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THE PREVENTION OF SEASICKNESS WITH HYOSCINE, BENADRYL, AND PHENERGAN

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AMONG the many drugs used as remedies for motion sickness, hyoscine hydrobromide is one of the best (Holling et al. 1944, Hill and Guest 1945, Tyler 1946, Tyler and Bard 1949, Strickland et al. 1950, 1951). It is safe in doses of up to 1.2 mg. (Holling et al. 1944) and in a hot climate (Hill and Guest 1945). Moreover, repeated doses, amounting to 2.25 mg. daily, have been given with no other relevant side-effects than dryness of the mouth in most people and blurred vision in some (Chinn et al. 1950).

Anti-histamine compounds have also been widely used in the treatment of motion sickness since the simultaneous and accidental discovery of their efficacy by Gay and Carliner (1949a and b) and McEvedy (1949). A particularly strong claim was made out for diphenhydramine-8-chlorotheophyllinate ('Dramamine') by Gay and Carliner (1949a and b), and there is no doubt that this drug often prevents seasickness and airsickness (Chinn et al. 1950, Lewis et al. 1949, Strickland et al. 1950, 1951). There is much evidence, however, that only part of its molecule is responsible for this action; for 8-chlorotheophylline has no effect on vomiting (Chen and Ensor 1950, Chinn and Oberst 1950, Nickerson 1950), while diphenhydramine hydrochloride ('Benadryl') prevents motion sickness in much the same way as dramamine (Chinn et al. 1950, Chinn and Oberst 1950, Wright 1950). Mitchell (1950) has suggested that 8-chlorotheophylline may prevent vomiting after the administration of emetine in cats, but he himself considered some of his data inconclusive.

Promethazine-8-chlorotheophyllinate ('Avomine') is another anti-histamine substance which has been claimed to prevent motion sickness (Harper 1951). Since 8-chlorotheophylline has no such action, the effects of avomine must be those of promethazine. There was, indeed, some reason to regard promethazine hydrochloride ('Phenergan') as the most promising among the anti-histamine drugs because of its well-marked "central or hyoscine-like" action (Bain 1951, Burn 1950). In an isolated observation Ambrus and Ambrus (1950) found phenergan useful, but Chinn et al. (1950) dismissed it as ineffective.

The purpose of the present experiment was to test the most promising drugs in safe doses, and it was decided to compare hyoscine hydrobromide, benadryl, and phenergan in a controlled experiment which could be interpreted objectively. Motion sickness is best studied in a rough sea, but changes in the weather may cause errors. The use of fast patrol boats, however, made it possible to obtain similar boat movements under varying

sea conditions, and "crossing over" further reduced the risk of such errors.

MATERIAL AND METHODS

Subjects

68 soldiers were used who had volunteered from various Army units in England, Scotland, and Wales. Their ages ranged from 18 to 42, but 52 (76.5%) were aged 18-21. There were 51 private soldiers (or equivalent rank), the others being non-commissioned officers. 46 of them were on National Service and 22 were regular soldiers. All branches of the Army were represented. Preliminary questionnaires gave the following information about previous exposure and experience of motion sickness:

38 men (56%) had never sailed in a rough sea, seldom or never flown, and never had motion sickness.

13 men (19%) had either sailed in rough seas or often flown without becoming sick.

7 men (10%) had been exposed to seasickness or airsickness and had become sick.

10 men (15%) were regarded as very susceptible to motion sickness either because they became sick in a calm sea or because they were both often sick at sea and had other forms of motion sickness. (The men's own assessments of a rough sea may have been influenced by whether they were seasick or not, but the purpose of this questionnaire was to find out whether there was a predominance of those who believed themselves to be particularly susceptible or resistant to motion sickness.)

It may be concluded that a fairly representative sample of the Army's lower ranks had volunteered for this experiment.

