three of the six detrimental responses. Subject 4 also manifested only one beneficial response (promethazine (25 mg) and ephedrine (50 mg)) and accounted for one detrimental response (scopolamine (0.3 mg) and amphetamine (5 mg)). Three subjects (2, 8, 9) manifested five beneficial responses, the first two in response to administration of the same drugs. It is noteworthy that the single best therapeutic response elicited in the 11 subjects involved all seven drugs.

When the subjects are considered as a group, the number of beneficial responses ranged from 33% (amphetamine 10 mg) to 80% (promethazine(25 mg) and ephedrine (50 mg)) and the average for all treatments was 52%.

EXPERIMENT II

In this experiment some procedural changes were introduced and half of the treatments involved promethazine and ephedrine.

PROCEDURE

The procedure described in Experiment I was used with the following changes:

SUBJECTS

Eleven male students, 21 to 24 years of age, were selected to serve as paid volunteer subjects but two soon withdrew because our schedule did not fit theirs.

Motion Sickness Endpoint

A score of 11 points which must include at least 2 points (stomach discomfort) in the nausea syndrome was used.

Drugs and Administration

The following drugs were given:

1. l-scopolamine hydrobromide (0.6 mg)
2. dimenhydrinate (50 mg)
3. promethazine hydrochloride (25 mg)
4. d-amphetamine (10 mg)
5. ephedrine sulfate (50 mg)
6. l-scopolamine hydrobromide (0.6 mg) + d-amphetamine sulfate (10 mg)
7. dimenhydrinate (50 mg) + ephedrine sulfate (50 mg)
8. promethazine hydrochloride (25 mg) + ephedrine sulfate (50 mg)

Modified (4 unit) Latin squares were designed with five placebos arbitrarily placed, one at the start and finish and one separating every pair of drugs.

Plan

The tests were conducted every other day in order to meet scheduling requirements. Subjects were requested to appear two hours and fifteen minutes before the test and to refrain from drinking alcoholic beverages beginning the afternoon prior to testing. The drug or placebo was always administered two hours before testing to ensure sufficient time for absorption. Orange juice and crackers were available if desired when the drugs were administered in order to avoid complaints that a drug "upset" their stomach.

RESULTS AND DISCUSSION

One subject withdrew from the experiment after experiencing a "dizzy spell" during the fourth test at 24 rpm.

Table III shows that on six of the drug assays the ceiling on the test (30 rpm) was reached before the elicitation of the motion sickness endpoints. This problem was handled in the manner described in Experiment I. Three aborts resulted from unexplained loss of power in the SRR; placebos had been administered in all of these instances and a satisfactory estimate of the placebo level could be made except in the case of Subject 13.

The individual variations in response to treatments were less striking than in Experiment I. Beneficial responses ranged from 25% in Subject 19 (who also accounted for the only detrimental response) to 100% in the case of Subject 15; the average for all subjects was 65%.

For the group of 8 subjects who completed the experiment the beneficial responses ranged from 37% in the case of amphetamine (10 mg) to 87% for the combination promethazine (25 mg) and ephedrine (50 mg). Neither of these two preparations at all of the remaining five drugs accounted for the "highest efficacy" ratings.

EXPERIMENT III

In this experiment an effort was made 1) to reduce the number of tests in which the motion sickness endpoint was not reached by increasing the intensity of the stressor, 2) to improve the measurement of the placebo baselines by increasing the number of placebos, and 3) to test the efficacy of the drug combination promethazine-ephedrine when the amount of ephedrine was halved.

Table III

Individual Responses To Eight Different Antimotion Sickness Drugs (Experiment II)

