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The effect on motion sickness and oculomotor function of GR 38032F, a 5-HT_3-receptor antagonist with anti-emetic properties

J. R. R. STOTT, G. R. BARNES, R. J. WRIGHT & C. J. S. RUDDOCK
R.A.F. Institute of Aviation Medicine, Farnborough, Hampshire GU14 6SZ

1 The 5-hydroxytryptamine (5-HT_3) receptor antagonist, GR 38032F, which possesses potent anti-emetic properties in vomiting induced by cancer chemotherapeutic drugs, has been tested to determine its value in the prophylaxis of motion sickness induced by cross-coupled stimulation. The double-blind trial compared GR 38032F with both a placebo (lactose) and with hyoscine. In addition, studies of ocular pursuit and saccadic eye movements were carried out following the administration of each drug.

2 The prophylactic effect of GR 38032F on motion-induced nausea was indistinguishable from that of placebo, whereas following hyoscine subjects showed a highly significant ($P < 0.001$) increase in tolerance to cross-coupled stimulation. Tests of oculomotor function showed no effect on saccadic eye movement from either drug. However, both drugs produced a significant ($P < 0.05$) though small reduction in eye velocity gain during pursuit eye movement.

3 These findings suggest that the 5-HT_3 receptor is not involved in the neural pathways that bring about motion sickness, but that it may have a role in the control of ocular pursuit. The absence of an anti-motion sickness effect from a drug that is effective in the treatment of vomiting induced by cancer chemotherapy serves to emphasize that different neural mechanisms are involved in the generation of motion sickness.

Keywords 5-hydroxytryptamine antagonist hyoscine motion sickness eye movements anti-emetic GR 38032F

Introduction

Recent studies in the ferret to investigate the effects of selective 5-HT_3-receptor antagonists have shown that they possess potent anti-emetic properties in vomiting induced by cytotoxic drugs such as cis-platin (Costall *et al.*, 1986), and cyclophosphamide, and by irradiation (Andrews *et al.*, 1987).

Preliminary results using this class of compounds in man have shown that ICS 205-930 (Liebundgut & Lancranjan, 1987) and GR 38032F (Cunningham *et al.*, 1987) are effective in controlling nausea and vomiting induced by a variety of chemotherapy regimens in patients who had obtained inadequate benefit from currently available anti-emetic therapy.

The drug used in the present study, GR 38032F (1,2,3,9-tetrahydro -9- methyl-3 [(2-methyl-1H-imidazol-1-yl) methyl] -4H-carbazol-4-one, HCl $2H_2O$) is a highly selective competitive antagonist at the 5-HT_3 receptor (Brittain *et al.*, 1987). Apart from its anti-emetic properties animal studies indicate that GR 38032F may also possess anti-psychotic and anxiolytic properties (Costall *et al.*, 1987; Jones *et al.*, 1987).

Toxicity studies in man have shown GR 38032F to be essentially free of side-effects. In particular

Correspondence: Dr J. R. R. Stott, R.A.F. Institute of Aviation Medicine, Farnborough, Hampshire GU14 6SZ

drowsiness, which is a feature of many established drugs used in motion sickness prophylaxis, was absent.

The present study was undertaken to determine whether the anti-emetic properties of GR 38032F would also be evident in motion-induced vomiting in man by comparing its effects against a placebo and against hyoscine, a well-established anti-motion sickness drug. In addition, oculomotor function tests were carried out in order to assess whether GR 38032F would cause an impairment of oculomotor performance in the manner previously demonstrated for hyoscine (Stott *et al.*, 1984).

Methods

The study was carried out as a randomised, double-blind, three way trial of GR 38032F, 8 mg, hyoscine hydrobromide, 0.6 mg, and placebo (lactose).

