Prevention of peripheral side-effects of transdermal hyoscine by adjunctive therapy with low dosage of pyridostigmine

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1 The value of low dosage of pyridostigmine (30 mg three times daily) in preventing peripheral anti-muscarinic side effects of a transdermal controlled-release formulation of hyoscine, was tested in a double-blind placebo-controlled study, involving 47 healthy subjects.

2 Salivary excretion was repeatedly measured during 48 h of combined therapy of two transdermal hyoscine patches with pyridostigmine and 14 h after its cessation. Blood acetylcholinesterase activity was also measured, serving as an index of pyridostigmine bioavailability.

3 The adjunctive therapy with pyridostigmine was highly effective in preventing the substantial impairment in salivary flow caused by the transdermal formulation. An associated 23% inhibition of blood acetylcholinesterase activity was observed.

4 Small doses of pyridostigmine may therefore have a role in increasing the tolerability of transdermal hyoscine therapy. In some patients this drug combination might also allow some increment of the hyoscine dose.

Keywords motion-sickness hyoscine pyridostigmine transdermal side-effects

Introduction

Motion sickness presents a constant challenge for pharmacological management. Its prevalence is high, it causes substantial disability (Daunton, 1983; Wood, 1979), and to date, the optimal drug regimen that will prevent the evolvement of this syndrome without causing disturbing side-effects, has not yet been found.

One of the major advances in this field in recent years was the development of a transdermal controlled-release preparation of hyoscine, a competitive blocker of the muscarinic cholinergic receptors. This formulation was developed to utilize the potential of hyoscine as one of the most effective drugs for motion sickness, while constantly maintaining drug levels within its relatively small therapeutic window (Clissold & Heel, 1985).

However, accumulated experience with the transcutaneous formulation shows, that along with its remarkable performance (40%–80% protection against motion sickness), it cannot fully address the problem of hyoscine side effects (Babin et al., 1984; Clissold & Heel, 1985; Homick et al., 1983). Some of these effects, (e.g. hypo-salivation, impairment of near vision, drowsiness) are caused by very low drug levels (Shaw & Urquhart, 1980), and thus cannot be avoided unless the efficacy of the drug regimen is abolished.

A second step, that might be useful as the approach of pharmacokinetic modulation has been exhausted, is to combine transdermal hyoscine therapy with treatment with a second drug. That drug should selectively suppress hyoscine adverse-effects, while preserving its anti-motion-sickness activity.

It is generally agreed, that the effect of hyoscine in motion sickness is due to its activity within the central nervous system (CNS) (Stott et al., 1989; Watt, 1983; Wood, 1979). As some of the most prevalent side effects of hyoscine are due to its peripheral anti-muscarinic activity, we suggest pyridostigmine, a peripherally-acting acetylcholine-esterase inhibitor as the adjunctive drug to suppress them.

Pyridostigmine is very widely used (in doses of up to 300–600 mg day−1) for myasthenia gravis. As a quarternary amine its penetration through the blood-brain
barrier is low, and as was recently demonstrated in several studies (performed in the context of protective treatment against organophosphate poisoning), oral low dosage of 30 mg three times daily is not associated with any significant side effects in healthy subjects (Borland, 1985; Gall, 1981; Graham et al., 1984; Gilks et al., 1991).

We therefore designed the double-blind placebo controlled study, aimed to test the value of this low dosage of pyridostigmine (30 mg three times daily) in preventing the peripheral adverse effects of transdermal hyoscine.

As impairment of salivation is the most frequent side effect reported during transdermal hyoscine therapy (experienced by over two thirds of patients) (Clissold & Heel, 1985), it was chosen as the pharmacodynamic parameter through which drug interaction was to be characterised.

A challenge of a double dose of transdermal hyoscine patches was applied for 48 h. Salivation was repeatedly measured during that period, as well as 14 h after cessation of therapy. Measurements of blood acetylcholinesterase activity were also performed, serving as an index of pyridostigmine bioavailability.

