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The effects of transdermal scopolamine and four dose levels of oral scopolamine (0.15, 0.3, 0.6, and 1.2 mg) upon psychological performance

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Abstract. Four dose levels of oral scopolamine (0.15 mg, 0.3 mg, 0.6 mg, 1,2 mg), transdermal scopolamine, and placebo, were investigated for their effects upon a battery of psychological performance measures in normal subjects. Oral scopolamine produced significant linear dose-related decrements on tasks involving continuous attention, continuous performance, memory storage for new information, and on self-rated feelings of alertness and sociability. Transdermal scopolamine produced significant performance impairments on these same assessment measures. Resting heart rate levels were significantly reduced by all scopolamine conditions. Side effects (dry mouth, dizziness) were frequent following transdermal scopolamine and the higher oral dose conditions. The overall effects of the transdermal scopolamine patch were broadly equivalent to the effects of 0.8 mg oral scopolamine. This oral dose equivalence for transdermal scopolamine is higher than expected, and possible reasons for this are discussed.

Key words: Scopolamine – Acetylcholine – Anticholinergic drug – Transdermal drug delivery – Psychological performance – Memory – Alertness – Attention

Scopolamine hydrobromide (hyoscine) has frequently been shown to be the most effective single drug against motion illness (Brand and Perry 1966; Wood and Graybiel 1972). Recently, the transdermal method of administering scopolamine has been developed (Shaw 1983). This transdermal system displays certain advantages over oral and parenteral methods of drug administration. Firstly, it provides continuous drug delivery for approximately 72 h, compared with 5–6 h for the duration of effect of a single oral dose; drug levels also remain fairly constant over this time period (Chandrasekeran 1983). Secondly, it has been suggested that drug concentration levels are comparatively low following transdermal delivery; an oral dose equivalence of 0.2 mg has been suggested, compared with the standard oral dose of 0.6 mg (Shaw 1983). Lastly, by avoiding the oral route, transdermal delivery may be useful with people who are already vomiting. Transdermal scopolamine has been demonstrated to provide significant protection against motion illness, both under laboratory conditions of motion (Graybiel et al. 1976, 1981, 1982; Homick et al. 1983; Hordinsky et al. 1982), and at sea (Price et al. 1981).

Scopolamine is a muscarinic acetylcholine antagonist (Shutt and Bowes 1979; Warburton 1975). Current models of motion illness suggest that this anticholinergic activity is the basis of scopolamine's protective properties (Reason and Brand 1975; Kohl and Homick 1983). Central nervous system cholinergic systems are also important with respect to psychological functions such as memory, attention, and alertness (Warburton 1975). The storage of newly presented material into memory is significantly impaired by scopolamine (Crow and Grove-White 1973; Drachmann and Leavitt 1974; Ghoneim and Mewaldt 1975; Jones et al. 1979). Continuous sustained attention and vigilance are also significantly impaired by scopolamine (Colquhoun 1962; Lukomskya 1971; Poulton and Edwards 1974; Wesnes and Warburton 1983). In contrast to these significant decrements, scopolamine does not generally impair psychomotor or response speed measures (Payne et al. 1952; Poulton and Edwards 1974; Wood et al. 1984). The effects of transdermal scopolamine upon psychological performance have been reported in two published studies. Hordinsky et al. (1982) compared transdermal scopolamine and transdermal placebo on two information processing, and three psychomotor tasks. No drug decrements were noted 5 and 8 h following patch administration. Parrott and Jones (1985) investigated transdermal scopolamine with three performance tasks. Choice reaction time and code substitution were not affected, but letter cancellation (a task involving continuous attention), was significantly impaired. Subjective side effects reported with oral and transdermal scopolamine include dry mouth, drowsiness, and blurred vision (Glaser 1953; Homick et al. 1983; Parrott and Jones 1985; Price et al. 1981). Cardiovascular effects have also been reported, with significant bradycardia following both oral and transdermal scopolamine (Brand et al. 1968; Graybiel et al. 1976).

