

# Transdermal Scopolamine: Effects of Single and Repeated Patches upon Aspects of Vision

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Transdermal scopolamine and transdermal placebo patches were administered on alternating days to 12 normal volunteer subjects. Visual near-point values and self-reports of blurred vision were systematically assessed 24 hours following each transdermal patch. Blurred vision was not reported following the first scopolamine patch, but became increasingly frequent following successive scopolamine patches. Six of the 12 subjects reported blurred vision by their fourth scopolamine patch. Subjects reporting blurred vision had long initial visual near-points (i.e. were comparatively hypermetropic), whereas subjects not reporting blurred vision had short initial visual near-points (i.e. were comparatively myopic). The visual near-point values of the (hypermetropic) subjects who developed blurred vision became longer following each successive scopolamine patch, whereas the visual near-point values of the (myopic) subjects not reporting blurred vision remained basically unchanged. Visual changes following scopolamine have been previously shown to be slow to develop and slow to dissipate; this slow time course probably produced the cumulative visual problems reported here.

**KEY WORDS**—Scopolamine, hyoscine, anticholinergic, transdermal drug, vision, visual near point, blurred vision, visual accommodation.

## INTRODUCTION

Scopolamine hydrobromide (hyoscine) is a muscarinic acetylcholine antagonist, reducing cholinergic neurotransmission in both the autonomic and central nervous systems (Innes and Nickerson, 1975; Warburton, 1975). The central nervous system effects of scopolamine include impaired memory for new information, impaired vigilance and attention, and reduced feelings of alertness (Ghoneim and Mewaldt, 1975; Parrott, 1986; Warburton and Wesnes, 1984; Wesnes and Warburton, 1984). The autonomic nervous system effects of scopolamine include dry mouth and reduced sweating—these reflect reduced cholinergic neurotransmission with the salivary and sweat glands (Innes and Nickerson, 1975). The autonomic control of some visual functions is also affected, as described by Innes and Nickerson (1975): 'The atropinic drugs (atropine, scopolamine) block the responses of the sphincter muscle of the iris and the ciliary muscle of the lens to cholinergic stimulation. Thus they dilate the pupil (mydriasis) and paralyse accommodation (cycloplegia)...the lens is fixed for far vision, near objects are blurred'.

Mirakur (1978) reported dose-related changes in visual near-point and pupil diameter, following oral and intramuscular scopolamine. Herxheimer

(1958) similarly reported a dose-dependent lengthening of visual near-point following subcutaneous injections of scopolamine; there were, however, marked differences between subjects, with hypermetropes (i.e. individuals with long initial visual near-points) showing large increases in visual near-point, and myopes (i.e. individuals with short initial visual near-point values) showing weak and irregular changes.

Scopolamine is the most effective single drug for the prophylaxis and treatment of motion illness (Brand and Perry, 1966; Wood and Graybiel, 1972; Wood, 1979). Traditionally it has been administered either orally or parenterally, by intramuscular, intravenous, or subcutaneous injection. Recently, however, a transdermal drug delivery system for scopolamine has been developed (Chandrasekaran, 1983; Shaw, 1983). The transdermal system comprises a small patch containing a drug reservoir, a microporous membrane controlling the rate of drug release, and an adhesive surface which is applied to the skin. The drug is absorbed from the patch through the skin into the systemic circulation. Drug delivery from the patch remains at a fairly constant level for 72 hours (Shaw, 1983). The transdermal patch represents a practical advance over previous methods of drug administration.

For instance, oral dosing would need to be repeated every 6 hours for 3 days to provide a period of cover equivalent to that provided by the transdermal patch (Shaw, 1983).