Twenty-four fit male volunteers in the age range 18–50 years underwent four test sessions at the same time of day at weekly intervals. Subjects were excluded from the trial if they had a previous history of vertigo or symptoms of neuro-otological disease, or were currently taking any medication. Subjects were instructed to avoid alcohol for 24 h before each test and this was confirmed on each occasion. No selection of subjects was made on the basis of their susceptibility to motion sickness. All subjects completed the Reason Motion Sickness Questionnaire (Reason, 1968). The first test session was used to familiarise the subject with the test procedure and, in particular, to allow him to experience the progression of motion sickness symptoms induced by head movements during yaw axis rotation (cross-coupled stimulation). Every 30 s during the test the subject was asked to rate his overall level of malaise using a number scale from 1 to 10 in which 1 represented complete well-being and 10 the level of malaise at which he wished to stop the test. No attempt was made to standardise the end-point of the test between subjects. Rather, subjects were instructed in the first session to choose a level of malaise to which they would be willing to progress in the three subsequent tests. At the end of each test a list of seven symptoms (dizziness, bodily warmth, headache, sweating, stomach awareness, increased salivation, nausea) and one sign (pallor) were assessed as being absent (0), mild (1), moderate (2) or severe (3). The response scores were added to give an overall symptom score for each test. These scores were examined to ensure that there were no marked discrepancies in the degree of end-point malaise, but were not used in the statistical analysis of results. Drugs were dispensed in identical capsules; the order of administration was randomised according to a balanced Latin square design.

At 1 h 45 min after taking the drug subjects underwent a test of oculomotor function. The test investigated two types of eye movement, pursuit tracking and saccadic eye movement. The subject, seated in the dark, was required to follow the horizontal movement of a light spot projected on to a semicircular screen.

The stimulus that was used to assess the performance of the saccadic system consisted of 32 step displacements of the target within one test session. Four different displacement amplitudes were used, 5°, 10°, 15° and 20°. These were either positive (from left to right) or negative (from right to left), and were arranged in such a way that the target was moved no more than 10° either side of the centre of the screen. Each displacement amplitude occurred four times within the test session, and the order of presentation was randomised. The length of time between steps was also varied randomly from 0.80–1.76 s so that the overall movement of the target was unpredictable. Subjects were instructed simply to fixate the position of the target as accurately as possible after each displacement.

Two different stimulus conditions were used for the pursuit tracking task. In both, the target motion was composed of five sinusoids of harmonically unrelated frequency each with a peak velocity of $4° s^{-1}$. The four lowest frequencies were maintained at 0.112, 0.156, 0.240, 0.368 Hz in both conditions, but the highest frequency took a value of 0.39 Hz in condition 1 and 1.56 Hz in condition 2. The stimulus of condition 1, although pseudo-random, normally results in high gain smooth pursuit whereas the substitution of the higher frequency in condition 2 leads to a breakdown in the response with reduction in eye velocity gain. Subjects were instructed to follow the movement of the target as accurately as possible.

Eye movements were recorded using both DC electroculography (EOG) and an infra-red limbus tracking technique. The wider range of the EOG technique ensured that any large saccadic displacements which were outside the limits of linearity of the limbus tracking recorders were still accurately measured by EOG.

At 2 h after drug ingestion the subject commenced the motion sickness test. The subject was seated on a rotating chair surrounded by an enclosure that rotated with the chair and obscured his view of the room. Rotation of the chair was started at $3° s^{-1}$ to the right and incremented by

$3° s^{-1}$ every minute up to a maximum of $90° s^{-1}$ and maintained at this speed for a further 10 min. During chair rotation the subject made 60° head movements to the left and right in roll and forward and backwards in pitch. The forward movement also involved forward flexion of the trunk to bring the forehead into contact with a pad situated at arms length in front of him. The sequence of head movements was pre-recorded and so arranged that the subject made a head movement to and from each of the four directions in random order over a 30 s period. Every 30 s the subject reported his symptoms using the 1–10 scale. The test was discontinued either after 40 min or, more usually, when the subject reached a malaise score of 10.

Data analysis

The data from the pursuit tracking task and the saccadic eye movement task were analysed by computer (Hewlett-Packard model 310). The analysis procedure for pursuit eye movements has been described previously (Barnes, 1982; Barnes *et al.*, 1987) and involves the extraction of the rapid resetting components of eye movement in order to reveal the underlying smooth pursuit eye velocity. The ratio of eye velocity to target velocity (gain) and its associated phase shift may then be used as indicants of the effectiveness of pursuit.

Analysis of the saccadic eye movements was carried out by examination of each individual step response. Four measures of eye movement were determined: (a) the peak velocity of the primary saccade; (b) the amplitude of the primary saccade; (c) the reaction time between onset of the step displacement and initiation of the primary saccade; and (d) the duration of the primary saccade. Peak eye velocity was determined from a computation of the eye velocity profile, using a two-point digital differentation technique. Saccade initiation and termination were determined from the time at which this velocity profile exceeded or fell below a threshold of $10° s^{-1}$.