Methods

Subjects

Forty-seven volunteers, age 18–21 years, were enrolled in the study. Inclusion criterion was normal medical status as assessed by medical history, physical examination, ECG, routine blood analysis, and normal blood acetylcholinesterase (AChE) activity. Informed consent was obtained from all subjects, and the study protocol was approved by the local Helsinki committee. The subjects were assigned to three treatment groups, matched for salivary flow rate and body surface area, and were treated as follows:

1. Two transdermal hyoscine patches (Scopoderm TTS®), and tablets of pyridostigmine-bromide (the S₂P₁ group, n = 16).
2. Two transdermal hyoscine patches, and placebo tablets (the S₂P₀ group, n = 15).
3. Two placebo patches, and placebo tablets (the S₀P₀ group, n = 16).

Drugs

1. Tablets pyridostigmine-bromide 30 mg (Duphar, Netherlands).
2. Transdermal hyoscine patches (Scopaderm TTS Ciba-Geigy, Switzerland).
3. Placebo tablets, identical to the pyridostigmine tablets.
4. Placebo patches, identical to the transdermal patches.

Previous analysis of drug samples confirmed the content of the patches and tablets.

Each subject was treated with two patches, applied bilaterally to a clean and healthy area of the post-auricular skin, for 48 h. Tablets were taken every 8 h. Aiming at steady-state blood concentrations of both drugs during measurements, pyridostigmine and transdermal hyoscine treatments were initiated 27 and 14 h, respectively, before the first measurement of salivation.

Measurement of salivary flow

Salivation was measured by determination (by analytical scales) of the increment of weight of two dental cotton-wool rolls (waterrolls) after 6 min in the patient’s mouth (under the tongue, one at each side of the frenulum). This method was chosen for its being quick, accurate with relatively minor subjective influence on the results.

Several training sessions were held to acquaint the subjects with the measurement technique. Salivation was measured twice a day (morning and afternoon), four times before drug therapy (baseline), at 14, 21.5, 38 and 45.5 h of transdermal hyoscine therapy, and 14 h after the removal of the patches (Table 1).

Measurements were performed by the same examiners, at constant hours, 3.75 h after the ingestion of a standard meal, 1 h after drinking 500 ml water. Daily schedule and physical activity were kept constant for all subjects during the study. No smoking was allowed. Air temperature and humidity were continuously monitored, and no significant inter-day variations were observed.

Blood acetylcholinesterase (AChE) activity

Whole — blood AChE activity was measured by the radiometric method described by Johnson & Russel (1975). Blood samples were obtained by venipuncture, and stored in heparin at −20 °C. Analysis was performed within 3 h. According to our previous experience, no significant in vitro decarbamylation is expected under these conditions. Intra-day and inter-day variabilities of the assay were 3.5% and 6.5%, respectively. AChE activity was measured before drug therapy (baseline), and three times during therapy, 2.5 h after the morning pyridostigmine dose (Table 1).

Table 1  Study schedule

<table>
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<th>Ts</th>
<th>Tp</th>
<th>Tp₀</th>
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<td>13.5 *</td>
<td>2.5</td>
</tr>
<tr>
<td>Salivation</td>
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<td>10.00</td>
<td>14 *</td>
<td>3</td>
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<td>21.5 *</td>
<td>2.5</td>
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<td>37.5 *</td>
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<tr>
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<td>(3)</td>
<td>10.00</td>
<td>38 *</td>
<td>3</td>
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<td>13.5 **</td>
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<tr>
<td>Salivation</td>
<td>(5)</td>
<td>10.00</td>
<td>14 **</td>
<td>19</td>
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</table>

Ts = Transdermal hyoscine therapy: (* time (h) from patch application, (**) time (h) after removal of the patches. Tp = Time (h) from the last pyridostigmine dose. Tp₀ = Time (h) from the beginning of pyridostigmine treatment.
Data analysis

Study groups were compared by the average change from baseline values. Three-way analysis of variance [drug therapy and time as constant factors, and the subject (within the group) as variable], and the Duncan method of multiple comparisons were used to assess statistical significance.