The transdermal scopolamine patch has been demonstrated to provide a significant degree of protection against motion illness, both under laboratory conditions of controlled motion (Graybiel *et al.*, 1976, 1981, 1982; McCauley *et al.*, 1979), and at sea (Price *et al.*, 1981). Objective performance impairments with the scopolamine patch have, however, been reported on tests of sustained attention, and memory for new information (Parrott and Jones, 1985; Parrott, 1986); while significant increases in self-reported levels of dry mouth and drowsiness have also been noted (Parrott and Jones, 1985; Gordon *et al.*, 1986; Parrott, 1986). Subjective reports of blurred vision have generally not been noted following single scopolamine patches (Graybiel *et al.*, 1976, 1981, 1982; Hordinsky *et al.*, 1982; Price *et al.*, 1981; Gordon *et al.*, 1986), although visual changes have sometimes been found, particularly when objective visual assessment measures were employed (Larsen and Peitersen, 1983; Pyykko *et al.*, 1985; Parrott, 1986). Visual problems have, however, been reported more frequently following repeated applications of transdermal scopolamine. Homick *et al.* (1983) found 'increasingly severe' accommodation problems with one subject following repeated scopolamine patches, while 36 per cent of the remaining subjects reported blurred vision in this repeated patch study. Parrott and Jones (1985) reported an inability in focusing on written test material with several subjects following repeated scopolamine patches. Graybiel *et al.* (1982) also reported visual problems following a second patch, which had not been evident following the initial patch. Johnson *et al.* (1984), noted that passengers on a large cruise ship commonly presented at the sick bay with blurred vision and dilated pupils, although percentage occurrence rates, and the duration of patch application, were not systematically reported.

There are therefore consistent indications in the literature of visual problems with transdermal scopolamine, particularly following repeated patch applications. The present trial was undertaken to assess objective and subjective measures of visual functioning, following single and repeated applications of the transdermal scopolamine patch.

## MATERIALS AND METHODS

### *Subjects*

The subjects comprised 12 medically screened males (age range 18–27 years). All were informed volunteers, and were paid for participation. The trial was run in accordance with the Declaration of Helsinki.

### *Drug conditions*

Standard scopolamine patches, and placebo patches identical in appearance, were applied to the hairless skin behind the ear, following the procedure recommended by the patch manufacturers. Scopolamine and placebo patches were applied on alternative days for 24-hour periods. Placebo patches were also used during two initial training days. Four scopolamine patches were applied to each subject. Drug administration was varied between subjects, with some subjects on scopolamine and some on placebo, on any one day. Drug administration and testing were double-blind.

### *Assessment procedures*

In the morning of each trial day, 22–24 hours following the application of the previous patch, a battery of psychological performance tests, visual assessments, physiological measures, and a feeling state questionnaire, was presented. Following these tests the transdermal patch was removed and a new patch applied (note: no patches became accidentally dislodged during the trial).

### *Visual assessments*

Visual near-point was measured using the RAF near-point rule; the cursor on the rule was moved until the subject reported that it was just in focus (Price, 1978). Each eye was tested separately, by the psychophysical method of limits. The non-tested eye remained open, but was shielded behind grey card. The average of four measures was recorded. The presence/absence of blurred vision was indicated from the question on blurred vision in the self-report questionnaire. The blurred vision question was one of several, so that undue importance to a question on vision was not evident. (Note: contrast sensitivity functions were also assessed using the procedure described by Arden (1978). This visual measure was included

for exploratory reasons. The effects of scopolamine upon contrast sensitivity functions are not known to have been previously investigated. Arden (1978) suggested that contrast sensitivity functions were sometimes reduced without loss of visual acuity; the present trial allowed contrast sensitivity functions to be assessed under conditions where visual acuity was expected to be impaired. Contrast sensitivity function values remained basically unchanged throughout the trial, with no significant ANOVA effects due to any factor. The contrast sensitivity function measure will not be discussed further.) The performance test and questionnaire findings are being presented elsewhere; (note: transdermal scopolamine was associated with significant impairments in memory for new information, sustained attention, and self-ratings of alertness, while sleep was also affected).

*Data analysis*

Visual near-point values were analysed by split-plot analysis of variance (ANOVA), with repeated measures for drug (scopolamine, placebo) and patch number (1st, 2nd, 3rd, 4th), and non-repeated measures for subject group (subjects reporting blurred vision, subjects not reporting blurred vision).

