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(–)-HYOSCINE AND CYCLIZINE AS MOTION SICKNESS REMEDIES

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There is much well-documented evidence for the efficacy of (–)-hyoscine in the prevention of motion sickness in man, and this has been drawn from experiments carried out in a variety of situations (Brand & Perry, 1966).

However, in most of these studies the drug was given at single fixed dose levels, usually 1 mg of the hydrobromide (0.7 mg (–)-hyoscine base), with the result that the dose-response relationship of the drug has never been clearly defined. The relative activity of different dose levels of the drug is thus unknown, as is its potency relative to that of other motion sickness drugs.

Although 1 mg of the hydrobromide protected some 95% of subjects in the various trials, it also gave rise to troublesome complaints of dry mouth and blurred vision (Chinn, Bayne-Jones, Gersoni, Henderson, Zeransky, Schein, Karsner, Phillips, Yarbrough, Duffner, Kinsey, Melton, Voas, Jones, Maag, Trumbull, Shaw, Smith, Bauer, Sweeney & Weiner, 1956 ; Brand, McCance & Perry, 1963). It is also known to cause drowsiness and impair mental performance (Colquhoun, 1962). However, recent work has shown that the anti-emetic potency of (–)-hyoscine does not depend on peripheral anti-acetylcholine activity, and there are indications that the drug may give good protection against motion sickness at doses much smaller than those used previously (Brand & Perry, 1966). This raises the possibility that a good anti-emetic effect might be obtained with doses less than 0.7 mg of the base, together with a reduction of unpleasant peripheral effects.

There is also, as yet, no dose/response information for the depressant central effects of the drug (which might, for example, produce an impairment in mental efficiency), so it is not possible to state whether this depressant effect would be present at doses low enough not to produce troublesome dry mouth or blurred vision. There is, however, some evidence that the effect of the drug on certain mental performance tests at a dose of 0.7 mg of the base is small (Colquhoun, 1962).

A similar situation exists with regard to cyclizine hydrochloride. The results of several trials show that it is undoubtedly effective in preventing motion-sickness (Brand & Perry, 1966), but since most of the studies were made at single dose levels (50 mg), no

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dose/response data are available. There are no troublesome peripheral effects with this drug, and it possesses no measurable anti-acetylcholine activity *in vitro*, but, in common with most anti-histamine drugs and also with hyoscine, it possesses central depressant properties and causes drowsiness (Lederer & Putnam, 1958). As in the case of hyoscine the dose/response relationships for this central effect have not yet been established, so it is quite unknown whether protection against motion sickness could be obtained with smaller doses which would not impair mental performance.

The present experiment was designed to confirm the protective effect of small doses of (−)-hyoscine, and to obtain dose/response information for cyclizine in the same situation, so that an estimate could be made of the comparative potencies of the two drugs. It was also hoped to compare their central depressant effects, in so far as these can be measured by mental performance tests.

METHODS

Incidence of motion sickness

The method used was essentially similar to that described by Glaser & Hervey (1952) and Glaser & McCance (1959), where volunteer subjects in naval 20-man life-rafts were exposed to the motion of artificial waves in a large tank for 1 hr.

In the present experiment approximately 100 different men took part on five consecutive Saturdays. On each day of the experiment the subjects were divided into six groups. An observer was put in charge of each group and he gave a trial number at random to each man. All subjects then did a mental performance test which lasted for 20 min, to establish a base-line. Two hours before being exposed to the wave motion, each man took a capsule which contained either cyclizine or a placebo. They then completed a questionnaire giving details of their previous sea experience, with an estimate of their susceptibility to motion sickness.

One hour before the wave motion each man took a second capsule, which contained either hyoscine or a placebo. The drugs were administered at these times to allow for their different rates of absorption. They were allocated to the subjects according to a randomized block design, and a double-blind procedure was employed.

One hour after taking the second capsule the men boarded the life-rafts in groups of about 16, each with their observer. The wave motion then started and continued for 1 hr. During this period the observers noted the time of onset and frequency of vomiting as it occurred, and supervised the second mental performance test, which began ½ hr after the wave motion started, and lasted for 20 min as before.

On disembarking from the rafts, the men completed a second questionnaire, designed to obtain details of the incidence of side-effects which might be attributable to the two drugs.