Results

Blood AChE activity

Baseline AChE activity was 6.0 ± 0.85 units (mean ± s.d. 1 unit of activity = decomposition of 1 μmol of acetylcholine in 1 ml whole blood in 1 min). The group treated with pyridostigmine (S₂P₁) showed an average 23% inhibition of blood AChE activity during drug therapy, which was not observed in the groups treated with placebo tablets (P < 0.001, Figure 1). There was no difference in enzymatic activity between the first and second days of treatment, confirming steady-state blood levels during the measurements of salivary flow. A significant (P < 0.05) 7% average AChE inhibition was still observed in the S₂P₁ group, 18.5 h after the last pyridostigmine dose.

Salivation (Figure 2)

Baseline salivary flow rate was 0.633 g min⁻¹ (mean ± s.d.) The group treated with two transdermal hyosynine patches (S₂P₀) showed an average reduction of 48% in salivation during the 48 h of drug therapy, significantly (P < 0.01) different from the 24% and 13% reduction observed in the S₂P₁ and S₀P₀ groups, respectively.

The hyposalivation in the S₂P₀ subjects was observed from the first sessions (14 h after application of the patches), and was maintained throughout therapy, with a tendency to be more accentuated in the morning (43% vs 27% in the afternoon).

Salivation in the subjects treated with transdermal hyoscine + pyridostigmine (S₂P₁) did not significantly differ from that of the placebo-treated group (S₀P₀).

No drug effect on salivation was detected 14 h after the removal of the transdermal patches (19 h after the last pyridostigmine dose).

Discussion

Severe conditions of movement, especially rapid changes in angular and linear acceleration, will induce motion sickness in almost any subject. As estimated by Wood (1979), two thirds of the population share a moderate to high tendency to develop this syndrome. These facts, along with the proved efficacy of transdermal hyoscine in motion sickness, call for measures that will increase the tolerability of the transdermal formulation.

The present study suggests, that adjunctive treatment with low dosage of pyridostigmine is beneficial in preventing the peripheral side-effects of transdermal hyoscine. Its main finding is that combined treatment of the transcutaneous formulation with 30 mg three times daily of pyridostigmine is not associated with the substantial decrease in salivary excretion, that is otherwise encountered during therapy with the hyoscine patches. This finding is emphasized by the fact, that a dose of two transdermal patches (twice the usual recommended dose) was tested.

The pyridostimine-induced blood AChE inhibition observed in the study was about 23%, values that are in accordance with previous reports, that also confirm, that at these drug dosage and enzymatic inhibition levels no significant side-effects should be expected in healthy subjects (Borland, 1985; Gall, 1981; Graham et al., 1984; Glikson et al., 1991).

The assumption that pyridostigmine will not impair the efficacy of hyoscine is based on the generally accepted concept, that the evolvement of motion sickness is mediated through neural pathways within the central nervous system (CNS), where integration of sensory information about the motion of the body in space takes place. Motion sickness occurs when these pathways face overwhelming and conflicting sensory input through the visual, vestibular and kinaesthetic sources (Daunton, 1983; Watt et al., 1983). Several
lines of evidence support this concept (which, however, has to be further tested):
1. There is a direct correlation between the anti-motion-sickness activity of drugs and their CNS action (Stott et al., 1989).
2. It has been shown, that the symptom-complex of motion sickness can be produced by physostigmine, a centrally acting cholinesterase inhibitor. However, this could not be achieved by peripheral AChE inhibitor (neostigmine) (Davis & Davis, 1980; Janowsky, 1984).

Thus, pyridostigmine is not expected to interfere with the CNS mediated, anti-motion sickness activity of hyoscine.

In conclusion, this study presents pyridostigmine as a new and effective tool for the physician who strives to construct the optimal motion sickness prophylactic regimen for the individual patient. Low and adverse-effect-free dosage of the drug can suppress the peripheral anti-cholinergic effects of transdermal hyoscine and increase the convenience of therapy. In some patients, in whom these side effects predominate, this drug combination might even allow some increment in the transdermal hyoscine dose, a measure that has been proved (Pyykko et al., 1985; Larsen & Peitersen, 1983) to increase its anti-motion-sickness activity.

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References


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