Scopolamine Bioavailability in Combined Oral and Transdermal Delivery

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Scopolamine is one of several potent drugs that are used as a prophylactic treatment against motion sickness. However, when given orally or intramuscularly, the drug has a relatively short half-life and may have considerable adverse effects. Transdermal scopolamine has been in use for more than 10 years, and relieves the signs and symptoms of motion sickness in 50 to 74% of the users (Graybiel et al., 1976; Price et al., 1981; Noy et al., 1984; Gordon et al., 1986; Attias et al., 1987; Parrott, 1989; Shupak et al., 1989). When the transdermal route is used, adverse effects are very limited, and the drug has no significant effects on performance (Gordon et al., 1986; Shupak et al., 1989; Gonen et al., 1998).

Transdermal therapeutic system scopolamine (TTS-S; Novartis, Basel, Switzerland) contains a reservoir of 1.5 mg of scopolamine released at a constant rate of 5 µg/h over a period of 72 h. The patch also contains a priming dose of 140 µg, which serves as a loading dose. The overall dose of scopolamine released over 72 h is assumed to be approximately 0.5 mg (Chandrasekaran, 1983; Clissold and Heel, 1985). The main disadvantage of transdermal delivery is that therapeutic plasma levels are obtained very slowly (6 to 8 h after application in the case of scopolamine) (Price et al., 1981; Chandrasekaran, 1983; Clissold and Heel, 1985). Thus, the use of TTS-S poses a problem when immediate treatment is required for seasickness, as in the case of naval crews who are often required to sail at short notice and in any sea conditions. In a previous study, in which we investigated the rate of scopolamine absorption through the skin, we found that therapeutic levels of scopolamine were achieved only 5 to 6 h after patch application (Doweck et al., 1996). In a further study, we evaluated the effect of sonophoresis on transdermal scopolamine absorption (Doweck et al., 1996). This technique was shown to be safe, and enhanced the rate of absorption to reach therapeutic levels at 1 to 3 h post-application, but only in 33% of the subjects.

Scopolamine tablets have been in use since the 1960s, and have been found effective in the prevention of seasickness (Reason and Brand, 1975; Pingree and Pethybridge, 1994). In repeated high doses, the tablets may have adverse effects (mainly dryness of the mouth, drowsiness, and blurred vi-
sion), which may be minimized or prevented by taking a single small dose (Wood et al., 1984; Schmedtje et al., 1988; Kennedy et al., 1990; Pingree and Pethybridge, 1994; Regan and Ramsey, 1996). Kennedy et al. (1990) reviewed a number of studies investigating the detrimental effects of various doses of oral scopolamine on performance and the complaints of adverse effects. They concluded that a single dose below 0.15 mg had no effect on performance, and up to 0.5 mg had only a slight effect on self-reported performance decrements on complex tasks. Doses above 1 mg are likely to affect performance, whereas the effects of doses between 0.5 mg and 1 mg are still in dispute.

Plasma levels of scopolamine were monitored in subjects who took either 0.6-mg scopolamine tablets (swallowed or sucked) or capsules (Golding et al., 1991). The absorption in all these forms was similar: peak plasma scopolamine levels of approximately 350 pg/ml were measured about 50 min postingestion, and the average clearance half-time was 170 min. Mild adverse effects were reported by subjects in all three groups; these were not correlated with the measured plasma levels.

The purpose of the present study was to evaluate the bioavailability and safety of a combination of transdermal and oral scopolamine, particularly during the first hours post-treatment.

Materials and Methods

Subjects. The study was conducted on 25 healthy, male naval crew members, aged 18 to 20 years, at their naval base. All subjects were volunteers, with a normal physical examination. Informed consent was obtained from all participants before commencing the study, and the study protocol was approved by the Medical Corps Helsinki Committee. Subjects were drug free for at least 72 h before the study. They were required to refrain from strenuous physical activity during the study.

Randomization. The study was conducted using a double blind, parallel group design. Subjects were divided randomly into three groups: group 1, nine subjects, in whom a TTS-S patch was applied to the postauricular region and a tablet of 0.3 mg of scopolamine was administered orally; group 2, eight subjects, in whom a TTS-S patch was applied to the postauricular region and a tablet of 0.3 mg of scopolamine was administered orally; and group 3, eight subjects, in whom a TTS-S patch was applied to the postauricular region and a placebo tablet was administered orally.

Plasma Scopolamine Levels. Blood samples, 10 ml each, were collected with heparin from each subject before treatment and 0.5, 1, 1.5, 2.5, 3.5, 6, 8, and 22 h after treatment. Each plasma sample was separated using a cooled centrifuge (4°C) at 1000 g for 10 min. Scopolamine levels were analyzed in a blinded fashion using the radio-receptor assay described by Cintron and Chen (1987).