Subject	Drug 1. Scopolamine (0.6 mg)					Drug 2. Dimenhydrinate (50 mg)					Drug 3. Promethazine (25 mg)					Drug 4. Amphetamine (10 mg)					
	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change[2]	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	
	I Drug rpm[1]	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%		I Drug rpm	II Placebo rpm	rpm	%		
12	13.0	9.0	+ 4.0	+44[5]	B	11.0	9.0[4]	+ 2.0	+ 22	B	10.0	9.0	+1.0	+11	I	9.0	9.0	0	0	I	
13	28.0	16.5	+11.5	+70	B	24.0					24.0	20.0	+4.0	+20	B	18.0	18.0	0	0	I	
14	30.0[3a]	22.6	+ 7.4	+33	B	30.0[3b]	22.0	>+ 8.0	>+ 36	B	22.0	19.0	+3.0	+16	I	23.0	17.0	+ 6.0	+35	B	
15	24.0	14.4	+ 9.6	+67	B	28.0	13.0	+15.0	+116	B	24.0	15.0	+9.0	+60	B	21.0	16.0	+ 5.0	+31	B	
16	16.0	14.3	+ 1.7	+12	B	15.0	14.3	+ 0.7	+ 5	I	15.0	14.3	+0.7	+ 5	I	17.0	14.3	+ 2.7	+19	B	
17	9.0	10.0	- 1.0	-10	I	13.0	9.0	+ 4.0	+ 44	B	13.0	11.0	+2.0	+18	I	12.0	10.0	+ 2.0	+20	I	
18	15.0	11.8	+ 3.2	+27	B	17.0	13.0	+ 4.0	+ 31	B	17.0	13.0	+4.0	+31	B	13.0	11.6	+ 1.4	+12	I	
19	8.0	8.0	0	0	I	6.0	8.0	- 2.0	- 25	D	10.0	8.0	+2.0	+25	B	8.0	8.0	0	0	I	
	n = 8				B I D	n = 7				B I D	n = 8				B I D	n = 8				B I D	
$\bar{X}$ =	17.9	13.3	+ 4.6	+35	75% 25% 0%	17.1	12.6	>+ 4.5	>+ 36	72% 14% 14%	16.9	13.7	+3.2	+23	50% 50% 0%	15.1	13.0	+ 2.1	+16	37% 63% 0%	

Subject	Drug 5. Ephedrine (50 mg)					Drug 6. Scopolamine (0.6 mg) + Amphetamine (10 mg)					Drug 7. Dimenhydrinate (50 mg) + Ephedrine (50 mg)					Drug 8. Promethazine (25 mg) + Ephedrine (50 mg)						B I D
	I Drug rpm[1]	II Placebo rpm	Column I minus Column II rpm	rpm Change %	Significance of rpm Change[2]	I Drug rpm	II Placebo rpm	Column I minus Column II rpm	rpm Change %	Significance of rpm Change	I Drug rpm	II Placebo rpm	Column I minus Column II rpm	rpm Change %	Significance of rpm Change	I Drug rpm	II Placebo rpm	Column I minus Column II rpm	rpm Change %	Significance of rpm Change		
12	10.0	9.0	+ 1.0	+11	I	13.0	9.0	+ 4.0	+ 44	B	9.0	9.0	0	0	I	11.0	9.0	+ 2.0	+22	B		1 4 0
13	17.0	19.0	- 2.0	-10	I	30.0[3c]	16.0	>+14.0	>+ 88	B	24.0	20.0	+4.0	+20	B	30.0[3e]	17.0	>+13.0	>+76	B		5 2 0
14	23.0	20.4	+ 2.6	+13	I	30.0[3d]	24.2	>+ 5.8	>+ 24	B	26.0	18.0	+8.0	+44	B	30.0[3f]	21.5	>+ 8.5	>+40	B		6 2 0
15	21.0	16.4	+ 4.6	+28	B	24.0	13.5	+10.5	+ 78	B	23.0	16.0	+7.0	+44	B	21.0	14.0	+ 7.0	+50	B		8 0 0
16	19.0	14.3	+ 4.7	+33	B	22.0	14.3	+ 7.7	+ 54	B	22.0	14.3	+7.7	+54	B	18.0	14.3	+ 3.7	+26	B		6 2 0
17	12.0	9.0	+ 3.0	+33	B	15.0	8.0	+ 7.0	+ 88	B	15.0	9.4	+5.6	+60	B	15.0	9.9	+ 5.1	+52	B		5 3 0
18	15.0	12.5	+ 2.5	+20	B	11.0	11.2	- 0.2	- 2	I	11.0	11.0	0	0	I	15.0	12.0	+ 3.0	+25	B		5 3 0
19	8.0	8.0	0	0	I	7.0	8.0	- 1.0	- 13	I	12.0	8.0	+4.0	+50	B	9.0	8.0	+ 1.0	+13	I		2 5 1
	n = 8				B I D	n = 8				B I D	n = 8				B I D	n = 8				B I D		n = 63
$\bar{X}$ =	15.6	13.6	+ 2.0	+15	50% 50% 0%	19.0	13.0	>+ 6.0	+ 46	75% 25% 0%	17.7	13.2	+4.5	+34	75% 25% 0%	18.5	13.2	>+ 5.4	>+41	87% 13% 0%		B I D
																						65% 33% 2%

[1] rpm = revolutions per minute

[2] B = beneficial; I = inconsequential; D = detrimental. See text.

[3] rpm ceiling. Motion sickness scores: 3a 6 points; 3b 7 points; 3c 11 points; 3d 3 points; 3e 6 points; 3f 5 points

[4] Placebo test inconclusive due to device control problem.