Drugs

To avoid entirely arbitrary dosage it was decided to use each drug in the largest dose which, according to published reports, was certain not to cause undesirable side-effects in adult men. It was understood, however, that the optimal doses might have to be determined later. There was reason to believe that 1 mg. of hyoscine would be a safe dose (Martindale 1941, Holling et al. 1944). Both 100 mg. of dramamine and 50 mg. of benadryl, however, have been found to be toxic (Shaw 1949, Rust and Fosbery 1949, Strickland et al. 1950, 1951, Wright 1950), although others considered such doses safe (Gay and Carliner 1949a, Chinn et al. 1950). On the above criterion a dose of 25 mg. of benadryl was chosen. A dose of 25 mg. of phenergan also seemed safe (Bain et al. 1949). Harper (1951), moreover, had given repeated doses of 25 mg. of avomine without any side-effects. Since phenergan is excreted very slowly (Bain et al. 1948), this confirmed the view that single doses of 25 mg. of phenergan would be safe.

The drugs were given in indistinguishable capsules. They were kept in identical tins inconspicuously marked with numbers, and the issuing was done entirely by numbers. The code to these numbers was kept in sealed envelopes at the Admiralty and at the Department of Experimental Medicine, Cambridge. Nobody connected with the experiment knew the code until after the results had been worked out. The remaining capsules were then checked by qualitative chemical analysis which showed that there had been no error in the coding. The subjects of the experiment were told that various safe drugs would be tested, and that the same drug might or might not be issued on different occasions, but they were not told that a dummy substance was included. These precautions were well justified, because those who were seasick sometimes blamed the drug, but it was subsequently found that the "drug" was usually the placebo. Holling et al. (1944) also observed that experimental subjects tended to think that drugs had made them sick.

Experimental Routine

Four tests were made forty-eight hours apart, and

in each test a quarter of the subjects (17 men) received

each drug. The men were divided into twenty-four groups at random, and each group received each substance in turn in one of the twenty-four possible sequences. This was designed to cancel out the effects of variations in the sea conditions on different days, and of such possibilities as adaptation to the motion or modification of the action of one drug by another given forty-eight hours earlier.

When an experiment was going to be done, the men had their usual breakfast at 7.30 A.M. and then remained in their quarters. At 10.45 A.M. they were given a meal of tea, sandwiches, cakes, and biscuits, which never varied from man to man or day to day. Before the men ate anything, they filed up with their tea to a desk, where they were given a capsule which they were made to swallow. They could not see how many tins there were or what manipulations were going on. Three persons worked as a team to make sure that each man was given the correct capsule and that he swallowed it before returning to the table.

At 11.30 A.M. the men walked a mile to the boat base and were distributed between two boats. Parties were made up differently on each experimental day but included equal numbers of recipients of each drug. The men sat in the forward mess deck all the time, and they were somewhat tightly packed. They were not allowed to sing, smoke, eat, or organise games or debates, but they were allowed to read, talk, and play cards. The temperature in the mess decks was always about 18°C (65°F).

Sailors who had been trained in experimental methods for over a year acted as additional observers. There was always one observer on each mess deck. He had a nominal roll and entered the exact time against the name of any man who vomited. Although the mess decks were comparatively small, the men were moved around two or three times during each trip so that no error could have been caused if the motion had varied in different parts of the mess decks. Paper bags and buckets were available, but this fact was neither overemphasised nor tactfully concealed, for either extreme might have made the men wish to use them.

The ships left harbour at noon, 1 $\frac{1}{4}$ hours after the drugs were taken. During the four experimental days rough motion was always encountered within 1 $\frac{1}{4}$ -2 hours after the drugs were taken, and it always ceased within another 2 hours. Identical or very similar sister ships were used.

Questionnaires

Although Wendt (1951) has found that questionnaires are rarely falsified in this type of experiment, answers so obtained are inevitably subjective, and they will be dealt with separately. Besides the one which has been referred to before, questionnaires were filled in by all men immediately on landing after each test. These were designed to show whether the men had any symptoms of seasickness or side-effects, and whether symptoms were noticed at times when the sea was not rough or before boarding the ships. Except after the first of the four tests the men were also asked which of the substances they preferred. The questionnaires were self-explanatory, and only general instructions were given verbally. All questions and possible answers were put in random order, and the men were asked to underline whichever answer was true.

space was allowed for remarks.