Cardiovascular Changes and Adverse Effects. Heart rate and blood pressure were monitored in each subject before treatment and before each blood sampling. Adverse effects were evaluated using a self-assessment questionnaire completed by the subjects at 0, 1, 6, and 22 h post-treatment. These included dry mouth, drowsiness, blurred vision, headache, urinary disturbances, palpitations, shortness of breath, depression, restlessness, difficulties in concentrating, and physical and mental fatigue. Accommodation distance was measured at 0, 1, and 6 h by a senior ophthalmologist using Snellen’s chart. A battery of computerized performance tests was used, containing tests for working memory, visual perception, concentration, divided attention, and vigilance (Kay, 1995), and decision and reaction time (Schuhfried, 1992). Performance tests were conducted just before treatment and at 1 and 6 h post-treatment.

Statistics. Plasma scopolamine levels, performance test results, physiological measures, and reported adverse effects were compared between groups for each time interval using one-way ANOVA. Significant differences were examined by post hoc (Tukey) tests. Fisher’s exact test was used to compare differences in the proportion of subjects reaching therapeutic levels of the drug between the groups. The statistical program was SPSS for Windows (SPSS, Inc., Chicago, IL). Two-tailed P < 0.05 was considered statistically significant.

Results

Scopolamine levels in all three groups, up to 22 h after drug administration, are presented in Fig. 1. Significant differences were found between the three groups at specific time intervals: between groups 1 and 3 at 0.5, 1, 1.5, and 2.5 h; between groups 2 and 3 at 1 and 1.5 h; and between groups 1 and 2 at 1 and 1.5 h. Thereafter, plasma levels of scopolamine did not differ significantly between the groups.

Plasma levels >50 pg/ml are generally accepted as affording prophylactic protection against motion sickness (Norfleet et al., 1992; Dowell et al., 1995, 1996; La Rovere and De Ferrari, 1995). In the present study, such levels were monitored during the first 2.5 h in all the subjects of group 1 and in seven subjects (88%) of group 2, compared with two subjects only (25%) of group 3 (P < 0.05, Fisher’s exact test) (Fig. 2). As shown in Fig. 2, there were no significant differences between groups 1 and 2 for the number of subjects who achieved protective levels of the drug throughout the course of the study.

Eight hours after treatment, protective levels of scopolamine (>50 pg/ml) were monitored in 89, 75, and 88% of the subjects in groups 1, 2, and 3, respectively. Thus, 11 to 25% of the subjects failed to achieve protective levels of the drug even 8 h post-treatment, a finding which is in accord with two previous studies conducted in our laboratory (Dowell et al., 1995, 1996).

Heart rate, blood pressure, accommodation, and subjective complaints of adverse effects did not differ significantly between the groups. No subject was required to terminate the experiment due to adverse effects. When the results of the computerized performance tests were compared, no intra- or intergroup differences were observed.

Fig. 1. Scopolamine levels (±S.E.M.) in plasma up to 22 h after treatment for the three experimental groups. *P < 0.004, when group 1 is compared with group 3. #P < 0.04, when group 2 is compared with groups 1 and 3.
Combined Oral and Transdermal Scopolamine Delivery

Discussion

The present study evaluated the effects of combined transdermal and oral scopolamine administration on the pharmacokinetics of scopolamine in plasma, on cognitive and psychomotor performance, and on the incidence of adverse effects. Plasma levels of scopolamine high enough to prevent seasickness were obtained 0.5 to 2.5 h after the oral administration of 0.3 or 0.6 mg of scopolamine as a supplement to the TTS-S patch. The results of the present study are in accord with those of previous studies, which conducted separate investigations of the absorption of scopolamine from the TTS-S patch (Doweck et al., 1995, 1996) and from scopolamine tablets (Golding et al., 1991).

One of the nine subjects in group 1, two of the eight in group 2, and one of the eight in group 3 did not reach the required levels of scopolamine in plasma even 8 h after treatment. These results are also in accord with those of our previous studies (Doweck et al., 1995, 1996), which may explain at least some of the cases in which TTS-S failed to prevent seasickness (Clissold and Heel, 1985).

No difference was observed in either the monitored adverse effects or the self-reported complaints between the groups, nor were differences found between the results of the performance tests. It appears that transdermal and oral scopolamine, which were found to be safe when given separately (Wood et al., 1984; Schmedtje et al., 1988; Kennedy et al., 1990; Doweck et al., 1995, 1996; Gonen et al., 1998), are also safe after combined administration. In addition, the combination was extremely efficient in achieving therapeutic levels much faster than the patch alone, and in maintaining them for a prolonged period of time.

In light of these results, we intend using the combination of a TTS-S patch and a 0.3-mg tablet of scopolamine (to use the minimal effective dose of the drug) to prevent seasickness among our crew members. If there is insufficient clinical response, we shall use the higher dose of 0.6 mg. It is concluded that the combination of transdermal and oral scopolamine (0.3 or 0.6 mg) is probably optimal for both fast and prolonged prophylactic protection against motion sickness, with no significant adverse effects.

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