*Further experimental conditions*

The subjects lived in a suite of environmentally controlled experimental rooms during the trial. Temperature was maintained at  $22 \pm 2^\circ\text{C}$ , and relative humidity at  $55 \pm 5$  per cent, throughout. Lighting remained constant, and spectacles, if used, were worn during all testing. Alcoholic or caffeine-containing beverages were not allowed during the trial, but decaffeinated coffee was freely available. Smoking was not allowed during testing.

**RESULTS**

The number of subjects reporting blurred vision increased following successive scopolamine patches (first patch,  $n = 0$ ; second patch,  $n = 1$ ; third patch,  $n = 4$ ; fourth patch,  $n = 6$ ;  $p < 0.01$ , Cochran Q test). Visual near-point values following each patch are presented in Figure 1. Group mean values for the six subjects reporting blurred vision are presented separately from the values

for the six subjects not reporting blurred vision (Figure 1). The initial (pre-drug) visual near-points were longer for subjects who reported blurred vision (mean = 16.3 cm), than for subjects who did not report blurred vision (mean = 11.1 cm). The subjects who developed blurred vision therefore tended to be hypermetropic (i.e. with long visual near-points), whereas the subjects who did not develop blurred vision tended to be myopic (i.e. with short visual near-points). Visual near-point values following successive scopolamine and placebo patches are also shown in Figure 1. Subjects reporting blurred vision demonstrated lengthened visual near-points with successive scopolamine patches (visual near-points following successive patches: first = 19.7 cm; second = 22.3 cm; third = 23.6 cm; fourth = 24.8 cm; Figure 1). In contrast, subjects who did not report blurred vision demonstrated basically unchanged visual near-points throughout (visual near-points following successive patches: first = 11.5 cm; second = 12.7 cm; third = 12.7 cm; fourth = 12.7 cm; Figure 1). These visual near-point differences were statistically confirmed in the analysis of variance results (Table 1). There were significant effects for subject group, drug condition, patch number, and subject group  $\times$  drug interaction. Two further aspects of these data should be noted. Firstly, the lengthening of the visual near-point preceded the reporting of blurred vision. Following the first scopolamine patch, although none of the subjects reported blurred vision, the average visual near-point value had lengthened (Figure 1). Secondly, during the intervening 24-hour periods on placebo, visual near-point values shortened

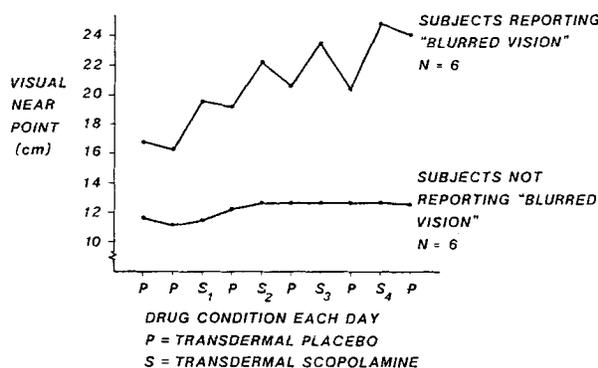


Figure 1. Visual near-point values following transdermal scopolamine and transdermal placebo patches

Table 1. Summary of visual near point ANOVA findings

Source of variation	d.f.	F	p
Subject group (vision blurred/not-blurred)	1,10	9.89	<0.05
Drug (scopolamine/placebo)	1,10	13.93	<0.01
Subject group × drug	1,10	10.92	<0.01
Patch number (1st, 2nd, 3rd, 4th)	3,30	9.57	<0.001
Patch number × subject group	3,30	2.84	<0.10
Drug × patch number	3,30	0.15	ns
Subject group × drug × patch number	3,30	0.28	ns

d.f. = degrees of freedom

F = variance ratio

p = two-tailed probability

slightly but they did not return to pre-drug values (Figure 1).

## DISCUSSION

Visual changes have been noted in many investigations of oral or parenteral scopolamine, with subjective complaints of blurred vision, and objective indications of reduced visual near-point, reduced accommodative power, and increased pupil diameter, each reported (Chinn, 1956; Elkin *et al.*, 1965; Innes and Nickerson, 1975). They have been shown to be dose-related (Herxheimer, 1958; Mirakur, 1978). These visual changes reflect reduced cholinergic neurotransmission in the autonomic fibres controlling the sphincter muscle of the iris, and the ciliary muscle holding the lens of the eye (Innes and Nickerson, 1975).