Devising test of effect of drugs on mental performance

This posed a new problem, in that a test had to be devised which could be carried out in a moving life-raft. The "vigilance test" used previously (Colquhoun, 1962) measured the ability of subjects to maintain concentration for a period of 1 hr, and involved checking printed sheets of numbers for errors against a voice on a tape-recorder. This was unsuitable for use under cramped conditions in a moving life-raft. A new test was therefore devised, which involved adding together two-figure numbers for a period of 20 min. This had been compared with the vigilance test in an experiment on land, and was found to be a sensitive test and to give reliable information (Colquhoun & Brand, 1964).

In the present experiment the subjects were given prepared books of sums and instructed to work as quickly and accurately as possible during the 20 min allowed to them. Their work was timed and supervised by the observers, first on land, and subsequently in the raft.

RESULTS

Incidence of nausea and vomiting in the rafts

The incidence of nausea and vomiting in the rafts was obtained from the records made by the observers, and from the second questionnaire, and is presented as Table 1.

From these data dose/response curves were obtained for the protective effects of the drugs. The protective effect was expressed as an "index of protection" by taking the ratio of the sickness rate with the drug to the sickness rate with placebo, and subtracting from unity.

TABLE 1

INCIDENCE OF NAUSEA AND VOMITING

$$\left(\text{Index of protection} = 1 - \frac{\text{sickness rate with drug}}{\text{sickness rate with placebo}}\right)$$

Treatment (mg)	Men (no.)	Nausea (no.) (%)	Vomiting (no.) (%)	Nausea plus vomiting (no.) (%)	Percentage protection†	Index of protection (%)
Placebo	58	12 (21)	32 (55)	44 (76)	—	—
Hyoscine, 0·1	58	10 (18)	15 (26)	25 (43)	74	0·53
Hyoscine, 0·7	57	3 (5)	4 (7)	7 (12)	93	0·87
Cyclizine, 15	58	7 (12)	20 (34)	27 (47)	66	0·38
Cyclizine, 25	58	9 (17)	20 (34)	29 (50)	66	0·38
Cyclizine, 40	58	15 (26)	16 (28)	31 (53)	72	0·50
Cyclizine, 65	58	9 (15)	14 (24)	23 (40)	76	0·56
Cyclizine, 100	57	8 (14)	12 (21)	20 (35)	79	0·62

† Percentage protection = percentage of subjects in each treatment group who did not vomit.

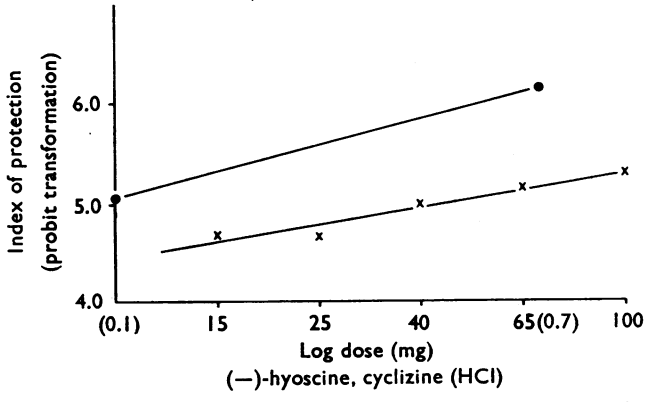

Fig. 1. Log. dose/response curve. (−)-Hyoscine (●) and cyclizine HCl (×) (placebo vomiting rate, 55%).

	Dose (mg)	Response index of protection, as probit
(−)-Hyoscine	0.1	5.08
(−)-Hyoscine	0.7	6.14
Cyclizine	15	4.68
Cyclizine	25	4.68
Cyclizine	40	5.0
Cyclizine	65	5.16
Cyclizine	100	5.30

Figure 1 shows the relationship between log. dose and the probit transformation of this index of protection for the individual treatment groups.

Incidence of side-effects

The incidence of side-effects was taken from the second questionnaire which each volunteer completed on disembarking from the raft, and is purely a subjective estimate. Table 2 gives the incidence of side-effects separately for those subjects who did and did not vomit.