Results

(a) Motion sickness

The results of the motion sickness provocation tests, shown in Table 1, are expressed in terms of the tolerated cross-coupled stimulus dose. This value is derived by scoring each head movement sequence according to the current rotational speed of the chair, in rev min^{-1}, and summing scores over the total number of head movement sequences made during the test. Also shown in Table 1 is the Reason Motion Sickness Questionnaire percentile score for each subject.

On three occasions in three different subjects the test procedure ran the full set length of 40 min without the subject having reached a malaise score of 10. In all three cases the subject had taken hyoscine prior to the test. Two subjects omitted one of the test sessions. One subject vomited about 30 min after taking the drug (placebo), the other subject, after taking the test drug (GR 38032F) decided to report sick with left upper chest pain which had first occurred following a sporting injury sustained during the previous evening.

Side-effects following hyoscine were noted by 14 subjects; light headedness was noted by eight subjects, dry mouth by eight subjects and dizziness or unsteadiness on walking by five subjects. Three subjects reported effects following GR 38032F consisting of slight headache and queasiness in one subject, slight light headedness and increased salivation in another, and slowness of thought in the third. Light headedness was also reported by two subjects following placebo.

Analysis of variance was carried out using as a variable the logarithmic transformation (log [x + 50]) of the stimulus dose in order to obtain a more normal distribution of the variance. This analysis used adjusted figures for the three censored values obtained when subjects tolerated the maximum motion dose without reaching the malaise endpoint, and also used estimated values for the two missing test results. Subsequent statistical analyses also used the adjusted censored values, but excluded the two missing values. Subjects were divided into six groups on the basis of the order of administration of prophylactic drugs. The results of this analysis are shown in Table 2. They indicate a significant treatment effect ($P < 0.001$) that was entirely due to hyoscine. In addition, a significant ($P < 0.01$) group by treatment interaction was found.

This interaction cannot be accounted for by the main effect of sequence. However, from clinical experience and as noted in a previous similar experiment (Stott *et al.*, 1984), individuals show wide differences in the rate at which they adapt to repeated nauseogenic stimuli, most subjects tending to become more tolerant, but others apparently becoming less so. In order to take account of this possible effect a subject × linear sequence interaction was postulated which partitioned the error term into subject × linear and subject × quadratic components. A standard F test indicated that subject × linear sequence

Table 1 Cross-coupled stimulus dose tolerated during each test session. Values of 765+ indicate that the subject completed the test profile before reaching the level of malaise at which he wished to stop. Numbers in brackets indicate the order in which drugs were tested in each subject

Subject	*Stimulus dose*			*MSQ (%ile)*
	GR 38032F	*Hyoscine*	*Placebo*	
1	264.5 (3)	338 (1)	276 (2)	57
2	60.5 (1)	153 (3)	98 (2)	24
3	585 (1)	765+ (2)	378 (3)	0
4	112.5 (3)	231 (2)	72 (1)	93
5	112.5 (2)	105 (3)	112.5 (1)	43
6	— (2)	242 (1)	200 (3)	85
7	264.5 (2)	465 (1)	253 (3)	86
8	364.5 (2)	406 (3)	406 (1)	15
9	128 (1)	325 (2)	162 (3)	50
10	420.5 (1)	765 (3)	615 (2)	17
11	144.5 (3)	220.5 (2)	91 (1)	82
12	98 (3)	98 (1)	91 (2)	22
13	312.5 (3)	120 (1)	242 (2)	36
14	120 (3)	128 (2)	55 (1)	87
15	60.5 (2)	200 (1)	78 (3)	94
16	136 (1)	406 (2)	153 (3)	75
17	510 (2)	765+ (3)	540 (1)	0
18	450 (1)	765+ (3)	510 (2)	94
19	242 (3)	378 (1)	338 (2)	0
20	220.5 (1)	300 (3)	— (2)	72
21	420.5 (2)	675 (3)	392 (1)	67
22	364.5 (3)	570 (2)	276 (1)	0
23	276 (1)	392 (2)	276 (3)	8
24	264.5 (2)	585 (1)	351 (3)	71
Mean	257.9	391.6	259.4	

Table 2 Analysis of variance table for stimulus dose (log transformed). Factors: G, sequence of drug administration (6), S, subject (24), T, drug treatment (3). (a) original analysis and (b) showing elimination of a significant treatment by group interaction after adjusting for order and individual subject × linear sequence

Source	*Sums of squares*	*d.f.*	*Mean squares*	F *ratio*	*Probability*	*Significance*
a						
G	3.2362	5	0.6472	0.761	0.589	NS
S(G)	15.3138	18	0.8508			
T	2.1888	2	1.0944	35.584	0.000	***
TG	1.1709	10	0.1171	3.807	0.002	**
TS(G)	0.9534	31	0.0308			
Total	22.8631	66				
b						
T	2.1889	2	1.0944	54.448	0.000	***
TG	0.1199	3	0.0400	1.986	0.165	NS
TS(G)	0.2616	13	0.0201			

was significant when tested against subject × quadratic sequence ($P < 0.01$). The original analysis of variance was then re-examined (Table 2b), using 24 subject × linear sequence covariables, the effect of which was to eliminate the treatment × group interaction.