The effects of the transdermal scopolamine patch upon subjectively reported aspects of vision have been investigated in several trials. Following single patches, visual complaints have generally not been noted, as in the following investigations: Hordinsky *et al.* (1982) with nine subjects on the patch for 8 hours; Graybiel *et al.* (1976) with eight subjects on the patch for 24 hours; Graybiel *et al.* (1981) with eight subjects on the patch for ½ day; and Graybiel *et al.* (1982) with six subjects on their initial patch for 72 hours. Similarly, Gordon *et al.* (1986) noted identical rates of blurred vision following scopolamine and placebo, with 23 subjects on the patch for 19 hours. The results of the above trials are therefore in close agreement with the present findings, where none of the 12 subjects complained of blurred vision after 24

hours on their first scopolamine patch. Some investigations have, however, reported visual changes following single patches. Larsen and Pietersen (1983) noted significant increases in ratings of visual disturbance, with 14 subjects on the patch for 72 hours. Pyykko *et al.* (1985) measured visual near-points in 16 subjects, 12 hours after either transdermal placebo, one transdermal scopolamine patch, or two scopolamine patches applied simultaneously. Visual near-point values were lengthened significantly by two simultaneous scopolamine patches, while a non-significant increase was also evident following the single scopolamine patch. In a recently completed sea trial, Parrott (unpublished report) found a small but significant increase in visual near-point, with 28 subjects administered the patch for 24 hours, although subjective reports of blurred vision did not differ significantly between placebo and scopolamine. The increases in visual near-point following a single patch, noted by Pyykko *et al.* (1985) and Parrott (unpublished report) are therefore similar to the lengthening in visual near-point after the first scopolamine patch found in the present study (Figure 1). It may therefore be concluded that although subjective reports of visual problems have generally not been noted following single scopolamine patches (although they have occasionally occurred), when objective measures of visual functioning have been employed (e.g. visual near-point), then a lengthening of visual near-point has been consistently reported.

Blurred vision became increasingly frequent following successive scopolamine patches, so that by the fourth scopolamine patch half of the

subjects had complained of blurred vision. Previous investigations have similarly noted visual problems following repeated patches, which were not apparent following the first scopolamine patch. In an investigation of repeated patch applications, Homick *et al.* (1982) screened potential volunteer subjects for 'Adverse reactions to the transderm-scop system, which was applied for 24 hours before the main study....Evidence of significant side-effects, such as impaired vision or motor incoordination, disqualified candidate subjects.' Despite this initial screening procedure, visual problems became apparent as the trial progressed. Homick *et al.* (1982) noted: 'One female subject reported increasingly severe visual accommodation problems with each successive transderm-scop application and withdrew from the study.' With the remaining subjects, blurred vision was reported by 36 per cent of the group after 72 hours on the scopolamine patch, compared with 6 per cent of the group after 72 hours on transdermal placebo. Graybiel *et al.* (1982) reported no visual problems following the first scopolamine patch, but one of the six subjects reported blurred vision after 72 hours on the second scopolamine patch. Parrott and Jones (1985) reported that several subjects were unable to focus upon written performance test materials; all cases followed transdermal scopolamine and none followed transdermal placebo; 3 per cent of subjects on their first scopolamine patch were so affected, compared with 25 per cent of subjects on their second scopolamine patch. The present findings are therefore in close accord with the reports in the literature of visual problems developing with repeated applications of the scopolamine patch.