[5] ═══ = subject's best response; ☐ = detrimental response.

PROCEDURE

SUBJECTS

Twelve male students, 19 to 28 years of age, served as paid volunteer subjects. They comprised part of a pool of 20 subjects who were available for a 6-week experiment. The medical assessment used was the same as that in Experiments I and II. None was selected on the basis of susceptibility to motion sickness. All had participated in experiments, however, involving the execution of head movements in the SRR. All agreed to refrain from the use of drugs, including alcohol, during the experimental period.

The Stress Profile

The stress profile differed from those previously used in one important respect, namely, the cadence was set at 4 seconds, i.e., each discrete head movement was executed in the usual manner followed by a delay together totaling 4 seconds. This cadence was chosen after experimental probes indicated that the 4-second cadence was more stressful than 1, 2, or 3-second cadences (findings to be published elsewhere).

The Endpoints

The motion sickness endpoint was set at 12 points or slight nausea, whichever came first. The rpm ceiling on the test was reached after execution of 40 head movements at 30 rpm.

Drugs

The following drugs were used:

1. l-scopolamine hydrobromide (0.3 mg)
2. l-scopolamine hydrobromide (0.6 mg)
3. ephedrine sulfate (25 mg)
4. l-scopolamine hydrobromide (0.3 mg) + d-amphetamine sulfate (5 mg)
5. l-scopolamine hydrobromide (0.3 mg) + ephedrine sulfate (25 mg)
6. l-scopolamine hydrobromide (0.6 mg) + d-amphetamine sulfate (5 mg)
7. dimenhydrinate (50 mg) + ephedrine sulfate (25 mg)
8. promethazine hydrochloride (25 mg) + ephedrine sulfate (25 mg)

Plan

The twelve subjects were divided into three groups (A, B, C), and the drugs were administered in a modified 5-unit Latin-square design, with a placebo intervening between each pair of drugs and with two placebos before the first and two after the

last drug administered in each series. The design for Group C was the same as for Group A. The groups were staggered so that beginning with the fifth day one group was tested every third day.

The subjects were assigned bunks in a ward (adjacent to the SRR) the evening before the test-day. The next morning tests were conducted at 2-hour intervals beginning at 0800. Prior to administering the capsule (2 hours before the test) the subject completed a "pre-experiment" questionnaire. Thirty minutes before the test began the subject was queried in order to learn if side effects were being experienced. The subject was interviewed immediately after the test (with the aid of a questionnaire) and again before departure; usually two hours after the test.

RESULTS AND DISCUSSION

The findings in Table IV show at a glance the number of tests (involving drugs) that either were not carried out or for which problems were encountered: 1) Subject 25 was injured (falling off a horse), 2) Subject 29 was ill, and 3) two envelopes (containing the correct drug) were switched in one series. This experimenter-error, involving the combination scopolamine (0.6 mg) and amphetamine (5 mg) and the single drug ephedrine (25 mg) resulted in Subjects 21 and 23 receiving two doses of one drug and none of the other.

But by far the most important difficulty involved Subjects 21 and 22 who quickly reached the ceiling on the test. In the first two baseline tests (when placebos were given) the mean motion sickness endpoints were, respectively, 11 and 14 rpm. However, in the third and fourth tests, respectively, these subjects reached the test ceiling without scoring any motion sickness points, implying either that they adapted with unusual rapidity to the motion environment or the drugs were highly efficacious. In the third test when scopolamine (0.3 mg) + amphetamine (5 mg) was administered to Subject 21 the ceiling on the test was reached. Subject 22 reached the ceiling on the fourth test when scopolamine (0.3 mg) was given. In view of these responses a change in procedure was made in the hope of reducing the acquisition of adaptation effects, namely, arbitrarily stopping the test when the rpm was 10 above the placebo level. This arbitrary halting of a test was quickly abandoned when the ceiling on the test was reached even when placebos were administered. Subjects 21 and 22 remained participants in the experiments (using the scoring procedure described in Experiment I) but in retrospect, such subjects as 21 and 22 could, with advantage, be tested with more stressful stimuli or a longer period allowed between tests to permit decay of adaptation effects.