Wasted Trips

Only the results of four successive trips carried out according to the above plan are given below. Twice during the previous week, however, the men were given drugs and went to sea. On the first occasion an unsuccessful attempt was made to distribute the men over a number of inflatable floats, but as a result of technical difficulties in a rough sea only some of the men got on

TABLE I.—RECORD OF BOAT MOVEMENTS OBTAINED WITH A DOBBIE MCINNES ACCELEROMETER

Date	Speed (kt.)	* Sea †	Swell (ft.)	Wind †	Average acceleration (g)	Average period (sec.)
March 12, 1951	21	10	2 × 50 increasing to 4 × 150	4	+0.28 -0.18	2.75
March 14, 1951	12	32	8-10 / 175	6	+0.20 -0.15	2.45
March 16, 1951	25	11	3 / 50	3	+0.19 -0.19	2.1
March 18, 1951	12	32	5-6 / 120 increasing to 8-9 × 200	6	+0.33 -0.26	2.4

* Combined sea and swell scale. † Beaufort scale.

to these craft, and their activities, the grouping, and the timing could not be controlled according to the experimental plan. The findings, however, in no way contradicted those reported below. The first attempt to do the test in fast patrol boats was also a failure because, in spite of a weather forecast to the contrary, the sea was calm and no amount of seamanship could produce adequate motion. These wasted trips, however, eliminated any apprehension or overexuberance the men may have had before the experiment.

Boat Motion

A record of the sea conditions and the boat motion is given in table 1. By varying the speed of the boats it was possible to obtain very similar degrees of movement over a wide range of sea conditions. Records of vertical acceleration were taken at short intervals with a Dobbie McInnes recording accelerometer placed amidships in the centre of the forward mess deck. Occasional peaks of about 1 g were obtained in all trips, and these were particularly frequent in one test (March 14, 1951), when there was also some horizontal "rolling." Most of the men receiving a dummy substance were sick on that day (see below).

Non-starters

One man who had been very sick throughout the tests (except when he had had hyoscine) asked to be excused before the last run and was allowed to return to his unit. Another man was absent on one day because he had to attend a court of inquiry, and a third man missed one trip because of a bad toothache. It is unfortunate that all 3 men happened to miss the day when they should have taken phenergan.

RESULTS

Vomiting

Table II shows that after hyoscine hydrobromide only 2 of the 68 men vomited, whereas more men did so after phenergan and benadryl. About half the men

vomited after the placebo. If the results are worked out

TABLE II—INCIDENCE OF VOMITING AND NAUSEA

	Placebo	Hyoscine 1 mg.	Phenergan 25 mg.	Benadryl 25 mg.
No. receiving sub- stance	68	68	65	68
% vomiting ..	32 (47%)	2 (3%)	12 (18.5%)	18 (26.5%)
% protected from vomiting*	94	61	44
Total no. affected (vomiting or nausea)	45 (66%)	10 (15%)	15 (23%)	31 (46%)
% protected from vomiting and nausea*	77	65	30

* Calculated from formula (Holling et al. 1944):

$$\frac{\% \text{ affected after placebo} - \% \text{ affected after treatment}}{\% \text{ affected after placebo}} \times 100$$

to show the proportion of susceptible men who were protected by any particular substance (Holling et al. 1944), hyoscine hydrobromide protected 94% of those who might otherwise have vomited, while phenergan protected 61% and benadryl 44%. The 3 men who did not have phenergan could not have altered the figure for that drug outside the range of 58-64%.