Hyoscine prophylaxis enabled the subjects to make an average of 10.9 more head movement sequences than with placebo. This was equivalent to a 50% increase in stimulus dose.

The prophylactic effect of GR 38032F was indistinguishable from placebo. The mean number of tolerated head movement sequences differed by only 0.26 and subjects were almost equally divided between those who were able to make more head movements and those who made fewer head movements when GR 38032F had been taken.

A comparison was made between the motion sickness questionnaire percentile score and the tolerance to motion sickness induced by cross-coupled stimulation, as indicated by the number of head movement sequences that subjects made during the tests. Regression showed a negative slope indicating, as expected, a lower tolerance to cross-coupled stimulation in subjects having a higher questionnaire score. The correlation coefficient of -0.42, though significant ($P < 0.01$), indicates that the measurement of tolerance to a cross-coupled stimulus is not a good predictor of overall susceptibility to motion sickness as determined by questionnaire.

(b) Oculomotor performance

Although the results did not show any effect of either GR 38032F or hyoscine on saccadic eye movement, significant reductions in pursuit performance were brought about by both drugs. The details are as follows:

(i) Saccadic eye movements

Peak eye velocity Peak velocity increased with increasing target displacement in accord with many previous observations (Figure 1a). Velocities of 400–500° s^{-1} were reached at the largest target displacement (20°). The amount by which velocity increased with each increase in target displacement tended to decrease at the higher levels of target displacement, the so-called main sequence effect (Bahill *et al.*, 1975). The results were analysed using the order in which the drugs were taken as a co-variate, to allow for the effects of time. The values of peak velocity were logarithmically transformed to obtain a more normal variance distribution. It was found that there was no significant difference between the means for each treatment condition, whether the pre-trial condition was included in the analysis or not. It was also found that the means were not significantly affected by the direction of target movement. Mean peak saccade velocity was somewhat higher (13%) in the pre-trial condition than it was in any other condition, but the effect was not significant.

Saccadic duration There was an approximately linear relationship between duration and target displacement (Figure 1b), the mean duration increasing from 38 ms for 5° displacements to 67 ms for 20° displacements. Positive displacements (from left to right) appeared to elicit saccades of slightly longer duration than negative displacements. Analysis of variance revealed that, when the pre-trial condition was included, this directional effect was significant ($P < 0.05$), and in addition, that saccadic duration was significantly ($P < 0.05$) longer after ingestion of hyoscine than after ingestion of the placebo. However, when the pre-trial condition was excluded from the analysis these two effects were no longer significant.

Saccadic amplitude At the lower levels of target displacement saccadic amplitude closely matched target amplitude, the average saccadic amplitude for a target movement of 5° having a value of 5.2°. As the target displacement increased, the amplitude of the primary saccade was consistently less than target amplitude, so that mean saccadic amplitude for a target movement of 20° was only 17.0° (Figure 1c). Analysis of variance showed that when the pre-trial condition was included there were some significant interactions between the drug treatments and the order in which they were taken ($P < 0.05$). However, when the pre-trial was excluded from the analysis the interactions were no longer significant and there was certainly no significant drug treatment effect. Mean saccade amplitude was slightly greater in the pre-trial condition when compared with all other conditions. Although this effect was not significant it could well have contributed to the higher peak velocities in the pre-trial condition.