The beneficial responses ranged from 25% to 87% of the treatments; Subject 23 (100% efficacy) is not included for he failed to receive ephedrine 25 mg, the least efficacious preparation. On one or more occasions 6 of the 8 drugs (scopolamine (0.3 mg) and ephedrine (25 mg) excepted) provided the highest efficacy ranking. It is

Table IV

Individual Responses To Eight Different Antimotion Sickness Drugs (Experiment III)

Subject	Drug 1. Scopolamine (0.3 mg)					Drug 2. Scopolamine (0.6 mg)					Drug 3. Ephedrine (25 mg)					Drug 4. Scopolamine (0.3 mg) + Amphetamine (5 mg)				
	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance[2] of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change
	I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo			
	rpm[1]	rpm	rpm	%		rpm	rpm	rpm	%		rpm	rpm	rpm	%		rpm	rpm	rpm	%	
20	8.3	5.8[1a]	+ 2.5	+43	B	10.2[1b]	5.8	+ 4.4	+76	B	5.2	5.8	- 0.6	-10	I	7.5	5.8	+ 1.7	+ 29	I
21	28.0[1f]	21.0[1a]	+ 7.0	+33	B	21.0[1g]	11.0	+10.0	+91	B	19.0	18.5	+ 0.5	+ 3	I	21.0[4c]	11.0	+10.0	+91	B
22	24.0	17.2	+ 6.8	+39	B	30.0[1g]	20.0	+10.0	+50	B	30.0[3h]	25.2	+ 4.8	+19	I	28.7[7]	21.3	+ 7.4	+ 35	B
23	10.8	6.3	+ 4.5	+71	B	8.3	6.3	+ 2.0	+32	B	[5]					10.0	6.3	+ 3.7	+ 59	B
24	15.0[10]	15.0	0	0	I	11.0	12.8	- 1.8	-14	I	16.0	13.1	+ 2.9	+22	I	11.0	13.7	- 2.7	- 20	I
25						5.4	4.2	+ 1.2	+29	I	3.5	4.2	- 0.7	-17	I	5.3	4.2	+ 1.1	+ 26	I
26	15.1	10.8	+ 4.3	+40	B	15.2	10.8	+ 4.4	+41	B	10.3	10.8	- 0.5	- 5	I	17.1	10.8	+ 6.3	+ 58	B
27	19.0	13.0	+ 6.0	+46	B	24.0	15.0	+ 9.0	+60	B	15.0	14.0	+ 1.0	+ 7	I	18.0	11.0	+ 7.0	+ 64	B
28	9.0	8.0	+ 1.0	+13	B	6.0	5.5	+ 0.5	+ 1	I	6.7	5.5	+ 1.2	+22	B	9.0	8.0	+ 1.0	+ 13	B
29	7.9	7.4	+ 0.5	+ 1	I	6.3	6.3	0	0	I	[11]					11.2	5.1	+ 6.1	+120	B
30	11.0	10.0	+ 1.0	+10	I	15.0	8.0	+ 7.0	+87	B	10.0	9.7	+ 0.3	+ 3	I	17.5	9.0	+ 8.5	+ 94	B
31	5.7	5.6	+ 0.1	+ 2	I	7.6	5.6	+ 2.0	+36	B	5.1	5.6	- 0.5	- 9	I	6.7	5.6	+ 1.1	+ 20	I
	n = 11				B I	n = 12				B I	n = 10				B I	n = 12				B I
X =	14.4	10.9	+ 3.1	+28	64% 36%	13.3	9.3	+ 4.0	+43	67% 33%	12.1	11.2	+ 0.9	+ 8	10% 70%	13.8	9.3	+ 4.5	+48	67% 33%