Effect on mental performance

The effect of the drugs on mental performance was estimated from the results of the calculation tests performed by the subjects both on land and in the moving life-rafts (Table 3). They are expressed as the means of the average number of correct answers given by each man in each treatment group both on land and in the life-raft. Impairment

TABLE 2

INCIDENCE OF SIDE-EFFECTS

Treatment (mg)	Subjects (no.)	Number suffering from: Headache	Giddiness	Sleepiness	Dry mouth	Blurred vision
(a) *Subjects not vomiting*						
Placebo	26	5	9	5	5	1
Hyoscine, 0·1	43	7	9	26	16	3
Hyoscine, 0·7	53	7	11	36	37	8
Cyclizine, 15	38	6	8	18	8	3
Cyclizine, 25	38	7	10	22	11	5
Cyclizine, 40	42	8	14	29	12	4
Cyclizine, 65	44	11	12	29	10	6
Cyclizine, 100	45	9	10	34	16	1
(b) *Subjects vomiting*						
Placebo	32	8	12	26	11	9
Hyoscine, 0·1	15	3	4	12	9	2
Hyoscine, 0·7	4	1	0	3	3	1
Cyclizine, 15	20	3	11	14	4	4
Cyclizine, 25	20	10	11	16	6	2
Cyclizine, 40	16	6	9	16	7	3
Cyclizine, 65	14	6	5	12	2	3
Cyclizine, 100	12	4	4	11	2	2

TABLE 3

EFFECTS ON MENTAL PERFORMANCE

(Index of behavioural protection: Average decrease % in treatment groups—placebo group.)

Treatment (mg)	Men (no.)	Average number of correct answers (a) On land	(b) In raft	Average decrease in number correct (a) minus (b)	Average decrease % $\frac{a-b}{a}\times 100$	Index of behavioural protection
Placebo	58	76·4	42·0	34·4	46·4	—
Hyoscine, 0·1	58	78·3	52·5	25·7	34·2	12·2
Hyoscine, 0·7	57	78·8	63·0	15·8	20·8	25·6
Cyclizine, 15	58	81·7	53·7	28·0	35·6	10·8
Cyclizine, 25	58	82·0	54·1	27·9	34·9	11·5
Cyclizine, 40	58	77·3	47·5	29·8	39·2	7·2
Cyclizine, 65	58	80·6	54·0	26·6	32·4	14·0
Cyclizine, 100	57	73·2	53·2	20·0	28·1	18·3

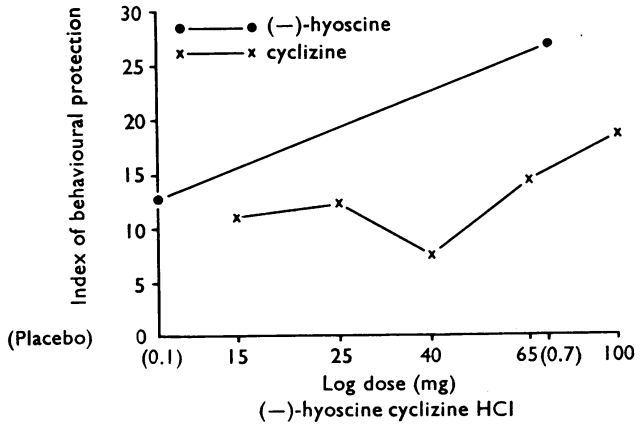

Fig. 2. Effect of treatments on mental performance (see Table 3 last column).

of mental performance is shown by the extent of the decreases in the number of correct answers in each situation. This is shown graphically for the eight treatment groups in Fig. 2. This was derived by subtracting the placebo score from the average percentage decrease in each of the treatment groups as set out in the last column of Table 3.

DISCUSSION

Incidence of nausea and vomiting

It can be seen from Fig. 1 that the log. dose/response line for cyclizine is approximately linear. Further analysis by the standard method of probit analysis (Finney, 1962) shows that the slope of the line best-fitting the cyclizine points is compatible with that joining the two doses of (−)-hyoscine. This permits the calculation of the relative potencies of the two drugs. Cyclizine, on a weight for weight basis, has 1/580th the potency of (−)-hyoscine base. The 95% confidence interval for this ratio is 1/180–1/1,900. The doses of the two compounds usually given in practice are 50 mg and 0.7 mg respectively—that is, a 70-fold difference. Some 400 mg cyclizine could therefore be expected to equal 0.7 mg (−)-hyoscine in anti-emetic effect, but would undoubtedly produce very serious sedation.

The dose/response line for hyoscine obtained in the present experiment is roughly parallel to that which was computed by an analysis of the results of previous experiments. By using this, and data for cyclizine taken from experiments where the incidence of vomiting in the placebo group was approximately the same, an estimate of the relative potencies of the two drugs had been produced (Brand & Perry, 1966). This gave the ratio of potencies of cyclizine/(−)-hyoscine as 200: 1, and the current findings confirm that this estimate was relatively accurate.

