Br. J. clin. Pharmac. (1988), **25**, 27–32

Evaluation of the antimuscarinic activity of atropine, terfenadine and mequitazine in healthy volunteers

N. BRION[1], D. BEAUMONT[2] & C. ADVENIER[1]
[1]Laboratoire de Pharmacologie, Centre Hospitalier de Versailles, 177, rue de Versailles, F–78150 Le Chesnay, France and [2]Laboratoires Merrell, 45–49, rue de Villiers, F–92203 Neuilly sur Seine Cedex, France.

1 The anticholinergic effects of atropine and two antihistamines (terfenadine and mequitazine) were investigated *vs* placebo in a double-blind study.
2 Salivary secretion, basal pupil diameter, pilocarpine (0.25%) induced miosis and heart rate were determined in eight healthy volunteers, seven male and one female, aged between 23 and 35 years. Each volunteer received all four separate courses of treatment: i.e. terfenadine 60 mg or mequitazine 5 mg twice daily for 3 days, and one single dose on the day of the trial; for the placebo or atropine courses they received the placebo twice daily during 3 days and, on the morning of test day, either the placebo again or atropine 1 mg. Pupillary diameter was measured under standardized conditions using a pupil gauge (Smith and Nephew Pharmaceuticals Ltd).
3 Atropine significantly reduced salivary output (-2.25 ± 0.36 ml from control values of 4.17 ± 0.42 ml, $P<0.001$) and heart rate (-9.7 ± 3.7 beats min^{-1} from 77.5 ± 2.7, $P<0.05$). These maximal effects were observed 3 h after atropine dosing for salivary secretion and 1 h for heart rate. Atropine did not affect basal pupil diameter or pilocarpine-induced miosis.
4 Mequitazine and terfenadine did not affect salivary flow, heart rate or pilocarpine-induced miosis.
5 Terfenadine and mequitazine had no anticholinergic effect in these tests involving a limited number of subjects.

Keywords atropine antihistamines salivary secretion ocular reactivity

Introduction

The prescription of drugs which, beside their desired pharmacological properties, possess undesired anticholinergic activity is limited on account of their side-effects (dry mouth, visual disorders, constipation, retention of urine), interactions with other drugs and contra-indications (e.g. prostatism, glaucoma) (Bowman & Rand, 1980). Such drugs have also been held responsible for disorders of memory (Iversen, 1986). Several antihistaminic agents exhibit anticholinergic activity.

The purpose of this study in healthy volunteers was to evaluate comparatively the anticholinergic effects of atropine and of two antihistamines: one, mequitazine, with anticholinergic activity (Dry *et al.*, 1980; Demaubeuge *et al.*, 1982; Richards *et al.*, 1984; Beaumont *et al.*, 1986), the other, terfenadine, without this activity (Kulshrestha *et al.*, 1978; Patel, 1987), by measuring salivary secretion, heart rate, basal pupil diameter and effect on pilocarpine-induced miosis.

Correspondence: Dr N. Brion, Laboratoire de Pharmacologie, Centre Hospitalier de Versailles, 177, rue de Versailles, F–78150 Le Chesnay, France.

Methods

Subjects

Eight healthy subjects (seven male, one female), aged from 23 to 35 years (mean 25.5 ± 2.8 years) volunteered and were found eligible to enter the study. All had blue or green eyes, the pupil of which is known to be more reactive than that of brown eyes (File & Patton, 1980; Patil, 1984). None of them was wearing contact lenses, and all were free from ophthalmic or systemic pathology likely to interfere with the tests.

During the week preceding the study and between treatment courses (see below) the subjects abstained from taking drugs, notably antihistamines or drugs with anticholinergic activity. During the test day, they were not allowed to smoke and to drink coffee, tea, coca-cola or alcohol.

All subjects had been acquainted with the nature and purpose of the study and had given their informed consent.

Procedure

The study was conducted in a double-blind manner, with placebo capsules and tablets identical in appearance with the corresponding preparations of active substances, i.e. mequitazine and terfenadine respectively. Each subject took four successive courses of drug and/or placebo in an order established by the latin square method. The courses consisted of:

Terfenadine 60 mg tablets: one tablet morning and evening on 3 consecutive days, and one tablet in the morning of test day. A placebo capsule was administered concomitantly with each dose.

