Psychopharmacology (1987) 92:513–519

Psychopharmacology

Promethazine, scopolamine and cinnarizine: comparative time course of psychological performance effects

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Abstract. Single oral doses of promethazine (12.5 mg, 25 mg), scopolamine (0.6 mg), and cinnarizine (30 mg), were compared in a double-blind, placebo controlled trial. Twelve normal volunteers undertook a battery of psychological performance tests and a feeling state questionnaire, before drug administration, and at 2-h intervals after. Promethazine and cinnarizine significantly impaired psychomotor performance, information processing and feelings of alertness. With promethazine these reductions were maximal 3–4 h post-drug, with performance returning near to baseline 8–9 h post-drug. With cinnarizine these impairments were maximal 5–6 h post-drug, and performance remained depressed 8–9 h post-drug. Scopolamine significantly reduced feelings of alertness, and memory task performance; the overall performance effects were most evident 1–4 h post-drug.

Key words: Promethazine – Scopolamine – Cinnarizine – Performance – Reaction time – Psychological assessment – Alertness – Feeling state – Psychoactive drug

Scopolamine hydrobromide (hyoscine) is widely used for the treatment and prophylaxis of motion sickness. Trials in the real motion environment have demonstrated significant motion sickness protection (Glaser 1953; Brand and Perry 1966; Reason and Brand 1975), while laboratory trials using controlled motion devices have demonstrated scopolamine to be the most effective single drug for motion sickness (Wood and Graybiel 1968; Reason and Brand 1975; Wood 1979). Scopolamine combined with amphetamine has been used for space sickness by astronauts and cosmonauts (Lukomskya and Nikolskay 1971; Graybiel 1980). Scopolamine, however, also affects psychological functions, particularly memory for new information, sustained attention, and feelings of alertness (Colquohoun 1962; Deutsch 1971; Lukomskya and Nikolskay 1971; Ghoneim and Mewaldt 1975; Wesnes and Warburton 1983, 1984; Parrott 1986), while autonomic side effects include dry mouth and blurred vision (Innes and Nickerson 1975).

Promethazine hydrochloride has also been demonstrated to provide significant motion sickness protection, both in the laboratory and the real motion environment (Glaser 1953; Brand and Perry 1966; Wood and Graybiel 1968; Wood 1979). Parenteral promethazine comprises a standard treatment for personnel already vomiting, although the consequent sedation is marked (McMurray 1973; Hordinsky et al. 1982). Oral promethazine significantly impairs psychomotor skills such as hand-eye coordination and adaptive tracking (Molson et al. 1966; Large et al. 1971; Clarke and Nicholson 1978), reduces critical flicker fusion threshold (Turner 1968; Hedges et al. 1971), and leads to lowered feelings of alertness (Hedges et al. 1971; Large et al. 1971). The effects of oral promethazine upon information processing and cognitive skills to not seem to have been investigated, although parenteral promethazine impairs information processing (Hordinsky et al. 1982).

Cinnarizine has been investigated in very few placebo-controlled trials. In sea trials it has occasionally demonstrated significant motion sickness protection (Trumbull et al. 1960; Hargreaves 1980, second trip), although it has also failed to demonstrate significant effects (Trumbull et al. 1960, both other trips). Laboratory studies using replicable motion conditions, have demonstrated comparatively slight protection. Wood and Graybiel (1970) showed less protection with cinnarizine than with scopolamine, promethazine, or cyclizine. Stott et al. (1984) showed both cinnerizine and scopolamine to be effective, although cinnarizine was significantly less effective than scopolamine. The effects of cinnarizine upon psychological performance have been rarely investigated. Stott et al. (1984) found no significant performance effects 1–2 h following oral cinnarizine. In a review of cinnarizine, Towse (1980) reported no performance studies, but suggested that drowsiness was the most frequent side effect.