Reaction time There did not appear to be any clear relationship between reaction time and target displacement (Figure 1d). For all four treatment conditions and all eight target displacements reaction times were in the range 170–205 ms, values which are comparable with those obtained previously (Robinson, 1964; Baloh *et al.*, 1979). On average, the shortest reaction times were elicited by a movement of 10°; the

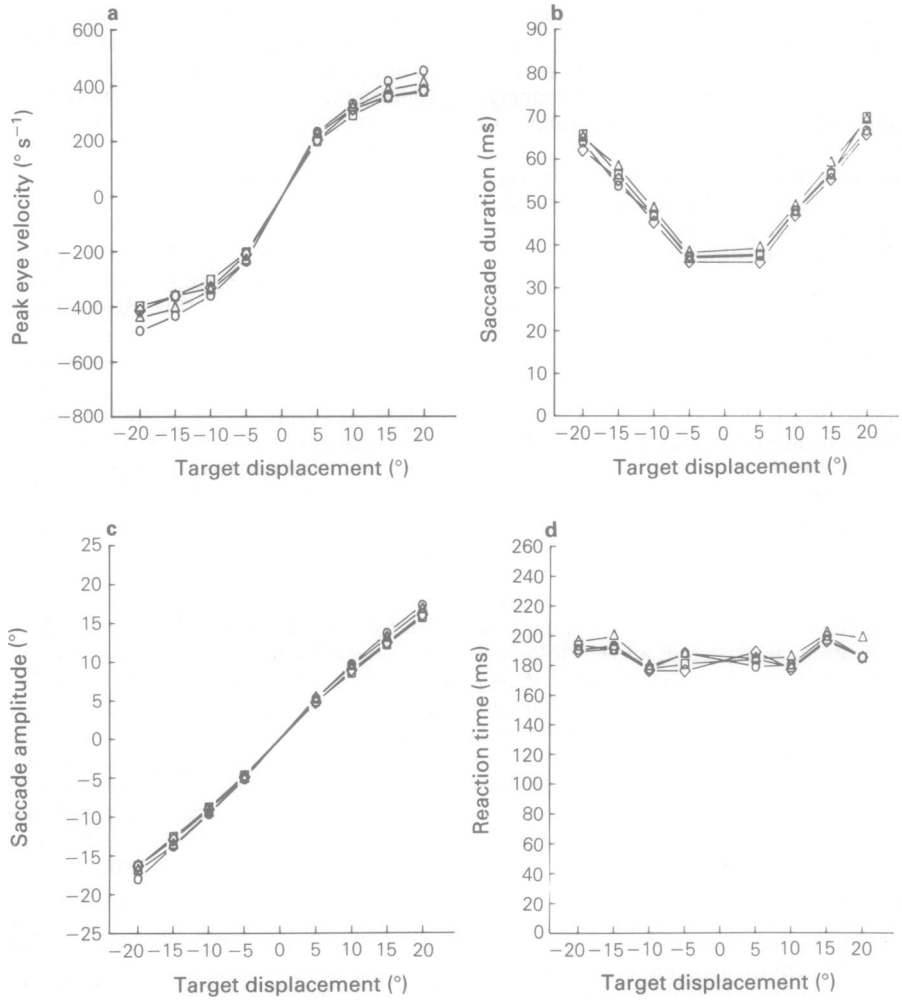

Figure 1 Measures of (a) peak eye velocity, (b) saccadic duration and (c) saccadic amplitude for the primary saccadic eye movement response to step target displacements of varying amplitude. The reaction time between the onset of target displacement and the initiation of the saccade is shown in (d). Symbols represent drug regimes as follows: (○) pre-trial session; (△) 8 mg GR 38032F; (□) 0.6 mg hyoscine; (◇) placebo. Means of twenty-two subjects.

longest were elicited by a movement of 15°. Analysis of variance, carried out on the logarithmically transformed variable, indicated no significant difference between the treatment means, when the results from the pre-trial condition were excluded. Inclusion of the pre-trial condition in the analysis revealed a significant interaction between the amount of target displacement, the direction of movement and the treatment condition ($P < 0.05$), an effect which is probably attributable to the somewhat shorter reaction times in the pre-trial runs.

(ii) Ocular pursuit

Eye velocity gain The overall level of eye velocity gain in the pursuit task was greater for the lower stimulus frequency combination (Figure 2a) than for the higher frequency combination (Figure 2b), reflecting the more predictable nature of the target motion when only low frequency components (< 0.4 Hz) were present (Barnes *et al.*, 1987). Analysis of variance indicated that there was a significant ($P < 0.05$) effect of drug treatment on eye velocity gain, although when