Mequitazine 5 mg capsules: one capsule morning and evening on 3 consecutive days, and one capsule in the morning of test day. A placebo tablet was administered concomitantly with each dose.

Placebo: one placebo tablet and one placebo capsule morning and evening on 3 consecutive days and in the morning of test day.

Atropine: one placebo capsule and placebo tablet morning and evening on 3 consecutive days, and one 1 mg capsule of atropine in the morning of test day. Contrary to terfenadine and mequitazine, atropine was administered as a single dose for ethical reasons and also because of the undesirable effects observed (dry mouth, impairment of speech and swallowing).

The treatments were separated by intervals of 2 weeks.

Products and placebos were prepared by Merrel Dow Laboratories, Egham, United Kingdom.

Quantitative evaluation of anticholinergic effects

Pilocarpine-induced miosis and measurement of pupil diameter Miosis was induced by instillation in the right eye of each subject of one drop, volume (50 μl), of a 0.25% pilocarpine eyedrops solution. The solution was prepared at the pharmacy of the Versailles Hospital Centre from a commercial 1% pilocarpine nitrate eyedrop preparation (Chauvin-Blache, Montpellier, France). Each fresh vial of the 0.25% solution was tested for effectiveness on a volunteer, and the results were compared with previous curves of pupil diameter variations.

The pupil diameter of each eye was measured in the morning of test day before ('basal value') and 3 h after the last dose of the product tested. This interval was determined from the results of studies on clinical effectiveness (Girard *et al.*, 1986) and on the pharmacokinetics of terfenadine (Garteiz *et al.*, 1982) and mequitazine (Fourtillan *et al.*, 1982); these results showed that maximal plasma levels of these drugs are measurable 1 to 2 h (terfenadine) or 6.01 ± 1.0 h ($n=4$) (mequitazine) after an oral single dose and that, at least with terfenadine, the therapeutic effect is maximal 2 to 4 h after single dosing. The pilocarpine eye drop was then deposited in the inferior conjunctival fornix of the right eye. Pupil diameter was measured again 10 min later and thereafter at intervals of 10 min during 1 h and 15 min during 3 h. Measurements of pupil diameter in the left eye were used as controls.

All pupil measurements were performed in the same 1.50 × 3.50 m room lit by a 40-watt fluorescent tube situated behind the subject. Light intensity, room temperature and humidity were kept as constant as possible throughout the test day. After getting accustomed to the light for 10 min or more the subject, sitting at a distance of 1.50 m from one of the walls, focussed his eyes on a fixed point to maintain constant accommodation. The pupils were measured by means of a pupil gauge (Smith and Nephew Pharmaceuticals). Previous studies have shown that the results obtained with this method are reproducible in the same subject (Brion *et al.*, 1985).

Measurement of salivary secretion The volume of saliva secreted was measured on test day before, and 1, 3 and 7 h after the last dose of the drug tested. On each occasion the subject swallowed his saliva, then sucked one acid drop for 3 min without swallowing. The saliva was collected in a graduated tube (Kingsley & Turner, 1974). Prior to saliva measurement each subject was asked whether or not he had a sensation of dry mouth.

Heart rate Heart rate was evaluated by manual palpation of the radial artery at the wrist on the test day before, and 1, 3 and 7 h after the last dose of the drug tested.

Statistical analysis of the results

Statistical analysis of the results obtained was performed using Student's *t*-test. All values in the text and table are expressed as mean ± s.e. mean.

Results

Pupil diameter

Basal pupil diameter No significant difference in basal pupil diameter was found between the four courses (Table 1). Terfenadine and mequitazine administered on 3 consecutive days did not produce mydriasis. It must be noted that there was no change in pupil diameter 3 h after administration of atropine 1 mg.

Effect on pilocarpine-induced miosis Miosis induced by a 0.25% pilocarpine eye drop was unmodified by the drugs tested, as shown by the absence of significant differences in absolute values of pupil diameter decrease, t_{max} or area under the curve of pupil diameter reduction between terfenadine, mequitazine or atropine and placebo (Figure 1, Table 1).