The time course profiles for the psychological effects of oral scopolamine, promethazine, and cinnarizine are not well documented. Most investigations of oral scopolamine have used single post-drug assessments, although some trials have used two post-drug sessions. Wood et al. (1985) reported performance decrements similar in extent 2 and 4 h following oral scopolamine (both 0.8 mg and 1.0 mg). Wesnes and Revell (1984) noted similar task impairments 1 and 2 h following 1.2 mg scopolamine (sucked tablets). Parrott (1986) reported significant impairments 1–2 h after 1.2 mg oral scopolamine, while performance returned near to baseline 5–6 h post-drug. With oral promethazine, Clarke

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and Nicholson (1978) demonstrated maximal impairments 5 h after drug administration, while performance remained below baseline 7 h post-drug. Hedges et al. (1971) demonstrated maximal decrements 6 h post-drug (later periods were not assessed). Large et al. (1971), Molson et al. (1966), and Wood et al. (1985) showed significant decrements 3 h post-drug (later performance was not assessed). It has been suggested that promethazine is effective for 24–48 h (Brand and Perry 1966; Reason and Brand 1975), but the empirical basis for this suggestion is weak. Time course data for the psychological effects of cinnarizine are not known.

The choice of drug in operational personnel depends upon both comparative effectiveness in preventing motion sickness, and relative severity of psychological performance effects. Comparative drug effectiveness trials are currently under way at the Institute of Naval Medicine. The present trial was undertaken to determine comparative psychological performance effects of cinnarizine, promethazine and scopolamine.

Methods

Subjects. The subject group comprised 12 medically screened male volunteers (aged 18–29 years). Subjects signed informed consent forms, and were paid for participation. The trial was conducted in accordance with the Declaration of Helsinki.

Familiarisation and training. A day of instruction, training and practice was given to all subjects before trial commencement. However, to further train the volunteers and familiarise them with the experimental conditions, an extra placebo condition was introduced. This was given as the first of six visits the subjects had to make. Neither the testers nor the volunteers knew this was a placebo day. The results were discarded.

Design. A within subjects design was employed. After the familiarisation session subjects received the five drug conditions over the remaining five weekly visits. The order of drug administration was counterbalanced using a 5×5 latin square, with the first two rows being used a third time for subjects 11 and 12. Drug administration and testing were double blind.

Testing sessions. On each study day five test sessions were given at the following times:

0800–0900 hours	Pre-drug administration
–0900 hour	Drug administration
1000–1100 hours	1–2 h post-drug
1200–1300 hours	3–4 h post-drug
1400–1500 hours	5–6 h post-drug
1700–1800 hours	8–9 h post-drug

Each test session was 1 h in duration.

Assessment measures. The assessment measures are described below. Unless otherwise stated, each test duration was 4 min.

Four choice continuous reaction time (Wilkinson and Houghton 1975). In this psychomotor task, four stimulus lights were matched with four response keys. Each stimulus required a response, with each response initiating the next (randomly determined) stimulus light. Continuous psychomotor responding was therefore required. Average response time and errors were recorded. The task was run on Wilkinson four-choice reaction time machines.

Target tracking (Schroeder et al. 1982). In this psychomotor accuracy task, a randomly moving stimulus was centered onto a central target, by compensatory control movements with a hand joystick. Root mean square error (average target-stimulus distance) was automatically calculated. The task was run on an Apple IIe computer.

Letter cancellation (Parrott and Jones 1985). In this information processing task, blocks of randomly ordered letters were scanned for a target letter (e.g. "T") printed at the top of the page. Each identified target was to be deleted. Response sheets and target letters were changed each test session. Average time per letter scan, and percentage omission error, were recorded.

Code substitution (Parrott 1986). In this information processing task, a series of random letters was coded into numbers, using a nine-item letter/number code presented at the top of the page. Average time per coding, and percentage error, were recorded.

Logical reasoning (Baddeley 1968). In the cognitive task, logical statements presented in a standardised format were judged as true or false (e.g. A does not precede B, this means BA. Is this true or false?). Average time per solution and percentage error were calculated.

Rapid visual information processing (Wesnes and Warburton 1984). In this test of information processing and sustained visual attention, a series of single digits was presented on a VDU screen at the rate of 100 digits per min. The task required the identification of targets (three consecutive odd or three consecutive even digits), by pressing a response button as quickly as possible. Total target detection, commission error, and average response time, were automatically calculated. The task was run on an RML 380Z computer.

Stroop test (Jensen and Rohwer 1966). In the colour patch condition, subjects consecutively named a series of randomly ordered colour patches. In the colour name condition, subjects consecutively named a series of colour words printed in colours which were different from the colour names. Patch identification time, name identification time, and patch-name difference time, were each calculated.

Immediate recall, delayed recall, and recognition memory. Lists of 15 words were presented over headphones at the rate of one word every second. Immediate written recall was then required. Delayed recall was required after 12 min. Recognition memory for the old words (present in the original list), was then tested, while the recognition of 15 new words (not present in the original list) was also assessed. The 30 words were presented in random order on a VDU screen; subjects pressed a "yes" button for an old word. Correct identifications and response times were calculated. The task was run on an RML 380Z computer.