Subject	Drug 5. Scopolamine (0.3 mg) + Ephedrine (25 mg)					Drug 6. Scopolamine (0.6 mg) + Amphetamine (5 mg)					Drug 7. Dimenhydrinate (50 mg) + Ephedrine (25 mg)					Drug 8. Promethazine (25 mg) + Ephedrine (25 mg)					B	I
	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change	Motion Sickness Endpoint		Column I minus Column II	rpm Change	Significance of rpm Change		
	I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo				I Drug	II Placebo					
	rpm	rpm	rpm	%		rpm	rpm	rpm	%		rpm	rpm	rpm	%		rpm	rpm	rpm	%			
20	8.5	5.8	+ 2.7	+47	B	7.1[5]	5.8	+ 1.3	+22	I	6.5	5.8	+ 0.7	+12	I	7.6	5.8	+ 1.8	+ 31	I	3	5
21	30.0[3d]	21.0	+ 9.0	+43	B	[4i]					19.0[6]	17.0	+ 2.0	+12	I	30.0[4e]	16.8	+13.2	+79	B	5	2
22	22.0[3]	13.9	+ 8.1	+58	B	30.0[4i]	18.0	+12.0	+67	B	26.0[9]	15.7	+10.3	+66	B	30.0	22.0	+ 8.0	+ 36	B	7	1
23	9.9	6.3	+ 3.6	+57	B	9.6	6.3	+ 3.3	+52	B	12.0	6.3	+ 5.7	+91	B	8.3	6.3	+ 2.0	+ 32	B	7	0
24	16.0[10]	13.0	+ 3.0	+23	I	19.0	15.0	+ 4.0	+27	B	14.0	13.0	+ 1.0	+ 8	I	16.0	11.0	+ 5.0	+ 45	B	2	6
25						7.1	4.2	+ 2.9	+69	B	4.3	4.2	+ 0.1	+ 2	I	7.0	4.2	+ 2.8	+ 67	B	2	4
26	15.0	10.8	+ 4.2	+39	B	14.4	10.8	+ 3.6	+33	B	11.2	10.8	+ 0.4	+ 4	I	13.0	10.8	+ 2.2	+ 20	B	6	2
27	20.0	13.0	+ 7.0	+54	B	19.0	14.5	+ 4.5	+31	B	18.0	15.0	+ 3.0	+20	B	25.0	14.5	+10.5	+ 72	B	7	1
28	8.0	8.0	0	0	I	5.0	5.5	- 0.5	- 1	I	6.0	5.5	+ 0.5	+ 1	I	7.0	5.5	+ 1.5	+ 27	B	4	4
29	9.1[3]	7.4	+ 1.7	+23	B	9.1	6.7	+ 2.4	+36	B	7.6	6.7	+ 0.9	+13	B	11.1	6.7	+ 4.4	+ 66	B	5	2
30	30.0[3]	12.0	+18.0	+150	B	17.0	9.0	+ 8.0	+89	B	12.0	8.0	+ 4.0	+50	B	15.0	10.0	+ 5.0	+ 50	B	6	2
31	8.0	5.6	+ 2.4	+43	B	6.6	5.6	+ 1.0	+18	I	6.1	5.6	+ 0.5	+ 9	I	9.5	5.6	+ 3.9	+ 70	B	3	5
	n = 11				B I	n = 11				B I	n = 12				B I	n = 12				B I	n = 91	
X =	16.0	10.6	+ 5.4	+51	82% 18%	13.1	9.2	+ 3.9	+42	73% 27%	11.9	9.5	+ 2.4	+25	42% 58%	15.0	10.0	+ 5.0	+50	92% 8%	B	I
																					63%	37%

rpm = revolutions per minute.
B = beneficial, I = inconsequential. See Text.
Subject 21 did not reach endpoint because he complained of "arm and back fatigue." Motion sickness score: No points.
rpm ceiling. Motion sickness scores: 4a - 2 points 4b - 2 points 4c - 2 points 4d - 11 points 4e - 3 points 4f - 8 point 4g - no points 4h - 11 points 4i - 9 points 4j - 8 points.
Experimenter error. See Text.
Subject 21 did not reach endpoint because he was extremely drowsy and fell asleep. Motion sickness score: 8 points.
Subject 22 did not reach endpoint due to equipment failure. Motion sickness score: 3 points.
Subject 22 did not reach endpoint because he complained of dizziness. Motion sickness score: 10 points.
Subject 22 did not reach endpoint because he had urgent need to urinate. Motion sickness score: no points.
Subject 25 missed due to injury
Subject 29 - no test due to illness.
— = subject's best response.

worth noting that although the single drug ephedrine (25 mg) accounted for only one beneficial response when administered to 10 subjects, the combination promethazine and ephedrine (25 mg of each) was the most effective among the eight preparations tested.

After the completion of the last test in the series each subject was interviewed with the aid of the questionnaire completed in connection with the 15 tests. A table was prepared (not shown) based on replies to the question, "Was a drug or placebo administered?" About two-thirds of the replies were correct when a placebo had been taken and about one-half when a drug was given. There were individual variations, e.g., two subjects nearly always thought they had taken a drug and three thought they always or nearly always had taken a placebo.

Possible Interactions Between Antimotion Sickness Remedies and Other Psychoactive Drugs

After Experiment III was underway we began to suspect that certain subjects were drug users. This conclusion was based partly on their appearance and behavior and partly on the experimental findings. These subjects were the opposite of active, alert and interested subjects (thus differing from other members of the group) and the effectiveness of some antimotion sickness drugs was less than expected.

After completion of the 15 scheduled tests, interviews brought out the fact that indeed some of the subjects had used marijuana in the past and two admitted they had not completely discontinued its use during the test period. It probably should be told in passing, that there was almost no difficulty eliciting this information; most of the users were of the opinion that marijuana was less harmful than alcohol. Some additional tests were carried out with these subjects using higher doses than in Experiment III, and the results are summarized in Table V.

In this series of tests there was little, if any, change in the placebo baselines when compared with the baselines in the "regular" series. In general, there was increased effectiveness with increased doses. None of the responses was detrimental and among the drugs demonstrating beneficial effects, the scopolamine and amphetamine combinations were outstanding.