The present trial had several aims: a) Firstly, to directly compare the effects of different dose levels of oral scopolamine, using a battery of performance measures covering a range of psychological function. Few previous investigations with oral scopolamine have used more than a single dose condition, and few studies have included more than two or three different assessment tasks; b) Secondly, to investigate the effects of the transdermal scopolamine patch upon the same battery of assessment measures: c) Lastly, to directly compare the effects of transdermal scopolamine with the effects of different doses of oral scopolamine, in

order to estimate the oral dose equivalence for the transdermal patch.

Materials and methods

Subjects. The subjects were 12 male volunteers, aged 19–38 (mean 24 years). Subjects were medically screened, signed informed consent forms, and were paid for participation. The trial was undertaken in accordance with the declaration of Helsinki.

Drug conditions. A complicated drug administration design was necessary because of the different pharmacokinetic profiles of oral and transdermal scopolamine. Oral scopolamine has peak effects 1–2 h following administration, and a duration of action of 5–6 h; transdermal scopolamine takes several hours to reach a stable level, but then remains at this level for 72 h (Chandrasekaran 1983; Shaw 1983). Each drug condition comprised both a standard transdermal patch, applied at 2300 h the day before testing, and an oral drug capsule, given at 1030 h on the testing day. The six drug conditions were as follows:

Oral dose	Transdermal patch
placebo	placebo
0.15 mg scopolamine	placebo
0.3 mg scopolamine	placebo
0.6 mg scopolamine	placebo
1.2 mg scopolamine	placebo
placebo	scopolamine

Drug administration and testing were double blind. Each subject underwent all drug conditions, with drug presentation order based upon 6×6 latin squares. (Note: a 13th subject, replicating the first row of the latin square, was also tested, but the performance data was not included in the latin square ANOVAS; the side effect data from this subject was however analysed).

Test days, test sessions, and assessment measures. The six drug conditions were investigated on 6 test days. Three practice days, involving nine practice sessions, were run beforehand. Test days were interspersed over a 4-week period. Three testing sessions were run each test day at the following times:

Session 1: 0900–1010 h,
Pre oral drug administration.

Session 2: 1130–1240 h,
1–2 h post oral drug.

Session 3: 1530–1640 h,
5–6 h post oral drug.

Test sessions were divided into seven 10-min periods. Each 10-min period comprised 8 min testing, and 2 min changeover. During each 8-min period, one set of assessment measures was given. The order of test presentation was counterbalanced between subjects. The assessment measures are briefly described below.

Memory storage for new information (Ghoneim and Mewaldt 1975). Lists of 16 words, matched for frequency of occurance in the English language, were presented at the rate of one word every 2 s; immediate written recall was required. Four word lists were presented. Total correct recall, and commission errors were recorded. Lists were presented on a high fidelity tape recorder.

Table 1. Summary of analysis of variance (ANOVA) drug effects

Assessment measure		All test sessions	Test sess. 1	Test sess. 2	Test sess. 3
Discrete choice reaction time (s)	short interstimulus interval				
Discrete choice reaction time (s)	long interstimulus interval				
Target tracking	(RMS error)				
Four choice reaction time	Time (s)	**	*	*	**
	Error				
Code substitution	Time (s)				
	Error				
One letter cancellation	Time (s)				
	Error		*		
Four letter cancellation	Time (s)	*		*	*
	Error	**	**	*	
Rapid visual information processing	Time (s)				
	% Omis. Error	**			
	Com. Error				
Memory storage	Tot Recall	**	*	**	**
	Com. Error				
Critical flicker fusion	(hz)				
Resting heart rate	(bpm)	**	**	**	**
Self-rated alertness	(mm)	**	**		
sociability	(mm)	**		*	**

* $P<0.05$; ** $P<0.01$

Rapid visual information processing (Wesnes and Warburton 1984). Single random digits (from 1 to 8) were displayed on a VDU screen, with one digit every 0.6 s. The task was to identify "targets", defined as either three consecutive odd digits, or three consecutive even digits, by pressing a response button. Response times, percentage of omission errors, and total commission errors were automatically recorded. The task was run on an RML 380Z computer.