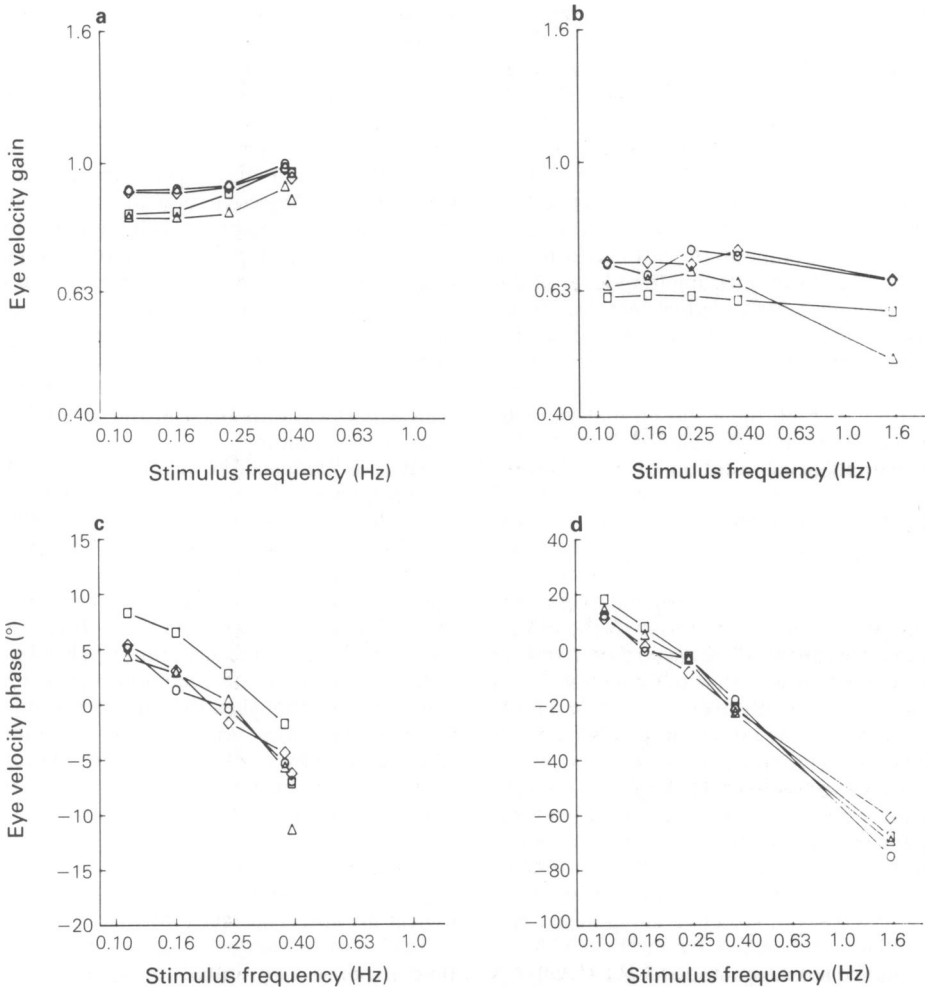

Figure 2 Eye velocity gain and phase during ocular pursuit of a pseudo-random target motion composed of five sinusoids of equal peak velocity (4° s^{-1}). In (a) and (c) the highest frequency was 0.39 Hz, whereas in (b) and (d) the highest frequency was 1.56 Hz. Responses are compared for the following conditions; (○) pre-trial session; (△) 8 mg GR 38032F; (□) 0.6 mg hyoscine and (◇) placebo. Means of twenty-two subjects.

the pre-trial condition was excluded from the analysis a significant ($P < 0.05$) interaction between frequency and treatment was revealed, which is evident in Figure 2. Taken separately, both hyoscine and GR 38032F caused a small (7% for hyoscine, 9% for GR 38032F), but significant ($P < 0.05$) reduction in eye velocity gain.

Eye velocity phase The most important change in eye velocity phase occurred between the two stimulus frequency combinations (Figures 2c and 2d). For the lower frequency combination there was significantly ($P < 0.001$) less phase advance at the lowest frequency and less phase lag at the highest frequency than for the higher frequency combination. These changes are consistent with the changes in gain observed in the two frequency combinations and are similar to the effects seen in previous experiments (Barnes *et al.*, 1987). The effect of drug treatment was complex. The only effect which stood out as being significant was the increase in phase advance associated with hyoscine in the lower frequency combination (Figure 2c), although there was also some tendency for this to occur with the higher frequency combination. GR 38032F had no significant effect on eye velocity phase.