The χ^2 distribution with a correction for continuity (Fisher 1934) was worked out for all possible comparisons between the effects of any two substances, and the results are shown in table III. The differences between the number of men who vomited after hyoscine hydrobromide and the number of men who vomited after any of the other substances were highly significant, and so was the difference between the number of men who vomited after phenergan and the number of men who vomited after the placebo. The difference between the numbers vomiting after benadryl and after the placebo was significant, but the difference between the numbers vomiting after benadryl and phenergan was not significant.

About 80% of those who vomited after phenergan and the placebo, and both men who vomited after hyoscine, began to do so within 30 minutes of reaching rough seas, but only 60% of those who vomited after benadryl did so during the first 30 minutes. This observation, however, does not justify any definite conclusions about the effect of these drugs on the time of onset of vomiting. The

TABLE III—STATISTICAL SIGNIFICANCE OF DIFFERENCES GIVEN IN TABLE II

(Values for P are shown in parentheses if they are not significant)

Substances compared	Vomiting		Nausea or vomiting	
	χ^2	P	χ^2	P
Hyoscine and placebo ..	32.980	<0.01	35.291	<0.01
Phenergan and placebo ..	11.018	<0.01	23.221	<0.01
Benadryl and placebo ..	5.345	0.02-0.05	5.043	0.02-0.05
Hyoscine and phenergan	6.929	<0.01	1.026	(0.3-0.5)
Hyoscine and benadryl ..	13.076	<0.01	13.966	0.01
Phenergan and benadryl	0.805	(0.3-0.5)	6.419	0.01-0.02

number of vomits among those who were sick was not

number of vomits among those who were sick was not affected by previous medication. On one day, when there were more vertical peaks than usual and some "rolling," all but 3 men receiving the placebo were sick. 8 men each vomited after phenergan and benadryl, but only 1 after hyoscine.

Answers given in the questionnaires tallied with the observers' records of those who vomited.

Nausea

Some men who did not vomit stated on the questionnaires that they felt sick. The results are shown in table II. Among those who did not vomit, phenergan seems to have given better protection from nausea than hyoscine or benadryl. If vomiting and nausea are considered together and the proportion of those protected is worked out according to the method of Holling et al. (1944), hyoscine protected 77% of those who might have felt or been sick, phenergan 65%, and benadryl 30%. (The correct number of those protected by phenergan must lie between 63 and 67%.)

Table III shows that, as regards the number of men who vomited or felt sick, there was a highly significant difference between hyoscine and benadryl and between hyoscine and the placebo. The difference between phenergan and the placebo was also highly significant, while the differences between benadryl and phenergan, and benadryl and the placebo, were significant. The

TABLE IV—SYMPTOMS OTHER THAN NAUSEA AND VOMITING

Symptom	Placebo	Hyoscine 1 mg.	Phen- ergan 25 mg.	Benadryl 25 mg.
Dry mouth	30 (44%)	59 (87%)	38 (58%)	37 (54%)
Giddiness	23 (34%)	16 (24%)	10 (15%)	12 (18%)
Headache	35 (52%)	21 (30%)	21 (32%)	26 (38%)
Drowsiness	30 (44%)	33 (49%)	30 (46%)	29 (43%)
Elation or excitement..	1	2	2	2
Confusion	0	0	0	0
Blurred vision ..	0	0	0	0
No. of men receiving substance	68	68	65	68

difference between hyoscine and phenergan was not statistically significant.

Minor Symptoms and Side-effects

Table IV gives the incidence of symptoms other than nausea and vomiting. Most of these symptoms were about equally frequent or rare whatever the medication, except that there were more headaches and giddiness after the placebo and more dry mouths after hyoscine. Both dry mouths and drowsiness were present in 44% of those receiving the placebo. Elation and excitement were rare, and there was no evidence of confusion or oculomotor disturbances. No other symptoms were reported, apart from occasional nausea immediately after taking the tablets. On one occasion the capsule was vomited immediately after it had been taken, but another capsule was given and retained. There was no evidence that the sight of other men vomiting caused many men to become sick or nauseated. There was no evidence that the men became accustomed to the motion during the experiment, because the highest number were sick on the second trip and the lowest on the third.