Four choice continuous reaction time task (Wilkinson and Houghton 1975). Four closely spaced stimulus lights were matched with four corresponding response keys. On stimulus illumination, the appropriate response key had to be pressed; this response initiated the immediate illumination of the next stimulus light and the position of this next light was determined randomly. Continuous psychomotor performance was therefore required in this task. Average response time, and total errors were recorded. The task was run on Wilkinson four choice reaction time machines.

Cognitive information processing tasks. Three pencil and paper tasks were given at this testing period: one letter cancellation, four letter cancellation, and code substitution.

Table 2. Group mean values for all assessment measures, 1–2 h following oral drug administration

Assessment measure		Oral drug conditions scopolamine/placebo difference					Linear dose resp effect
		Placebo baseline	0.15 mg	0.3 mg	0.6 mg	1.2 mg	
Discrete choice reaction time (s)	short interstimulus interval	0.63	+0.02	+0.01	+0.02	+0.06	
Discrete choice reaction time (s)	long interstimulus interval	0.72	−0.06	−0.04	−0.01	+0.03	
Target tracking	(RMS error)	71	−13	−23	+19	+26	
Four choice reaction time	Time (s)	0.47	−0.01	+0.02	+0.01	+0.04	*
	Error	63	+33	+2	+3	+22	
Code substitution	Time (s)	1.35	+0.08	+0.07	+0.06	+0.10	
	Error	0.4	−0.1	+0.4	−0.1	+0.4	
One letter cancellation	Time (s)	0.14	−0.01	0.00	−0.01	0.00	
	Error	6	+2	+3	+4	+4	
Four letter cancellation	Time (s)	0.37	0.00	+0.01	−0.02	0.00	
	error	8	+2	+3	+7	+10**	**
Rapid visual information processing	Time (s)	0.51	+0.01	−0.01	+0.03	0.00	
	% Omis. Error	42	−3	0	+4	+5	
	Com. Error	2.8	+3.1	+3.6	+1.0	+1.3	
Memory storage	Tot Recall	23.7	+1.2	+3.5	+1.2	+6.8**	**
	Com. Error	1.8	+0.8	+0.6	+0.3	+0.6	
Critical flicker fusion	(hz)	31.9	−0.6	−1.1	−0.6	−0.3	
Resting heart rate	(bpm: decrease)	64	+7**	+8**	+10**	+12**	**
Self-rated alertness	(mm)	53	+2	−2	+3	+10	*
sociability	(mm)	63	−1	+3	+4	+10*	**

Note: − score indicates better scopolamine than placebo performance; + score indicates worse scopolamine than placebo performance
Dunnet test: placebo/scopolamine comparison
Linear dose response effects: F test with orthogonal polynomials

* $P<0.05$; ** $P<0.01$ (two-tailed)

In letter cancellation, a sheet of 450 randomly ordered letters was scanned, and each instance of the target letter (or four letters) deleted. The target letter (or four target letters) was defined at the top of each sheet. Average time per letter scan, and omission errors were recorded. In code substitution, a nine-item letter/number code was presented, and a series of random letters then consecutively coded into numbers using the code. Average time per coding, and total errors were recorded.

Discrete choice reaction time, critical flicker fusion, and self-rated feeling states (Parrott et al. 1982). In discrete choice reaction time, response times to the occasional onset of one of six stimulus lights were automatically recorded. Following five practice responses, ten stimuli were presented at two different interstimulus intervals: a short interstimulus interval (average 3 s), and a long interstimulus interval (average 20 s). Critical flicker fusion (CFF) has been used in psychopharmacological trials as an index of alertness (Smith and Misiac 1976). CFF thresholds were recorded using the psychophysical method of limits, with two ascending and two descending thresholds; mean CFF thresholds were recorded. Choice reaction time and CFF were tested using the Leeds Psychomotor Tester. Subjective feeling states were recorded using bipolar visual analogue (100 mm) self report questions: for alertness and sociability. Side effects were recorded on binary "yes/no" questions for dry mouth, blurred vision, dizziness, and other comments.