Subject A took scopolamine (1.2 mg) and amphetamine (10 mg) on three occasions with excellent results, although after the first dose he complained of side effects. His response to promethazine (100 mg) + ephedrine (50 mg) was not beneficial, although when small doses (25 mg of each) were administered in Experiment III a beneficial response was obtained.

Subject B on successive tests received, respectively, 10 and 20 mg of amphetamine; after administration of 10 mg there were no side effects and after 20 mg he reported feeling a little "drowsy" and "groggy." The response to the larger dose was beneficial.

Table V

Some Changes in Effectiveness at Drugs Given in Higher Than Usual Doses

Drug	Subject A: Pretest Side Effects	Subject A: Change in rpm[1] %	Subject A: Change in rpm Significance[2]	Subject B: Pretest Side Effects	Subject B: Change in rpm %	Subject B: Change in rpm Significance	Subject C: Pretest Side Effects	Subject C: Change in rpm %	Subject C: Change in rpm Significance	Subject D: Pretest Side Effects	Subject D: Change in rpm %	Subject D: Change in rpm Significance
1. scopolamine (1.2 mg)							Dry mouth, "light-headed"	-112	B			
2. amphetamine (10 mg)				No side effects	+ 2	I						
3. amphetamine (20 mg)				"drowsy"	+36	B						
4. scopolamine (1.2 mg) + amphetamine (10 mg)	dizziness, dry mouth, "feel high"	-75	B	"light-headed"	+88	B	"light-headed"	+117	B	No side effects	+131	B
5. dimenhydrinate (100 mg) + ephedrine (50 mg)	"feel high"	+27	B	No side effects	+ 7	I	"light-headed"	- 88	B	drowsy, [illegible] awareness	- 24	I
6. promethazine (50 mg) + amphetamine (10 mg)				"light-headed"	+104	B						
7. promethazine (50 mg) + ephedrine (25 mg)										drowsiness	- 84	B
8. promethazine (50 mg) + ephedrine (50 mg)							No side effects	- 88	B	"feel[illegible]ill"	+ 74	B
9. promethazine (100 mg) + ephedrine (50 mg)	No side effects	-9	I				"light-headed"	- 58	B			
10. promethazine (100 mg) + ephedrine (100 mg)				"light-headed"	-96	B						
Change in placebo level from Experiment III		rpm -0.4			rpm -1.6			rpm -0.1			rpm 0	

	Percent change in rpm: Range		Mean
Table IV (usual doses)	-1	-37	- 9
Table V (higher than usual doses)	-9	-75	-30

	Percent change in rpm: Range		Mean
Table IV (usual doses)	-9	-70	-24
Table V (higher than usual doses)	+2	+104	+55

	Percent change in rpm: Range		Mean
Table IV (usual doses)	-10	-76	-31
Table V (higher than usual doses)	+58	+117	+93

	Percent change in rpm: Range		Mean
Table IV (usual doses)	-17	+6[c]	-29
Table V (higher than usual doses)	+24	+131	78

[1] rpm = revolutions per minute

[2] B = beneficial; I = inconsequential; none were detrimental. See text. 78% beneficial; 22% inconsequential.

In the regular series his response to scopolamine (0.6 mg) and amphetamine (5 mg) was not beneficial, but he manifested an excellent response when the doses were doubled.

Subject C demonstrated excellent responses to increased doses of all (five) drugs administered, including the only outstanding response to dimenhydrinate (100 mg) and ephedrine (50 mg).

Subject D in the regular series often manifested satisfactory responses in terms of percent of change in rpm, but the highest rpm reached was 7.1 after taking scopolamine (0.6 mg) + amphetamine (5 mg). When the doses were doubled on two occasions he reached 9.1 rpm in one test and 10.3 rpm in the other.

In summary, the possibility has been raised that antimotion sickness drugs do not have the same effect on persons who use marijuana and those who do not. If subsequent studies confirm this conclusion it would still not be a surprising finding but its practical significance is self-evident.

GENERAL DISCUSSION

The present study was undertaken to improve testing procedures for assessing the efficacy of antimotion sickness drugs based on group responses. The changes introduced substitute an incremental increase in the intensity of the stressful stimuli for stimuli of constant intensity and a systematic use of placebos rather than a random distribution in using a (modified) Latin-square design. The findings reveal that, within a group, there are substantial individual differences in response that must be dealt with systematically. A few subjects pose problems either by reaching the rpm ceiling on the test before the motion sickness endpoint or by requiring larger than usual doses of the drugs. The latter (and more common problem) can be handled by simply increasing the dose but indicates the need for measuring dose-response relations in a systematic manner. For subjects who quickly reach the rpm ceiling on the tests, a simple solution is to increase the interval between tests.