The results of the present experiment also lend support to certain other assumptions made after considering the evidence of previous experiments with the two drugs. It had been found possible to derive a dose/response line for (−)-hyoscine from the data

obtained in several different trials. From this it appeared that the potency of (−)-hyoscine against motion sickness was much higher than hitherto suspected, in that a dose as low as 0.1 mg (base) could protect 85% of subjects under conditions where there was an incidence of vomiting of 20% in the placebo group. In the present trial, where the incidence of vomiting in the placebo group was 55%, 0.1 mg of the base protected 74% of the subjects and this was equal to the effect of 50 mg cyclizine. This finding is also of great assistance in interpreting the results of a previous experiment (Brand, McCance & Perry, 1963): under closely similar conditions 5 mg (+)-hyoscine given to a group of 120 men appeared to afford some protection against vomiting. However, since the samples used contained 0.1 mg of the (−)-isomer as a contaminant, this could well have been responsible for the apparent protective effect.

Incidence of side-effects

The data in Table 2 reinforce earlier impressions that the incidence of side-effects tends to be very high in the placebo group in such experiments, presumably because motion sickness itself is frequently associated with headache, giddiness and visual disturbances. The incidence of side-effects has therefore been expressed separately, as these were found in subjects who did and did not vomit. This was done to prevent the effect of vomiting itself confounding the incidence of side-effects attributable to the various treatments.

From such an analysis it can be stated that neither of the drugs gave rise to headache or giddiness. Both, however, gave a definite incidence of sleepiness, which increased with increasing dose. There was no great difference between the drugs, but the overall incidence was higher in the group who vomited. (−)-Hyoscine produced dry mouth in both groups, but the incidence was halved at the lower dose level in the group which did not vomit. There was no evidence that cyclizine produced dry mouth. Neither drug gave rise to any subjective impairment of vision.

Effect on mental performance

The results of the mental performance test, set out in Table 3, although equivocal, are not wholly unexpected. In the placebo group the impairment of mental performance in the life-rafts is shown by a decrease in the number of calculations done correctly, compared with the first test done ashore. In each treatment group there is an improvement in performance, in that the decrease in the number of calculations done correctly is not as great as it is in the placebo group.

The data are readily understood if one assumes that the most important factor in impairing mental performance was the occurrence of sickness itself. Then even the very large doses of hyoscine and cyclizine do nothing but increase efficiency of performance, at a rate which is comparable to that by which sickness is decreased (Fig. 2). This might well be shown up by comparing scores in mental performance tests in those subjects who vomited and did not vomit respectively, and a further analysis is being carried out to determine this.

On land the effect on a test of this nature would be expected to be very different. If anything, the placebo group would be more efficient than the treatment groups, in which

efficiency would be expected to decline progressively with increasing doses of anti-emetic drugs. Further experiments are being carried out to clarify this.

SUMMARY

1. Two doses of hyoscine hydrobromide (0.1 and 0.7 mg of the base) and five doses of cyclizine hydrochloride (15, 25, 40, 65 and 100 mg) were compared in terms of their ability to prevent vomiting, and of their deleterious side-effects, particularly the impairment of mental performance. These comparisons were made on 462 naval subjects in life-rafts exposed to the motion of artificial waves.

2. A detailed dose/response curve for cyclizine was established from the results and found to be parallel to that of (−)-hyoscine. From the two dose-response curves the relative anti-emetic potency of (−)-hyoscine to cyclizine hydrochloride was calculated at 1:580: this agrees well with a previous estimate which put the ratio at 1:200.

3. The findings of earlier work, suggesting that (−)-hyoscine has considerable anti-motion-sickness potency at doses smaller than those in usual clinical use, was confirmed. Doses as low as 0.1 mg of the base protected 75% of susceptible volunteers from vomiting, while producing no subjective effect on vision and only a small incidence of dry mouth.

4. The results suggest that it might be possible to reduce the incidence of the disabling side-effects of motion sickness drugs by administering smaller doses, and yet retain adequate anti-emetic activity. To verify this hypothesis, dose/response curves for the effect of such drugs on both prevention of vomiting and undesirable side-effects are required, and further experiments are planned to provide this.

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