Target tracking. In target tracking, a randomly moving stimulus was centered on a central target using compensatory movements with a joystick. The average root mean square error was automatically calculated. The task was run on an Apple IIe computer.

Resting heart rate. Photophlethysmographic (PPG) sensors recorded blood flow characteristics to the fingers. Following 4 min rest on a couch, the basal heart rate during the 5th min of rest was recorded.

Data analysis. The data was analysed by four latin square ANOVAS, performed upon the data from the three separate test sessions, and the overall data from all sessions. Dunnet's test was used to compare placebo with each of the other drug conditions (Kirk 1968). Dose-response relationships for the oral drug conditions were analysed by means of the F-test for linear trends, using orthogonal po-

lynomials (Kirk 1968). Higher order trends were also investigated, but none were significant.

Further experimental restraints. The trial was run in an experimental suite of rooms with a controlled atmosphere; temperature was maintained at 22 (±2) ° C, and relative humidity at 55% (±10%). Alcohol- and caffeine-containing beverages were not permitted, but decaffeinated coffee was available; smoking was prohibited 10 min before and during testing.

Results

The ANOVA drug effects are listed in Table 1. Significant drug effects were present with several variables; these variables generally demonstrated significant oral or transdermal placebo/drug differences (see below). With the oral drug conditions at the first test session (before oral drug administration), no Dunnet test comparisons between the placebo and pre oral drug conditions were significant. Similarly, none of the linear dose response trends with this pre-oral drug administration data approached significance.

Group mean values for the oral drug conditions at the second test session, 1–2 h following drug administration, are presented in Table 2. Significant Dunnet test comparisons between placebo/oral scopolamine were present with several variables; these are listed in Table 2. Six variables demonstrated significant linear dose response relationships, with increasing decrements at the higher dose levels; these linear trends are presented graphically (Fig. 1). Linear dose-response relationships were also evident with one letter cancellation errors, and rapid visual information processing omission errors ($P<0.05$, one-tailed; $P<0.10$, two-tailed). The overall changes from all assessment measures were summarised by comparing the number of assessments showing decrements compared to increments, at each dose level (Fig. 2); binomial test comparisons on these data were significant with 0.6 mg ($P<0.05$), and 1.2 mg ($P<0.001$), and bordered on significance with 0.3 mg ($P<0.10$, two-tailed; $P<0.05$, one-tailed).

At the third test session, 5–6 h following oral drug administration, oral drug condition performance levels with many of the assessment measures were near to placebo values. Significant linear dose response reductions were, however, evident with three measures: four choice continuous reaction times, resting heart rates, and self rated sociability. Five Dunnet test placebo/scopolamine comparisons were significant: 0.15 mg, discrete choice reaction time long interstimulus interval (performance increment); 0.3 mg four choice continuous reaction time (performance decrement); 0.3 mg resting heart rate (reduced); 1.2 mg resting heart rate (reduced); 1.2 mg self-rated sociability (reduced). The overall changes from all assessment measures were again summarised by comparing the number assessment measures showing decrements, compared to increments, at each dose level. The following percentage decrements (and two-tailed binomial test significance levels) were evident: 0.15 mg, 44% (NS); 0.3 mg, 58% (NS); 0.6 mg, 55% (NS); 1.2 mg, 74% ($P<0.10$). A degree of performance impairment was therefore still apparent in the 1.2 mg condition.

Transdermal scopolamine/placebo difference scores are presented in Table 3. Dunnet test comparisons between placebo/transdermal scopolamine for the data from all sessions were significant on nine assessment measures. These com-