Critical flicker fusion (Smith and Misiac 1976). Critical flicker fusion (CFF) has been widely used in psychophar-

Table 1. Summary of Dunnet test placebo/drug differences

Assessment measure		Promethazine 12.5 mg					Promethazine 25 mg					Cinnarizine 30 mg					Scopolamine 0.6 mg				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Four-choice Reaction time	rt		**	*				**	**							+					
	er																				
Tracking	rms														+	+					
Letter cancellation	rt		+						**												
	om																				
Code Substitution	rt								*												
	er																				
Logical reasoning	rt					(+)									+						(+)
	er																				
Rapid visual information processing	tot								*												
	com																				
	rt														+	**					
Stroop: patch	rt																				
name	rt										+										
diff	rt										+										
Immediate recall																					
Delayed recall																					
Old word recognition	tot																				
	rt																				
New word recognition	tot																				
	rt							*					*	(+)				+			
Critical flicker fusion	Hz									**					*						
Alertness	mm		+	**				**	**					+					*		
Sociability	mm		+	**					*												

T1 = Pre drug; T2 = 1–2 h post-drug; T3 = 3–4 h post-drug, T4 = 5–6 h post-drug; T5 = 8–9 h post-drug

One-tail: + $P<0.05$; * $P<0.025$; ** $P<0.005$
Two tail: + $P<0.1$; * $P<0.05$; ** $P<0.01$

rt reaction time; er error; tot total correct; mm millimetre (VAS scale); Hz Hertz; rms root mean square error (accuracy); om omission error; com commission error

macological trials as a psychophysical index of alertness. The subject rested their head on a chin rest one meter in front of three diode lights. Following a predetermined signal, one of the three lights started to flicker. The subject identified the flickering light by pressing one of three response keys. Further light presentations followed. If the response was correct, then the flicker rate was increased, whereas if the response was incorrect, then the flicker rate was decreased. This procedure allowed the flicker fusion threshold to be determined without response bias. The task was run on an RML 380Z computer.

Subjective feeling state and side effect questionnaire (Parrott 1986). Bipolar 100 mm visual analogue scales were presented for two feeling states: alert/drowsy, and sociable/withdrawn. The side effect questionnaire assessed the presence/absence of headache, dizziness, dry mouth, blurred vision, and other negative symptoms.

Data analysis. The assessment measures were analysed using one-way repeated measures analysis of variance (ANOVA). The data from each test session was analysed separately. Dunnet test comparisons between placebo and four active drug conditions were then undertaken, to indicate the statistical significance of each placebo/active drug condition difference (Kirk 1968). One-and two-tailed values are both presented; one-tailed values being appropriate where performance decrements were predicted.

General experimental restrictions. Subjects remained in the general environment of the test rooms each day. Driving, the operation of machinery, alcohol, and caffeinated beverages were prohibited. Decaffeinated coffee was however freely available. Smoking was not allowed during testing.

Results

The Dunnet test comparisons between placebo and the active drug conditions are presented in Table 1. At the first test session there were no significant Dunnet tests effects, demonstrating that there were no significant differences between the placebo and active drug conditions, prior to drug administration. During the later test sessions, several placebo/active drug differences were evident (Table 1). Promethazine and cinnarizine demonstrated significant impairments on the psychomotor measures and alertness indices (Table 1). Figure 1 therefore presents the four choice reaction time, target tracking, critical flicker fusion, and self-

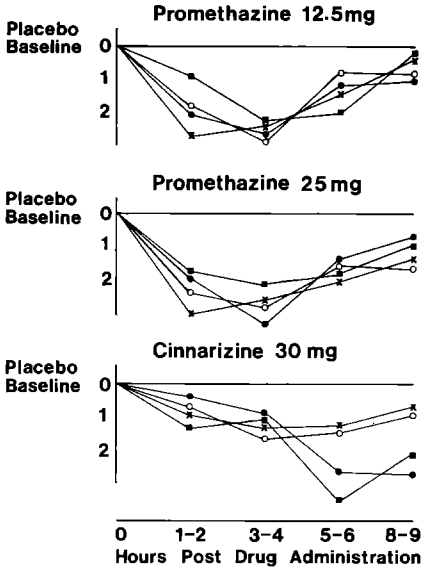

Fig. 1. Performance changes following promethazine and cinnarizine. Critical flicker fusion (1 Hz) ×——×; self rated alertness (10 mm) o——o; target tracking (2 rms) ■——■; 4-choice reaction time (0.02 s) ●——●

