Assessment of the anticholinergic effect of the new antihistamine mizolastine in healthy subjects

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- 1 Twelve healthy subjects were enrolled in a double-blind placebo controlled cross-over study in order to assess the possible anticholinergic effects of four doses of a new antihistamine compound, mizolastine, compared with hyoscine butylbromide (HBB) used as a reference anticholinergic drug.
- 2 Although mizolastine, a potent and selective H₁-receptor blocker has no affinity for muscarinic receptors and does not antagonize the effects of carbachol in rodents, a study was initiated to investigate its effects on various effectors possessing muscarinic receptors (eye, heart, sweat gland, salivary gland).
- 3 HBB (40 mg, s.c.) impaired accommodation, decreased salivary flow and inhibited cardiac sinus arrhythmia. Pupil diameter and maximum constriction speed, carbachol-induced skin sweating and Valsalva ratio were unaffected.
- 4 Mizolastine (5, 10, 20, 40 mg p.o.) did not affect any parameter at any time point, demonstrating a lack of anticholinergic effect.

Keywords antihistamine mizolastine anticholinergic hyoscine butylbromide
autonomic nervous system salivation pupil-size

Introduction

While the first generation promethazine-related, H₁-receptor blockers possess anticholinergic activity and sedative effects, the second generation of specific H₁-receptor antihistamines (e.g. terfenadine (Vargas *et al.*, 1989)) show a better tolerability with less effects on CNS function and are devoid of anticholinergic effects.

Mizolastine is a new benzimidazole derivative which binds with a nanomolar affinity to the H₁-receptor and inhibits mast-cell degranulation *in vivo* and *in vitro*. In healthy subjects mizolastine inhibits histamine-induced wheal and flare at a dose of 5 mg or more (Rosenzweig *et al.*, 1990). In clinical trials in allergic rhinitis, mizolastine was clinically effective at a dose of 10 mg daily.

Preclinical data suggest a lack of anticholinergic effect of mizolastine since it is devoid of affinity for muscarinic receptors, and does not antagonize carbachol-induced intestinal motilities in mice (Arbilla *et al.*, 1989).

In order to confirm preclinical data, the potential peripheral anticholinergic activity of mizolastine was investigated in a single dose, placebo controlled, cross-over study. A reference anticholinergic drug hyoscine butylbromide (Grainger & Smith, 1983; Herxheimer & De Groot, 1977; Herxheimer & Haefely, 1966), was selected as a positive control to assess peripheral anti-

cholinergic activity since its polar structure does not allow the drug readily to cross the blood to brain barrier.

Methods

Twelve healthy young male volunteers were enrolled in this study (mean age ($\pm$ s.e. mean) 24.7 ± 1.2 years and mean weight 69.7 ± 1.8 kg).

Subjects were considered as healthy following a normal physical examination, laboratory tests and ECG. Concomitant medication, alcohol and caffeine-containing drinks and smoking were prohibited during, and for the 12 h preceding, each experimental day. Their written informed consent was obtained and the protocol was approved by an Ethics Committee.

Experimental design

The study was performed in double-blind conditions according to a cross-over design. Each subject received six treatments (placebo, hyosine butylbromide and four doses of mizolastine), according to an unbalanced latin

square design with a 1 week wash out interval.

Test sessions took place before drug administration and then 30 min, 1, 2, 4, 8 and 24 h post dosing. Each test session lasted 30 min.

Drugs

The six treatments (placebo, mizolastine 5, 10, 20 and 40 mg, hyoscine butylbromide 40 mg) were administered using a double-placebo technique.

On each session subjects were administered a capsule containing mizolastine or its placebo, simultaneously with a subcutaneous injection of hyoscine butylbromide or saline in a volume of 2 ml.

Tests and procedures

Cardiovascular parameters Heart rate was measured by ECG (mean of six subsequent heart beats) after 30 min of rest in a supine position.

Respiratory sinus arrhythmia (RSA) The difference between the mean maximum rate during expiration and the mean minimum rate during inspiration was used as a measure of respiratory sinus arrhythmia (Freyschuss & Nelcher, 1975).

Valsalva manoeuvre After baseline training, the subject was instructed to blow into a mouthpiece hard enough to maintain the column of a mercury manometer at 40 mm Hg for 15 s, then to release and breathe at will. Heart rate (ECG) was recorded throughout the Valsalva manoeuvre and for 30 s afterwards. Measurements of R-R were the average of at least two breaths, the minimum R-R interval towards the end of blowing and the maximum R-R interval after release (Levin, 1966).

Salivary flow This was measured by using three dental rolls placed in the inferior gingival groove for 2 min. Salivary secretion was taken as the mean weight differences of three measurements.

Pupil diameter and pupillary response to light This was examined by infrared digital videopupillography (PupilscanTM PC, Fairville Medical Optics, Amersham, UK), as described by Millson *et al.* (1988). During the measurement, subjects were requested to focus on a target located at 3 m from the other eye, in order to avoid accommodation and subsequent changes in pupil size.

Near point of vision A meter rule was held on the bridge of the nose along the line of forward vision. A printed card was held on one edge of the rule and moved slowly toward the subject until he judged that the type was no longer sharply in focus. This point was considered as the near point of vision (expressed in cm). Measurements were made separately for both eyes.

Sweat gland activity Carbachol induced sweating was measured using the sweat spot test technique (Szabadi *et al.*, 1988).