Discussion

The cross-coupled stimulus has been widely used as a laboratory method to provoke the symptoms of motion sickness (Miller & Graybiel, 1970) and has been used as a test stimulus for the evaluation of prophylactic drugs (Wood & Graybiel, 1968). Individuals differ widely in their susceptibility to this stimulus just as they do to the motion environment of various forms of transport. The slowly incrementing level of the stimulus produced by a gradual increase in the rotational velocity of the chair ensured in this study that symptoms of motion sickness were elicited in all subjects, and that very few individuals failed to reach their chosen malaise endpoint before the scheduled end of the test. The rate of increment of rotation of $3° \cdot s^{-1}$ every minute was half that used in a previous similar trial which compared the prophylactic benefits of powdered ginger root, cinnarizine and hyoscine (Stott *et al.*, 1984). The lower rate of increment used in the present trial was designed to improve discrimination between the prophylactic effects of different treatments. The use in a similar drug trial of a ramp profile that incremented in its early stages more rapidly than $6° s^{-1}$ every minute tended to obscure the known prophylactic benefits of hyoscine (Pingree *et al.*, 1988).

5-hydroxytryptamine (5-HT) is found in many body tissues notably in blood platelets, enterochromaffin cells of the gut and also in the brain. Receptors for 5-HT are situated on cell membranes and can be subdivided into at least three types on the basis of selective antagonists. Receptors that are blocked by methysergide or cyproheptidine are designated as 5-HT_2-receptors and are involved in the action of 5-HT to bring about contraction of the vascular, gastrointestinal and bronchial smooth muscle. Metoclopramide and GR 38032F block the action of 5-HT at the 5-HT_3-receptor site. 5-HT_3-receptors are involved in the depolarisation of nerve cell membranes, reflex brachycardia (Bezold-Jarish reflex), pain, and the release of noradrenaline from sympathetic nerves. Other receptor sites for 5-HT that are resistant to antagonism by 5-HT_3- or 5-HT_3-receptor antagonists may be of more than one type, but are grouped together as 5-HT_1-like receptors. These receptors mediate a relaxation of smooth muscle, hypotension and tachycardia.

The results of the present study indicate that blockade of the 5-HT_3-receptor site offers no protection against the development of motion-induced nausea. The drug metoclopramide, in addition to blocking 5-HT_3-receptors, is also an antagonist at dopamine D_2-receptors. Despite an initial report of prophylactic benefit from a 23 mg dose of metoclopramide prior to 'roller coaster' aircraft manoeuvres (von Baumgarten *et al.*, 1980) a subsequent study (Kohl, 1987) has failed to show any benefit from doses of 10 and 20 mg in laboratory trials using cross-coupled stimuli and in parabolic 0–1.8 *g* flight manoeuvres. The latter author also reports the absence of subjective or objective benefit from multiple 10 mg doses used during orbital flight by 22 astronauts. This apparent lack of therapeutic benefit in motion-induced vomiting contrasts with the established effectiveness of metoclopramide and, from preliminary clinical trials, of GR 38032F in vomiting induced by cytotoxic drugs and is an indication of the different neurological pathways involved in the generation of nausea and vomiting.

There is evidence, however, that the 5-HT_1-like receptor may be involved in vomiting induced by motion stimuli (Lucot & Crampton, 1987). In a study using motion sickness susceptible cats, the drug buspirone, a partial agonist at 5-HT_{1A} receptors, produced a dose related suppression of motion induced vomiting. This drug also inhibited xylazine-induced vomiting. The ablation of the area postrema (chemoreceptor trigger zone) in cats abolishes the emetic response to xylazine, but does not affect motion-induced vomiting (Colby *et al.*, 1981). It is, therefore, postulated that buspirone acts within the vomiting centre where both emetic mechanisms converge.

Drugs that are active in motion sickness prophylaxis are drawn from a number of pharmacological groups. The fact that hyoscine, a muscarinic, anticholinergic drug, is more effective than atropine is attributed to its greater central nervous system action. Similarly the centrally active adrenergic drugs amphetamine and ephedrine also have some prophylactic effect. A number of antihistamines, cyclizine, diphenhydramine, cinnarizine and promethazine, are also active in motion sickness, but, as with hyoscine, drowsiness is a frequent undesirable side-effect. The site of action of these drugs is not known. While an intact vestibular system is a pre-requisite for the development of motion sickness symptoms it is generally accepted that symptoms arise not from vestibular overstimulation, but from conflicting sensory information derived from visual, vestibular and kinaesthetic sources about the motion of the body in space. Attention therefore focuses on those areas of the brain where sensory signals about motion converge, notably the vestibular nuclei and the vestibulo-cerebellum.