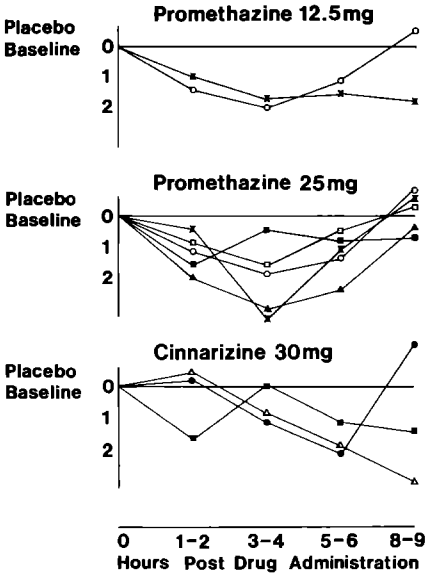

Fig. 2. Performance changes following promethazine and cinnarizine. Self rated sociability (10 mm) o——o; logical reasoning time (0.1 s) ●——●; letter cancellation time (0.01 s) ×——×; code substitution time (0.1 s) □——□; new word recognition time (0.2 s) ■——■; rapid vis info proc time (0.02 s) △——△; rapid vis info proc targets (5) ▲——▲

rated alertness data, for promethazine and cinnarizine; this figure allows the time course profiles of promethazine and cinnarizine to be compared with equivalent data sets. Other assessment measures also demonstrated significant effects with promethazine and cinnarizine; Fig. 2 therefore presents the data for each assessment measure showing a significant placebo/promethazine or placebo/cinnarizine Dunnet test effect. Scopolamine demonstrated a different profile of performance change to those shown by promethazine and cinnarizine (Table 1). Psychomotor performance was not significantly affected, although some non-significant reductions were evident, but self-rated alertness and new word

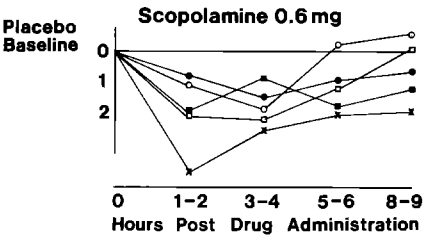

Fig. 3. Performance changes following scopolamine. Critical flicker fusion (1 Hz) ×——×; self rated alertness (10 mm) o——o; letter cancellation error (1 err) ●——●; immediate recall (0.5 word) □——□; new word recognition time (0.2 s) ■——■

Table 2. Summary of side effect questionnaire findings total responses from all post drug administration test sessions

Side effect	Placebo	Promethazine 12.5 mg	Promethazine 25 mg	Cinnarizine 30 mg	Scopolamine 0.6 mg
Headache	1	6	1	5	5
Dizziness	1	6	6	1	2
Dry mouth	0	3	5+	6*	8**
Blurred vision	1	8*	12**	5	6
Other negative comments	1	2	6	3	8*

Binomial test: One-tail: + $P<0.05$; * $P<0.025$; ** $P<0.005$
Two-tail: $P<0.10$; $P<0.05$; $P<0.01$

recognition time were significantly impaired. The data for these two measures are presented in Fig. 3, together with three further measures: critical flicker fusion (to allow comparison with self-rated alertness. Note: Dunnet test 1–2 h post-drug for CFF, $P=0.06$, one-tailed), immediate recall (as a memory index) and letter cancellation omission error (as a sustained attention index).

Side effects are summarised in Table 2. Dry mouth was significantly increased following promethazine 25 mg, cinnarizine and scopolamine. Reports of blurred vision were significantly increased following both dose levels of promethazine, and were comparatively more frequent following cinnarizine and scopolamine. Dizziness and headache were more frequently reported following the active drugs (non-significantly) as were other negative comments, the latter being significant following scopolamine (Table 2).