Individual Preferences

As stated above, the men were asked, after the last three trips, which of the substances they preferred. They were asked not to consider the capsules given before the two wasted trips, and this was also made clear on the questionnaires. They were allowed to express more than one preference. If all preferences expressed for any drug on any of the last three days are taken together, there were 73 for hyoscine, 58 for phenergan, 45 for benadryl, and 21 for the placebo. On the fourth day and looking back on the whole experiment 29 preferences were expressed for hyoscine, 24 for phenergan, 21 for benadryl, and 10 for the placebo. The number and proportion of preferences expressed was about equal on different days of the experiment.

DISCUSSION

The present findings strongly confirm previous observations that hyoscine hydrobromide effectively prevents seasickness in a large number of people, and that, at any rate in fit men, 1 mg. is a safe dose. Hyoscine, moreover, seems to be even more effective than previous trials have suggested (Holling et al. 1944, Hill and Guest 1945, Tyler 1946, Chinn et al. 1950). The difference may in part be due to the fact that some previous experiments did not separate those who vomited from those who felt sick, and that smaller doses of hyoscine were used in other experiments. The fact that efforts to eliminate subjective and accidental influences were more stringent in the present experiment than in previous ones and that every man was given each substance may, however, have contributed to this difference. Possibly the best effect of hyoscine is evident in small craft when the period of motion is short and the incidence of seasickness high.

The findings on the day when most men receiving the placebo were sick bear out this view but do not allow definite conclusions. Hyoscine did not prevent nausea with equal success; and, if nausea and vomiting are considered together, the apparent superiority of hyoscine over phenergan was not statistically significant. Since, however, for those affected the choice lay between feeling sick without vomiting or feeling sick and vomiting, there can be no doubt that hyoscine would be preferable. Subjective answers bear this out.

It can be concluded also that all three drugs in the present doses were remarkably free from side-effects. It seems that headaches, dry mouths, giddiness, and drowsiness are all symptoms of seasickness which are present in a large number of untreated men (table iv), and that these symptoms can be made a little worse or a little better by the drugs used. Hyoscine hydrobromide 1 mg. caused a feeling of dryness of the mouth in most subjects, but hyoscine should not be condemned on that account alone, especially since nearly half the men had that symptom after being given a dummy substance.

It was pleasing to note that the men's own assessment of their symptoms and their preferences conformed with objective observations, but this does not mean that it is safe to rely on subjective data alone. The large number of preferences expressed for the placebo shows that users' opinions on seasickness remedies can only give a rough idea of their efficacy.

It cannot be said how effective benadryl would have been in larger doses, but there is no reason to believe that the main conclusions of the present experiment would have been different if more had been used.

would have been different if more benadryl had been given, because both 50 mg. of benadryl and 100 mg. of dramamine have been found to protect fewer people from airsickness than 0.65 mg. of hyoscine (Chinn and Oberst 1950, Strickland et al. 1950, 1951). The superiority of phenergan over benadryl may in part be a result of its greater central depressant or "hyoscine-like" action, to which the effectiveness of anti-histamine drugs against motion sickness is probably due (Burn 1950, Bain 1951). Future tests will have to show whether the present results can be modified by different dosage.

SUMMARY

A controlled and crossed over experiment was made at sea in which 68 men were in turn given 1 mg. of hyoscine hydrobromide, 25 mg. of benadryl (diphenhydramine hydrochloride), 25 mg. of phenergan (promethazine hydrochloride), and a dummy substance.

96% of those who might otherwise have vomited were protected from vomiting by hyoscine, 61% by phenergan, and 44% by benadryl.

If nausea and vomiting are considered together, hyoscine protected 77%, phenergan 65%, and benadryl 30%.

Except for the difference between the numbers vomiting after benadryl and phenergan, and the difference between the numbers suffering from nausea and vomiting after hyoscine and phenergan, the differences were statistically significant.

All drugs were remarkably free from undesirable side-effects in the doses given.

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