In neuropharmacological studies of the vestibular nucleus of cats 80% of cells sampled showed

an excitatory effect with acetylcholine and 75% an inhibitory effect from amphetamine and noradrenaline (Kirsten & Sharma, 1976). Further evidence for the importance of cholinergic pathways in motion sickness derives from the finding that a pattern of symptoms resembling motion sickness is produced by physostigmine, a centrally acting cholinesterase inhibitor (Davis & Davis, 1980).

The results of the oculomotor function tests indicate that both GR 38032F and hyoscine may produce an undesirable detriment in ocular pursuit, though not in the performance of the saccadic system. The tests performed are sensitive indicants of function for a number of areas of the brain. Saccadic velocity is controlled primarily by the pontine reticular formation (Henn & Cohen, 1976; Keller, 1977) whereas saccade latency is controlled principally by the superior colliculus and the frontal eye fields (Schiller *et al.*, 1987). The accuracy and duration of saccades is influenced by the cerebellum, especially in long-term adaptive calibration (Optican & Robinson, 1980), but other brainstem areas are probably involved in short-term control. A variety of drugs have been shown to affect all these measures of saccadic eye movement. Thus alcohol has been shown to reduce saccadic velocity, though not latency (Wilkinson, 1976; Wilkinson *et al.*, 1979; Jantti *et al.*, 1983), and the additive effects of marijuana and alcohol on the reduction of both saccadic maximum velocity and reaction time have been demonstrated by Baloh and coworkers (1979). Diazepam and other benzodiazepines have been shown to produce dose dependent increases in saccadic duration and decreases in saccadic velocity (Jurgens *et al.*, 1981; Rothenberg & Selkoe, 1981a; Bittencourt *et al.*, 1981; Salonen *et al.*, 1986). By contrast, methadone has been shown to cause significant increases in saccadic undershoot and latency, without any change in saccadic velocity (Rothenberg *et al.*, 1980). These findings indicate the potential differentiation of effects which may be obtained.

The results of the experiments described here indicate that there is no significant effect of either GR 38032F or hyoscine on any of the four measures of saccadic eye movement examined. In a previous study (Stott *et al.*, 1984) it was shown that hyoscine did have a significant effect on the peak saccade velocity, though not on reaction time or amplitude. Mean peak velocity fell by 6% under the same drug dosage as that used here. The present study does not confirm this finding, although a direct comparison is difficult because Stott *et al.* (1984) did not measure peak velocity, but an average velocity. In the present study the lowest overall mean level of peak velocity was obtained under the influence of hyoscine but it was only some 4% less than that evoked with the placebo. The fact that in the pre-trial condition mean peak saccade velocity was 13% greater than for the placebo and that mean reaction time was 4% less may reflect a generally increased arousal level in the pre-trial condition. This was not unexpected because of the unfamiliar nature of the experimental apparatus. In particular the use of a dental bite system frequently engenders apprehension in naive subjects.

The pursuit reflex is also known to be sensitive to the effect of drugs. Its major pathways involve retinal ganglion cells, striate cortex, parietal cortex, brainstem oculomotor centres and the cerebellum (Eckmiller, 1987). Drugs such as the benzodiazepines (Rothenberg & Selkoe, 1981b; Bittencourt *et al.*, 1983) and alcohol (Wilkinson *et al.*, 1974; Baloh *et al.*, 1979; Lehtinen *et al.*, 1982; Barnes *et al.*, 1984) cause an impairment in the ability to match the velocity of the eye to that of the target. This necessitates the introduction of saccadic corrective movements leading to the observation of 'broken pursuit'. In a mixed-frequency pseudo-random stimulus of the type used in this experiment, the velocity of the smooth component of eye movement also becomes reduced whenever the highest frequency exceeds approximately 0.4 Hz (Barnes *et al.*, 1987). This finding is confirmed in the present experiment by the lower levels of eye velocity gain obtained when the highest frequency was increased from 0.39 Hz to 1.56 Hz. Both of the drugs tested produced a significant reduction in gain for both values of the highest frequency, but the reduction would not be sufficient to cause a severe impairment of performance. However, the results may indicate that a higher dosage of either drug could lead to a greater reduction in gain and hence a more significant impairment of visual performance. 5-HT is known to be a transmitter in areas such as the pontine reticular formation, which are associated with both pursuit and saccadic eye movements, and it is perhaps not surprising, therefore, that a 5-HT-antagonist should be found to modify oculomotor performance in this way.

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