In the three experiments (when the drugs were administered in usual doses) 225 tests were conducted involving 31 subjects; the responses were substantially beneficial in 135 tests, detrimental in 7 and inconsequential in 83 tests. By assuming that percent change in rpm had similar interpretive validity in all three experiments, it is possible to extract some additional information from the combined data.

Table VI shows the overall beneficial effectiveness of group responses to the 15 single drugs and fixed-dose combinations. The weighted responses take into account detrimental effects; one detrimental effect is made the equivalent of two inconsequential effects. Attention is directed to the roles played by promethazine (P's in squares) and ephedrine (E's circled).

Table VI

Drugs Ranked in Terms of Percent Response to Usual Doses of Antimotion Sickness Drugs Administered in Three Experiments. Weighted Responses Take Account of Detrimental Effects; One Detrimental Effect Equals Two Inconsequential Effects.

Drug	Number of Subjects	Overall Beneficial Effectiveness			
		Unweighted Response		Weighted Response	
		%	Rank	%	Rank
[P](25 mg)(E)(25 mg)	12	92	1	92	1
[P](25 mg)(E)(50 mg)	18	83	2	79	3
S (0.3 mg)(E)(25 mg)	11	82	3	82	2
S (0.6 mg) A (5 mg)	11	73	4	73	4
S (0.3 mg)	11	64	5	64	5
S (0.6 mg)	30	63	6	63	6
S (0.6 mg) A (10 mg)	19	63	6	63	6
D (50 mg)(E)(50 mg)	19	63	6	63	6
D (50 mg)	17	59	7	50	7
S (0.3 mg) A (5 mg)	22	55	8	50	7
[P](25 mg)	8	50	9	50	7
(E)(50 mg)	8	50	9	50	7
D (50 mg)(E)(25 mg)	12	42	10	42	8
A (10 mg)	17	35	11	35	9
(E)(25 mg)	10	10	12	10	10

A = d-amphetamine sulfate; D = dimenhydrinate; (E) = ephedrine sulfate; [P] = promethazine hydrochloride; S = l-scopolamine hydrobromide.

In doses of 25 mg the efficacy of ephedrine was 10% and promethazine 50% but combined the overall effectiveness was outstanding; among 12 subjects, 11 manifested a substantially beneficial effect and in the remaining subject, the effect (31% increase in rpm) was just short of being beneficial. Promethazine has long been used not only in the prevention of motion sickness (5, 6) but also for the prevention of nausea and vomiting in patients (7). In contrast, ephedrine has been used only under experimental conditions (5, 8) except in a fixed dose combination (promethazine (25 mg) and ephedrine (50 mg)) in Skylab IV (9). In the present experiments the combination promethazine (25 mg) and ephedrine (50 mg) ranked high but below the overall efficacy of the combination when the amount of ephedrine was halved. Experimental probes underway indicate that ephedrine has some advantages over amphetamine, especially when administered in repeated doses over periods measured in days. This advantage stems in part from the tachyphylaxis that develops to its peripheral actions. A central action remains but systematic studies have not been carried out.

Table VII shows the four subjects and four drugs involved in seven substantially detrimental (D's circled) responses. In these same subjects are shown, in parentheses, the responses that were not detrimental. Subject 3 differed from the others (whose responses were the least efficacious among the 31 subjects tested) in having four beneficial responses; this was only very slightly below the average for the entire group. It is interesting that among Subject 3's four best responses, promethazine (25 mg) plus ephedrine (50 mg) ranked best. Moreover, the fact that Subject 3 manifested his only inconsequential response when scopolamine (0.6 mg) plus amphetamine (10 mg) was administered, indicated that the detrimental response with half the dose represented a valid test. The responses of Subject 4 closely resembled those of Subject 3. Subject 11, with the worst record in the entire group of 31 subjects, manifested only one beneficial response which followed the administration of amphetamine (10 mg). The responses of Subject 19 resembled those of Subject 11; his two beneficial responses (not shown in the table) followed the administration of promethazine (25 mg) and the combination dimenhydrinate (50 mg) plus ephedrine (50 mg). The latter was Subject 19's best response by far and strongly contrasts with his response to dimenhydrinate (50 mg) alone.

The possibility must be raised that differences in procedure accounted for six of the seven detrimental responses appearing in Experiment I. Taking properly into account great variations in placebo responses is the most likely source of an error but in each instance these variations were small, hence did not pose a problem. The most reasonable explanation is one based on individual differences in response. Although one may not draw a generalization from tests on a few subjects the findings strongly indicate that even for highly efficacious antimotion sickness drugs, subjects show curious but consistent patterns in responses to these drugs.