Discussion

The three drugs investigated were all found to impair some aspects of psychological functioning, although differences were evident in the types of function affected, and the profiles of these changes over time. Psychomotor performance was significantly impaired by oral promethazine, with the greatest decrements generally being found 3–4 h after drug administration (Table 1, Figs. 1 and 2). The pattern of performance change over time was similar for both doses of promethazine, although the higher dose (25 mg) generally produced greater overall mean changes, as well as leading to significant decrements on a larger number of assessment tasks (Fig. 2). Promethazine has been shown to significantly impair psychomotor performance in several previous trials. Clarke and Nicholson (1978) demonstrated significant im-

pairments in adaptive tracking 3 and 5 h post-drug, and non-significant impairments 1.5 and 7 h post-drug, following 10 mg oral promethazine. The Clarke and Nicholson (1978) study comprises the only other investigation into the psychomotor performance effects of promethazine for longer than 3 h; their time course data closely matches the present findings (Fig. 1). Two previous studies have investigated performance for up to 3 h. Large et al. (1971) noted a non-significant decrement in hand-eye coordination 1.5 h post-drug, and a larger significant decrement 3 h after 25 mg oral promethazine. Molson et al. (1966) reported a similar time course for hand-eye coordination with 50 mg oral promethazine.

In the present study, several information processing measures were significantly impaired following promethazine: letter cancellation time, code substitution time, rapid visual information processing target detections, Stroop test reaction time, and new word recognition time. The time course profile for these changes was similar to that described above, with maximal decrements 3–4 h post-drug (Table 1; Figs. 1 and 2). Information processing was therefore significantly impaired by promethazine, particularly following the higher dose. Previous investigations of oral promethazine do not seem to have investigated laboratory information processing tasks, although Payne et al. (1953) reported a significant reduction in navigation skills following 25 mg oral promethazine. Feelings of alertness and sociability were significantly reduced by promethazine, as were critical flicker fusion (CFF) thresholds (Fig. 1). Hedges et al. (1971) demonstrated a significant reduction in CFF 6 h post-drug, and lesser reductions 2 and 4 h following 25 mg oral promethazine. Large et al. (1971) similarly noted marked drowsiness 6 h following 25 mg oral promethazine.

Psychomotor performance was impaired by cinnarizine, with significant reductions in target tracking accuracy and four-choice reaction time. Information processing was also affected, with logical reasoning time, rapid information processing time, and new word recognition time, each demonstrating significant drug effects. Feelings of alertness and CFF thresholds were also significantly reduced (Table 1; Figs. 1 and 2). Cinnarizine therefore impaired a range of psychomotor, information processing, and alertness indices, although the time-course profile for these changes was comparatively longer with cinnarizine than with promethazine. Performance impairments were generally maximal 5–6 h post-drug, with impairments still evident 8–9 h post-drug (Figs. 1 and 2). The effects of cinnarizine upon psychological task performance have, as far as is known, been reported in only a single study. Stott et al. (1984) investigated digit symbol substitution, critical flicker fusion, missing digit identification, saccade velocity, and self-rated alertness, at a single (2 h) post-drug session. No significant effects were present, although performance on some tasks was slightly depressed. The Stott et al. (1984) 2 h data therefore closely match the 1–2 h data from the present study (Figs. 1 and 2). Towse (1980) described drowsiness as the most frequent side effect of cinnarizine. Cobb et al. (1976) also reported drowsiness in 5 of 12 subjects, following 25 mg (QID) cinnarizine for 3 days. These reports of drowsiness are therefore consistent with the significant increase in drowsiness noted in this study.

Scopolamine demonstrated a different profile of performance change to those shown by promethazine and cinnarizine. Psychomotor performance was not significantly affected, but feelings of alertness were significantly reduced, and new word recognition time was significantly impaired (Table 1; Fig. 3). Previous investigations have also shown that moderate doses of oral scopolamine tends not to impair psychomotor functions (Payne et al. 1952; Poulton and Edwards 1974; Wood et al. 1985; Parrott 1986). Scopolamine has however been shown to affect memory for new information (Deutsch 1971; Ghoneim and Mewaldt 1975; Jones et al. 1979; Warburton and Wesnes 1984), and to impair sustained attention and alertness (Lukomskya and Nikolskay 1971; Colquohoun 1974; Poulton and Edwards 1974; Wesnes and Warburton 1983, 1984; Warburton and Wesnes 1984). However, these studies have generally demonstrated significant decrements with higher dose levels than that used here. Wesnes and Warburton (1984) and Parrott (1986) each noted significant decrements following 1.2 mg oral scopolamine, and non significant changes following 0.6 mg oral scopolamine. Parrott (1986) demonstrated that decrements in memory and attention were significantly related to dose in a linear fashion. In the present study, 74% of all assessment measures demonstrated a comparative decrement 1–2 h after 0.6 mg scopolamine (binomial test, $P<0{,}05$); similarly, Parrott (1986) reported that 75% of the assessment measures demonstrated a comparative decrement 1–2 h after 0.6 mg (binomial test, $P<0.05$).