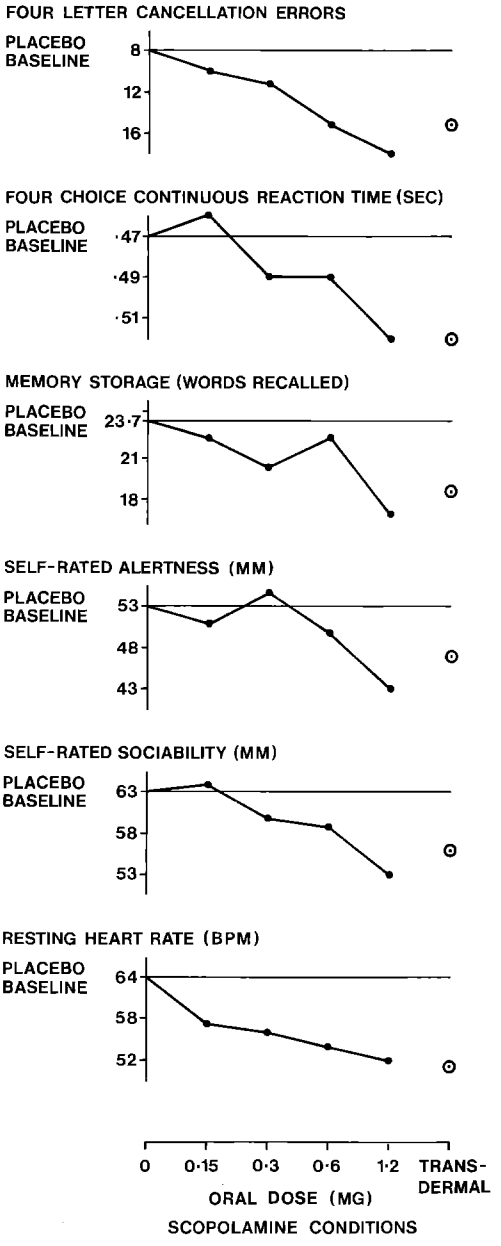

Fig. 1. Placebo/scopolamine difference scores for variables with significant linear dose-response relationships

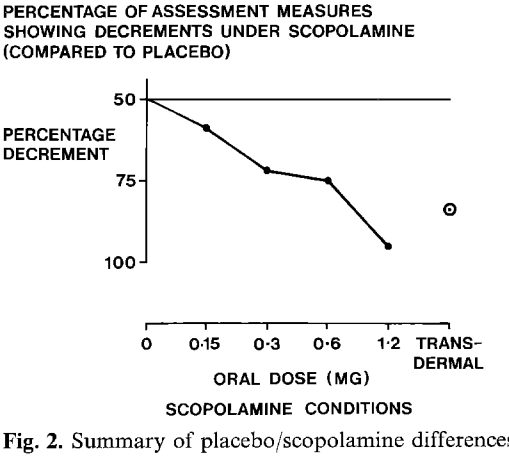

Fig. 2. Summary of placebo/scopolamine differences across all assessment measures

Table 3. Transdermal scopolamine/transdermal placebo difference scores for all assessment measures

Assessment measure		Transdermal scopolamine/transdermal placebo difference scores			
		Test session one	Test session two	Test session three	All test sessions
Discrete choice reaction time (s)	short interstimulus interval	+0.02	0.00	+0.03	
Discrete choice reaction time (s)	long interstimulus interval	0.00	−0.05	−0.07	
Target tracking	(RMS error)	+3	−12	−8	
Four choice reaction time	Time (s)	+0.02	+0.05	+0.05*	*
	Error	+17	+11	+16	
Code substitution	Time (s)	+0.04	+0.13	0.00	
	Error	+0.4	+0.1	0.0	
One letter cancellation	Time (s)	+0.01	+0.01	+0.01	
	Error	+6	0	−2	
Four letter cancellation	Time (s)	+0.03	+0.04	+0.05**	*
	Error	+7**	+7	+3	*
Rapid visual information processing	Time (s)	+0.01	+0.01	−0.02	
	% Omis. Error	+9*	+7*	+5	**
	Com. Error	−0.5	+1.9*	−0.1	
Memory storage	Tot Recall	+5.0**	+5.7**	+5.4**	**
	Com. Error	+0.8	+1.3	+1.0	*
Critical flicker fusion	(hz)	+0.7	−0.9	−0.5	
Resting heart rate	(bpm: decrease)	+14**	+13**	+11**	**
Self-rated alertness	(mm)	+17**	+6	+6	**
sociability	(mm)	+7	+7	+8*	*