Salivary secretion

Basal volume There was no significant difference in saliva volume measured before the last dose of terfenadine, mequitazine or placebo (Table 1).

Post-treatment volume No significant difference between saliva volume before and 3 h after the last dose was observed with terfenadine, mequitazine or placebo. In contrast, atropine produced a large and significant ($P<0.001$) fall in saliva volume. Moreover, in seven out of eight subjects the saliva volume had not returned to its initial value 7 h after administration of the 1 mg atropine tablet (Table 1 and Figure 2).

One of the subjects spontaneously complained of dry mouth when taking the mequitazine course. Five subjects reported dryness of the mouth after taking atropine; this effect was pronounced and interfered with feeding in one of these subjects.

Heart rate Comparisons of pulse rate values

Table 1 Effects of atropine, terfenadine and mequitazine on pupil diameter and salivary secretion in eight healthy volunteers: values are mean ± s.e. mean

	Placebo	*Atropine*	*Terfenadine*	*Mequitazine*
Basal pupil diameter before pilocarpine (mm)	6.40 ± 0.30	6.60 ± 0.10	6.5 ± 0.30	6.60 ± 0.20
Maximum reduction in pupil diameter induced by 0.25% pilocarpine (mm)	4.37 ± 0.31	4.12 ± 0.29	4.50 ± 0.34	4.50 ± 0.34
t_{max} of pilocarpine-induced miosis (h)	0.41 ± 0.04	0.47 ± 0.06	0.47 ± 0.06	0.59 ± 0.10
Area under the 0–4 h curve of pupil diameter reduction (mm h-1)	14.60 ± 1.10	14.10 ± 1.30	15.40 ± 1.60	13.20 ± 1.50
Basal salivary secretion (ml 3 min^{-1}) (before the atropine dose or the last dose of antihistamine agent)	3.97 ± 0.37	4.17 ± 0.42	3.75 ± 0.28	3.80 ± 0.42
Maximal changes in saliva volume (ml) after the atropine dose or the last dose of antihistaminic agents	+0.72 ± 0.41	−2.25 ± 0.36[b]	+0.57 ± 0.40	−0.61 ± 0.63
Changes in radial pulse (beats min^{-1}) 1 h after the dose of antropine or the last dose of antihistaminic agents	−6.12 ± 3.16	−9.75 ± 3.72[a]	−4.50 ± 2.25	−1.25 ± 2.47