A table was prepared (not shown) that summarized the findings when the effects were inconsequential (neither substantially beneficial nor detrimental) and ranked their effectiveness for comparison with the rankings when the effects were beneficial. These inconsequential effects ranged from a +31% increase to a -20° decrease in rpm.

Table VII

Drugs Involved in Seven Detrimental Responses Among 225 Evaluations in 31 Subjects

Subject No.	B.	I	D*	Dimenhydrinate (50 mg)	Promethazine (25 mg) Ephedrine (50 mg)	Scopolamine (0.3 mg) Amphetamine (5 mg)	Scopolamine (0.6 mg) Amphetamine (10 mg)
3	4	1	2	Ⓓ- 23%	(B - best of 4 + 54%)	Ⓓ- 17%	(I 0% change)
4	1	5	1	(I +3%)	(only B response +58%)	Ⓓ- 25%	(I +9%
11	1	3	3	Ⓓ- 27%	Ⓓ- 18%	(I 0% change)	Ⓓ- 18%
19	2	5	1	Ⓓ- 25%	(I +13%)	Not adm.	(I - 13%)

*B = beneficial

I = inconsequential

D = detrimental

The smaller the percentage of tests in the "inconsequential" category the higher the rank in terms of efficacy, hence these rankings were roughly in the reverse order of the rankings summarizing the beneficial responses. Two striking exceptions involved an increase in efficacy when dimenhydrinate (50 mg) was administered and a decrease in efficacy when this drug was combined with ephedrine (50 mg).

Table VIII compares the group responses in this series of experiments with previous findings on 60 subjects using the "old" procedure (1). These comparisons are limited to nine drugs administered in the same doses and the responses are specified in terms of the mean change in the number of head movements. Every change contributed an increase in number of head movements indicating that in every instance the net value was above rather than below the placebo level. When the rankings are compared the differences are small except in the case of the combination scopolamine (0.3 mg) and amphetamine (5 mg) which ranks far lower in the new compared with the old series. When the dose was doubled the rankings were similar.

The difficulties and approximations inherent in testing the efficacy of antimotion sickness drugs are visible at nearly every step in the procedure, hence the data are more suited to clinical application than to elucidation of underlying mechanisms. Nevertheless, the first question that came to mind after carrying out the present series of experiments was whether the results were in accord with a theory underlying our previous drug studies (2), namely, that summation effects were observed with certain combinations of drugs, one with central sympathomimetic and the other with parasympatholytic actions. This generalization has some face validity for group responses but does not explain the great differences in response to the same drug for individuals within the group. We share the opinion of other investigators (10, 11, 12) that the central actions of antimotion sickness remedies are largely unknown.

CONCLUSIONS AND RECOMMENDATIONS

1. A procedure for assessing antimotion sickness drugs has been described which can yield responses valid for a group and for each individual in the group.

2. A very limited exploitation of this procedure revealed great individual differences in response, inferring that for maximum benefits individual assessments must be made.

3. Among the drugs investigated the fixed dose combination promethazine and ephedrine (25 mg of each) provided substantial benefits for the greatest number but sometimes maximum protection. Tentatively, it would seem to be the drug of choice in moderately stressful motion environments.

4. For maximal benefits all of the drugs tested except ephedrine (in single usual doses) provided, for a given individual, the maximum benefit. Systematic human bioassays are required to identify and rank the most beneficial drugs when administered in single doses or in multiple doses over periods measured in days.

TABLE VIII

A Comparison of Group Responses Using the Old and New Procedures (See Text) When the Same Drugs Were Administered

Drugs (Listed in Order of Overall Beneficial Effectiveness)	Average Number Head Movements Increased Over Placebo Level	
	Previous Studies Using Dial Test* 60 Subjects	Present Study Using Incremental Stress
P (25 mg) E (50 mg)	100 (3)	>192 (1)
S (0.3 mg)	60 (5)	>124 (6)
S (0.6 mg)	70 (4)	>160 (3)
S (0.6 mg) A (10 mg)	140 (1)	>188 (2)
D (50 mg)	50 (6)	>140 (4)
S (0.3 mg) A (5 mg)	135 (2)	>120 (7)
P (25 mg)	70 (4)	128 (5)
E (50 mg)	40 (8)	80 (9)
A (10 mg)	45 (7)	> 84 (8)

A = d-amphetamine sulfate; D = dimenhydrinate; E = ephedrine sulfate; P = promethazine hydrochloride; S = l-scopolamine hydrobromide.

*Clin. Pharm. & Therapeutics, 11:621-629, 1970.

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