Note: − score indicates better scopolamine than placebo performance; + score indicates worse scopolamine than placebo performance
Dunnet test: transdermal scopolamine/placebo comparisons

* $P<0.05$; ** $P<0.01$ (two-tailed)

prised those measures which demonstrated decrements with oral scopolamine: four choice continuous reaction times, four letter cancellation errors, rapid visual information processing omission errors, memory storage total recall, resting heart rate, self rated alertness and sociability (Tables 2, 3); together with four letter cancellation times, and memory commission errors (Table 3). The effects of transdermal and oral scopolamine were compared directly using the data from the second test session. Transdermal scopolamine produced decrements in 84% of all assessment measures (binomial test: $P<0.01$); this was intermediate between the percentage decrements found with 0.6 mg (75%), and 1.2 mg (94%) oral scopolamine (Fig. 2). The oral dose equivalence for transdermal scopolamine can be estimated, from this overall data, to be approximately 0.8 mg. This conclusion is in broad agreement with the findings from those assessment measures which were sensitive to the effects of scopolamine (Fig. 1); transdermal scopolamine decrements were generally intermediate in extent between those found with the 0.6 mg and 1.2 mg conditions. Subjective side effects are listed in Table 4. Transdermal scopolamine caused significantly more reports of dry mouth, and non-significant increases in dizziness and blurred vision. Oral scopolamine caused significantly more dry mouth and dizziness, particularly in the 1.2 mg condition.

Discussion

Oral scopolamine produced significant dose-related decrements on several measures, particularly those involving sustained attention or memory for new information: rapid visual information processing omission errors, four letter cancellation errors, one letter cancellation errors, and memory storage total recall (Table 2; Fig. 1). Tasks involving sustained attention have been previously shown to be disrupted by scopolamine (Colquhoun 1962; Lukomskaya et al. 1971; Poulton and Edwards 1974), with greater decrements following higher doses (Wesnes and Warburton 1983). Similarly, significant impairments with the storage of new information into memory have been previously demonstrated (Crow and Grove White 1973; Jones et al. 1979; Safer and Allen 1971). Scopolamine has been shown not to impair the recall of information memorised before drug administration, in studies where the storage and recall of information (i.e. for information memorised after drug administration) was impaired (Drachmann and Leavitt 1974; Ghoneim and Mewaldt 1975). These studies therefore demonstrated that scopolamine impairs the memory storage mechanisms, rather than recall mechanisms. Sustained attention and memory storage have each been demonstrated to involve cholinergic neurotransmission (Deutsch 1971;

Table 4. Subjective side effects: number of subjects reporting side effects with each drug condition

	Oral drug conditions				
	Placebo	0.15 mg	0.3 mg	0.6 mg	1.2 mg
Session 1: pre-drug					
Dizziness	0	0	0	0	0
Dry mouth	1	1	1	0	0
Blurred vision	1	2	1	1	0
Other comments	3	3	3	2	4
Session 2: 1–2 h post-drug					
Dizziness	0	0	0	1	4*
Dry mouth	0	1	1	0	3
Blurred vision	2	2	1	2	4
Other comments	2	2	2	3	4
Session 3: 5–6 h post-drug					
Dizziness	0	0	0	0	0
Dry mouth	0	0	1	0	6**
Blurred vision	2	1	2	1	3
Other comments	2	2	3	5	3

	Transdermal drug conditions	
	Placebo	Scopolamine
All sessions: combined		
Dizziness	0	3
Dry mouth	1	6*
Blurred vision	2	5
Other comments	4	3

Transdermal scopolamine/placebo comparisons: binomial test
Oral condition comparisons: Cochran Q test

* $P<0.05$; ** $P<0.01$

Warburton 1975). The results of the present study are therefore in close accord with previous findings with this anticholinergic drug; scopolamine impairs tasks involving sustained continuous attention, or the storage of new information into memory.