One possible reason for the increase in visual effects following successive patches is the time course of visual changes following scopolamine, since they seem to be both slow to develop and slow to dissipate, when compared with the time course of changes in other functions (e.g. heart rate, sweating). Mirakur (1978) noted maximal effects upon heart rate and sweat gland activity 1-3 hours following oral scopolamine. In contrast, visual near-point values were still decreasing 6 hours post-drug, and although data after 6 hours were not systematically collected, Mirakur (1978) noted: 'Reading was difficult for more than 16 hours following 1.0 mg intramuscular scopolamine.' Mirakur concluded that the most persistent effect of scopolamine was blurring of

vision. Ostfeld *et al.* (1958) compared mental (memory, self-rated feeling state), autonomic (heart rate, salivation) and visual (pupil diameter) changes following oral scopolamine; they concluded: 'The time course of mental effects generally paralleled those of the autonomic effects, however, the pupillary dilation outlasted all other effects.' Herxheimer (1958) investigated the time course of changes in different functions; he concluded that 'The peak effect on the iris and ciliary muscle always occurred later than the effect on heart rate and salivary secretion.' Visual changes with a single scopolamine patch (and with two patches applied simultaneously), have also been reported to increase with time on the patch. Homick *et al.* (1983) noted that 12 per cent of subjects reported blurred vision following 24 hours on the patch, while 36 per cent of subjects reported blurred vision following 72 hours on the patch. Larsen and Pietersen (1983) similarly noted increased ratings of visual disturbance the longer the time on each scopolamine patch. The effects of repeated administrations of oral scopolamine also display a different time course for visual compared with other functions. Glaser (1953) administered oral scopolamine (0.6 mg; t.d.s.) over 4 days. Most subjective side-effects became less frequent over successive days, e.g. drowsiness, giddiness, dry mouth; the only side-effect not fitting this pattern was blurred vision, which increased in frequency over the 4 days of the study. The increased visual changes following repeated scopolamine patches therefore probably represent a cumulative drug effect, with the effects of the first dose not dissipated by the time the next dose is given. This pattern is shown in the present visual near-point data (Figure 1). Following the first scopolamine patch the mean visual near-point was increased; this increase was still largely present 24 hours later following the next placebo patch. The visual near-point baseline for the second scopolamine patch was therefore comparatively lengthened. Further increases in baseline were also present for the third and fourth scopolamine patches (Figure 1). Two possible explanations for the prolonged time course of visual changes following scopolamine may be proposed. Herxheimer (1958) has suggested that the aqueous humour of the eye may be acting as a drug reservoir. Warburton (personal communication) has suggested that the blood/eye barrier may be slowing the passage of drug both into, and out from, the eye.

In the present study, hypermetropes were visually sensitive to the effects of scopolamine, whereas myopes showed no visual decrements (Figure 1). Herxheimer (1958) similarly noted a difference in response to scopolamine between myopes and hypermetropes: 'The paralysis of accommodation varied greatly between subjects. Two subjects who were myopes showed weak and irregular responses. The three subjects with hypermetropia gave consistently big responses.' In a recent sea trial, Parrott (unpublished) found severe blurred vision with one particular hypermetropic subject (pre-drug visual near-point = 22 cm), and not with the other subjects. The pre-existing accommodative power of the individual therefore represents an important factor in determining whether visual changes will occur following scopolamine administration. One possible explanation for the sensitivity of hypermetropes may be that their normal (pre-drug) accommodative power is at threshold levels, so that reduced ciliary muscle power (following anticholinergic drug administration), leads to reduced accommodation and lengthened visual near-point. In contrast, the ciliary muscle power of myopes may exceed normal requirements, so that some reduction in ciliary muscle capacity can occur without visual near-points being affected.

In overall conclusion, the visual changes following short periods on a single transdermal patch are generally slight, and although they are apparent when objective measures such as visual near-point are employed, subjective reports of blurred vision will not generally occur, except with the more sensitive subjects. Visual problems increase in frequency following repeated patch applications, due probably to the perseveration of visual effects from the previous patch. These visual effects occur with hypermetropes (i.e. subjects with long visual near-points), rather than myopes (i.e. subjects with short visual near-points). Hypermetropes should therefore be specifically warned of the visual problems which are likely to develop with transdermal scopolamine.

#### ACKNOWLEDGEMENTS

Acknowledgement is gratefully given to Professor G. Arden for the loan of contrast sensitivity test materials, Mr T. Beames for help with the data collection, Ciba-Geigy for the transdermal patches, and Boots Pure Drug Company for the decaffeinated coffee.

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