Sweat gland activity was assessed on the skin of the back of subjects by the means of a quick-drying opaque plastic paint.

At each assessment four concentrations of carbachol 0, 10, 50 and 500 μM were injected intradermally in a volume of 50 μl . The skin was then immediately painted with a suspension of colloidal graphite (4.5 g) and polyvinyl Formal (4 g), di-*n*-butyl phthalate (1 ml) in 1,2 dichloroethane (to 100 ml). Two minutes later, the paint was removed with a Sellotape[®] and mounted on a 35 mm slide holder. Active glands appeared as holes which were counted by two independent raters while the slide was projected.

Self-assessments Self-assessment were done on the three main factors (vigilance, satisfaction and relaxation) yielded from 16 visual analogue scales (Bond & Lader, 1974).

Statistical analysis

All parameters except carbachol-induced sweating were compared using an analysis of variance testing treatment or subject effect with repeated measurements over time. The concentration of carbachol (0, 10, 50 and 500 μM) was added as another ANOVA factor for the assessment of carbachol induced sweating. Homogeneity of groups was tested at baseline in order to eliminate a carry-over effect. When a significant treatment-time interaction was observed, pairwise comparisons with placebo were done time by time, in order to determine the first active dose.

Results

No differences between treatments were evidenced at baseline on any parameter, indicating no carry-over effect.

Cardiovascular parameters

Hyoscine butylbromide significantly increased heart rate ($P < 0.05$) and decreased respiratory sinus arrhythmia ($P < 0.05$) without affecting Valsalva ratio. Mizolastine was inactive on these tests.

Salivary flow

The salivary flow was significantly decreased ($P < 0.05$) by hyoscine butylbromide 30 min after dosing (Figure 1) but remained unaffected by all doses of mizolastine when compared with placebo.

Ocular parameters

None of the pupillary parameters measured before or after light stimulation was modified by any of the treatments. Near point was significantly increased ($P < 0.05$) 30 min after hyoscine butylbromide but unaffected by mizolastine (Figure 2).

Sweat gland activity

The response curves were not shifted by any of the treatments, inclusive of the reference anticholinergic hyoscine butylbromide.

Figure 1 Salivary flow following mizolastine (5 mg: ■, 10 mg: △, 20 mg: ▲, 40 mg: □), hyoscine butylbromide (40 mg: ●) or placebo (○); * indicates differences ($P < 0.05$) from placebo in pairwise comparisons.

Figure 2 Near point of vision following mizolastine (5 mg: ■, 10 mg: △, 20 mg: ▲, 40 mg: □), hyoscine butylbromide (40 mg: ●) or placebo (○); * indicates differences ($P < 0.05$) from placebo in pairwise comparisons.

Self-assessment None of the VAS was affected significantly by the treatments but a trend to an increase ($P = 0.09$) in the sedation factor was observed after 40 mg mizolastine.

Discussion

The reference drug, hyoscine butylbromide (40 mg s.c.), which is considered as a peripheral muscarinic blocker (Grainger & Smith, 1983), since its ionized polar structure does not allow an easy crossing of the blood-to-brain barrier, produced some of the expected effects of an anticholinergic drug. Heart rate and sinus arrhythmia

were affected by hyoscine butylbromide as well as salivary flow and accommodation. No effect of mizolastine could be detected on these parameters. Only mild subjective sedative effects were seen after the highest dose (40 mg) of mizolastine, confirming previous results obtained at 45 mg but not at 15 mg (Danjou *et al.* 1990).

In the eye, an intense effect (two-fold increase of near point) was seen on the accommodation after hyoscine butylbromide with a time course similar to other tissues. The time course of mild changes in pupil diameter, described by Brownlee *et al.* (1965a,b), was different from that of accommodation impairment (Mehfeld & Bleichert, 1986).

Sweat spot test was not affected by a high dose of hyoscine butylbromide under carbachol stimulation while amitriptyline 75 mg did antagonize it (Theophilopoulos *et al.*, 1988). Amitriptyline possesses α_1 -adrenoceptor and M_1 -receptor blocking activity and the stimulation of both these receptors activate sweat glands (Szabadi *et al.*, 1980). Indeed the effect of amitriptyline is probably partly due to its adrenolytic properties (Longmore *et al.*, 1987), as it inhibits phenylephrine-induced sweating. It is quite possible that although this method is specific of a type of receptor, depending on the agonist used, its sensitivity might be insufficient when an adrenergic tone persists.

Other factors which could influence the response to carbachol such as anxiety, gender (Maple *et al.*, 1982), room temperature and humidity, were controlled and could not therefore explain the lack of sensitivity.

Dissociations between results observed with the various methods might be related to the fact that organs have several effectors possibly with different affinity or organ diffusion characteristics. For instance mianserin, amitriptyline, imipramine and maprotiline induce dissociated effects on salivary flow and finger sweating (Carlini *et al.*, 1985), related to anticholinergic or adrenolytic effects.

As with other H_1 -receptor blockers, such as cetirizine, loratadine, astemizole or terfenadine (Brion *et al.*, 1988; Vargas *et al.*, 1989), mizolastine has no anticholinergic properties, in both *in vitro* and clinical pharmacology studies. This might be clinically relevant in a population prone to a bad tolerance to anticholinergic drugs.

Mizolastine in these cases provides a safe solution, as at four times the therapeutic dosage (10 mg once daily) no effect related to blockade of muscarinic receptors was found.

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