Reaction time measures were generally not significantly affected following oral scopolamine: discrete choice reaction time, one letter cancellation reaction time, four letter cancellation reaction time, and rapid visual information processing reaction time (Table 2). Several previous studies have reported that scopolamine does not generally impair psychomotor speed measures. Payne et al. (1952) concluded that 0.65 mg oral scopolamine produced deleterious effects on information processing tasks rather than perceptual motor tasks. Poulton and Edwards (1974) reported significant decrements on qualitative (error score) task measures, but not on quantitative (reaction time) measures, following 1.0 mg oral scopolamine. Wood et al. (1984) reported unimpaired target tracking following 0.25 mg and 0.5 mg oral scopolamine. One psychomotor measure in the present trial demonstrated significant impairments following oral scopolamine: four choice continuous reaction time (Table 2; Fig. 1). This task involves continuous performance, and the decrement may be related to the continuous attentional requirements (necessary for optimal performance), rather than to basic psychomotor aspects of the task. Some psychomotor slowing was present with the high oral dose conditions (Table 2); these non-significant reaction time changes may follow from the reduced feeling of alertness found at these dose levels, or they may directly reflect a tendancy towards psychomotor slowing at higher dose levels.

At the third test session, 5–6 h following drug administration, oral scopolamine performance levels had generally returned to near placebo values, although some performance remained depressed, particularly in the 1.2 mg condition. In general, therefore, the performance impairments present at the 1–2 h test session were largely reduced by the 5–6 h session. A similar pattern of performance changes over time was demonstrated by Elkin et al. (1965) with iv scopolamine; impairments were maximal at the 2 h session, but steadily reduced in extent at the 4 and 6 h test sessions.

Transdermal scopolamine produced significant performance decrements on several assessment measures, particularly those involving sustained attention or memory for new information, and on self-rated feelings of alertness and sociability; these were measures which demonstrated impairments with oral scopolamine (Tables 2, 3; Fig. 1). Reaction time measures of performance were not generally affected by transdermal scopolamine, although as with oral scopolamine, continuous four choice reaction time performance was significantly impaired (Tables 2, 3; Fig. 1). The effects of transdermal scopolamine upon objective psychological performance measures have been reported in two studies. Hordinsky et al. (1982) investigated transdermal scopolamine with tests of manual dexterity, steadiness, tapping, code substitution, and mental arithmetic. The only significant performance change was reduced psychomotor tapping speed at the 2 h session, but this may well have been a chance artefact, as drug levels are not thought to reach effective concentrations at this time period (Shaw 1983). There were no significant performance changes 5 or 8 h following patch administration. Most of the tests of Hordinsky et al. (1982) were psychomotor measures; the absence of drug-related changes therefore confirms the findings reported here, that scopolamine tends not to impair psychomotor functions. Parrott and Jones (1985) investigated transdermal scopolamine with three performance tests at sea; letter cancellation errors were significantly increased, while code substitution, discrete choice reaction time, and letter cancellation time were not impaired. Those findings therefore agree closely with the present results; decreased performance on the measure involving sustained narrow attention (letter cancellation errors), but unchanged perfomance on the other measures.

Self-rated alertness and sociability were significantly reduced by oral and transdermal scopolamine (Tables 2, 3; Fig. 1). This confirms the reduced arousal previously reported with oral and transdermal scopolamine in land-based trials (Glaser 1953; Homick et al. 1983; Warburton 1975). It is, however, interesting to note that although significant reductions in drowsiness are reported from land-based trials, drowsiness has not generally been reported from sea-based trials, either with oral scopolamine (Glaser 1953) or transdermal scopolamine (Parrott and Jones 1985; Price et al. 1979). Drug and motion therefore seem to interact in their effects upon arousal, with arousal decrements following scopolamine only in static land based situations. Self-reported side effects were noticeable following both 1.2 mg oral and transdermal scopolamine, with dry mouth, dizziness, and blurred vision each reported (Table 4). Side

effects of this nature have been previously reported with the higher doses of oral scopolamine (Glaser 1953), and with transdermal scopolamine (Parrott and Jones 1985; Price et al. 1979), although following a low dose (0.3 mg) of oral scopolamine, side effects were "slight" (Tokola et al. 1984), confirming the general absence of side effects with the lower oral dose conditions in the present study. These "side effects" predominantly reflect the autonomic parasympathetic blockade produced by anticholinergic drugs (Shutt and Bowes 1979).