The time course profile for scopolamine suggested maximal performance decrements 1–2 and 3–4 h post-drug, with performance nearer baseline at the later test sessions (Fig. 3), Wood et al. (1985) noted decrements similar in extent 2 and 4 h following 0.8 mg and 1.0 mg oral scopolamine (later times were not investigated). Parrott (1986) reported maximal decrements 1–2 h post-drug, with performance nearer to baseline 5–6 h post-drug. Parenteral scopolamine also demonstrates a similar time course profile for performance change (Elkin et al. 1965; Ketchum et al. 1973).

The duration of drug effect is an important factor when comparing different drugs. Reason and Brand (1975, pp 216–220) showed that in life raft trials with drugs administered 1 h before motion, shorter acting drugs such as scopolamine were superior to longer-acting drugs such as meclozine or promethazine; in contrast, in troopship trials over 48-h periods, promethazine and meclozine were comparatively superior to scopolamine (Reason and Brand 1975, pp 216–220). Accurate time course data is therefore required, but is not always available. Promethazine has been stated to be effective for either 8 h (Wood 1979; p 476), or for 24–28 h (Brand and Perry 1966, p 903; Reason and Brand 1975, p 218). Similarly meclozine, a piperazine derivative similar to cinnarizine, has been stated to be effective for either 6 h (Wood 1979, p 475), or for 24 h (Reason and Brand 1975, p 217). These figures are generally not based upon firm empirical data. (Note: the 24–48 h period for promethazine arises from an early paper on antihistaminic reduction in skin wheal size, where time course projections suggested 24–48 h for the skin wheal to return to its original size (Bain et al. 1949). The present data confirm that these three drugs have different durations for performance effects, but does not confirm the prolonged time course suggested for promethazine. Future trials with cinnarizine should investigate performance for longer than 9 h, in order to determine the time taken for performance to return to baseline.

Promethazine and scopolamine are strong muscarinic acetylcholine antagonists, whereas cinnarizine displays comparatively weak anticholinergic activity (Brand and Perry 1966; Innes and Nickerson 1975; Bowman and Rand 1980). Acetylcholine is closely involved with memory storage, stimulus processing, sustained attention, and feelings of alertness (Deutsch 1971 Wesnes and Warburton 1983, 1984; Warburton and Wesnes 1984); hence the performance reductions in tasks involving these functions with all three drugs (Figs. 1 and 2). The side effects of dry mouth and blurred vision probably reflect antimuscarinic effects upon the acetylcholine fibres of the autonomic nervous system (Douglas 1975; Innes and Nickerson 1975). Promethazine and cinnarizine are H1-histamine antagonists, whereas scopolamine displays little antihistaminic activity (Brand and Perry 1966; Innes and Nickerson 1975; Towse 1980). H1-antihistamines which cross the blood-brain barrier commonly produce sedation and drowsiness, particularly following acute single doses (Douglas 1975; Nicholson 1985). The psychomotor slowing, reduced alertness, and impaired information processing with promethazine and cinnarizine, may therefore reflect central antihistaminic activity (Douglas 1975; Nicholson 1985). These proposed relationships are only tentative, since specific performance and neurochemical effects cannot be accurately defined.

In conclusion, each of these three drugs were associated with significant performance impairments, although different functions were affected, and the time course profiles of performance change were also different. Anticholinergic and noradrenergic drug combinations such as scopolamine-amphetamine and promethazine-ephedrine have recently been used for space sickness (Graybiel 1980; Kohl and Homick 1983). These combinations display increased effectiveness by acting synergistically on different neurochemical systems (Kohl and Homick 1983). Furthermore, their sedative and stimulant properties tend to cancel (Gaillard and Verduin 1983). Drug combinations therefore represent the next area in the search for an effective anti-motion sickness drug without deleterious effects upon performance.

Acknowledgements. The authors would like to acknowledge the experimental assistance provided by Janet Kilpatrick and Martin Le Good; Also Mr. Hellyer of the Royal Naval Hospital, Haslar for providing the matched drug capsule; also Boots Pure Drug Company for the decaffeinated coffee.

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Received November 24, 1986 / Final version February 10, 1987