Resting heart rates were significantly reduced by all oral scopolamine conditions 1–2 h after drug administration (Table 2), and remained somewhat depressed 5–6 h following oral dosing; this bradycardia was significantly related to doseage (Fig. 1). Dose-related bradycardia following oral scopolamine has been previously reported (Brand et al. 1968; Graybiel et al. 1976). Graybiel et al. (1976) also reported significant bradycardia (mean reduction 11.5 bpm) 14–20 h following transdermal scopolamine. This bradycardia with scopolamine contrasts with the tachycardia produced by other anticholinergic drugs such as atropine and methscopolamine. This difference has not been adequately explained (Domino and Corssen 1967), although Shutt and Bowes (1979) suggested that the bradycardia follows from reduced alertness. This explanation is not however supported by the present findings, since 0.15 mg and 0.3 mg produced significant bradycardia, but only very slight changes in self-reported levels of alertness (Table 2; Fig. 1).

The analysis of all drug conditions at the second test session, provided a direct comparison of the strength of transdermal and oral drug effects. With both the individual assessment measures (Fig. 1), and the average changes over all assessments (Fig. 2), it was apparent that transdermal scopolamine had deleterious effects generally intermediate in strength between those found with 0.6 mg and 1.2 mg oral scopolamine. Similarly, side effects were most frequent following the 1.2 mg and transdermal conditions (Table 4). Overall, a dose equivalence for transdermal scopolamine of approximately 0.8 mg oral scopolamine can be suggested (see Results section). This is higher than expected, particularly following predictions that the transdermal system would not deliver enough drug to produce deleterious performance effects. Shaw (1983) stated:

"Like other rate-controlled drug dosage forms, transdermal delivery can substantially reduce the total dose needed for therapy. The transdermal scopolamine system delivers only 0.5 mg scopolamine over 3 days, versus about 2.5 mg over 3 days from 6-hourly administration of 0.2 mg injections or tablets. Thus, side effects from the transdermal system are minimal" (p. 591).

Similarly, Chandrasekaran (1983) wrote:

"The goal of the development effort was to deliver scopolamine at the rate that would give the beneficial effects of control over motion sickness, but none of the side effects normally associated with the drug"

... also ..

"Dry mouth was the only significant drug effect ... two thirds of people experienced transient dry mouth and one sixth experienced drowsiness. Other central effects of scopolamine were observed infrequently" (p. 643, 645).

Neither Shaw nor Chandrasekaran used objective performance tests to assess performance effects, but instead relied upon subjective reports. These are, however, of limited applicability, and in order to assess functions such as vigilance, psychomotor skill, and memory, objective performance tests are necessary.

One possible explanation for the deleterious effects with the transdermal patch relates to the period of drug presence. The continuous infusion of scopolamine over many hours may be having a comparatively greater effect upon acetylcholine neurotransmitter systems than a single oral dose with its shorter period of drug availability. Recent studies have suggested that repeated dosing with scopolamine causes acetylcholine receptor "supersensitivity" (Sitaram et al. 1979); this may be occurring with the transdermal system, and lead to the heightened performance effects. Another possible reason could be the size of the dose delivered by the transdermal system. Shaw (1983) suggested a transdermal dose equivalence of 0.2 mg iv or 0.2 mg oral scopolamine (every 6 h). However, this comparison was based upon iv data only, and iv delivery provides higher drug concentration levels than oral delivery. Safer and Allen (1971) suggested that: "The ratio of oral to intravenous dose for scopolamine is approximately 4-to-1" (p. 351).

Using this conversion ratio, Shaw's data can be reinterpreted to suggest an oral dose equivalence for transdermal scopolamine of approximately 0.8 mg, a value which is in close agreement with the findings from the present trial.

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