Significant variations: a: $P < 0.05$; b: $P < 0.001$

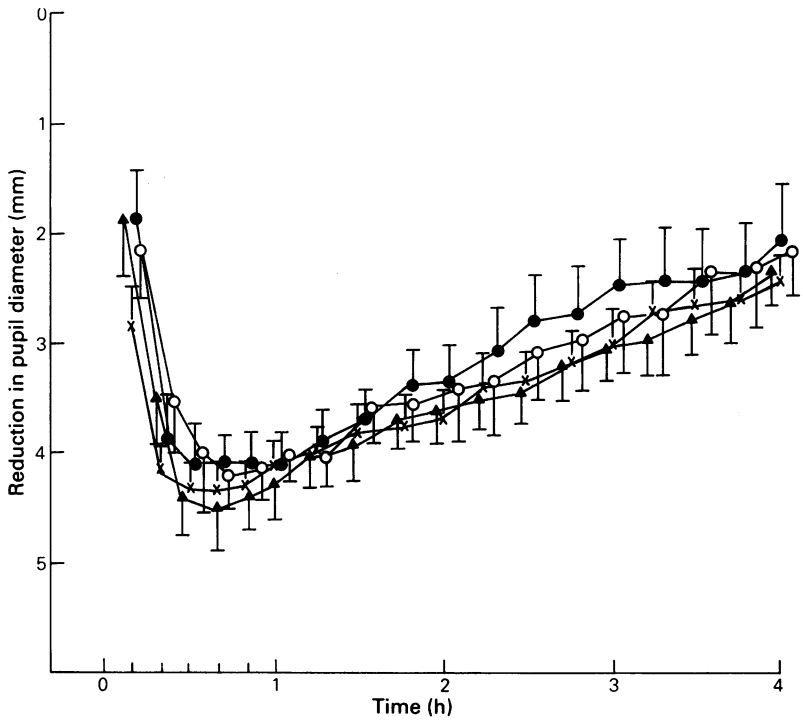

Figure 1 Changes in pupil diameter after instillation of one drop of a 0.25% pilocarpine eye drop preparation in eight volunteers, following the different treatments. (×) placebo, (•) atropine, (▲) terfenadine, (○) mequitazine. Points are mean ± s.e. mean.

measured 1 h after the last dose of the products tested showed no significant difference between terfenadine or mequitazine and placebo. In contrast, a significant decrease in pulse rate was observed 1 h after atropine (-9.75 beats min^{-1}; $P<0.05$). However, there was no significant difference between basal pulse rate and pulse rate values measured 3 and 7 h after the last dose with any of the products tested.

Discussion

In this study atropine significantly reduced saliva volume and, more briefly and to a lesser extent, heart rate in all eight volunteers, but it had no effect on basal pupil diameter or on pilocarpine-induced miosis. The two antihistaminic agents, terfenadine and mequitazine, had no activity in any of the tests.

Reduction of salivary secretion has been classically described with atropine (Iliopoulou *et al.*, 1981; Bowman & Rand, 1980; Weiner, 1985) and was expected, as was the transient bradycardia described with low doses (0.5 to 1 mg) of atropine and attributed to a central effect on the vagus nerve nucleus or to a direct effect on the heart (McGuigan, 1921; Rudolf & Bulmer, 1924; Kottmeier and Gravenstein, 1968; Hayes *et al.*, 1971; Bowman & Rand, 1980; Meyer *et al.*, 1986). However, we were surprised to find that atropine was devoid of the effect on pupil diameter or on pilocarpine-induced miosis observed with different products known to possess anticholinergic properties. Amitriptyline for example, when tested in doses of 50 and 100 mg in eight healthy volunteers, had no effect on basal pupil diameter but it reduced pilocarpine-induced miosis by about 20% with both doses (Szabadi *et al.*, 1980); it also reduced salivary secretion by 60 and 70% respectively (Szabadi *et al.*, 1980) or by 46 and 66% respectively (Longmore *et al.*, 1985). It must be noted that desipramine administered in doses of 50 and 100 mg to eight healthy volunteers reduced salivary secretion by 10 and 40% respectively, and in doses of 100 mg increased heart rate by 10 to 15%; but it had no effect on pilocarpine-induced miosis (Szabadi *et al.*, 1980). Yet Kerr & Szabadi

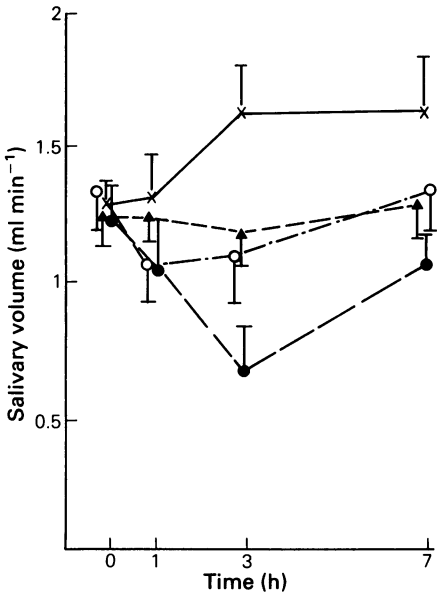

Figure 2 Changes in salivary secretion in eight volunteers following the different treatments: (×) placebo, (•) atropine, (○) mequitazine, (▲) terfenadine. Points are means ± s.e. mean.

(1985) have found that when administered during 4 weeks to nine volunteers in doses of 50 mg twice daily desipramine increased basal pupil diameter by 8.0 ± 1.6% ($P<0.001$) and potentiated pilocarpine-induced miosis (+89.2 ± 9.1%; $n=6$; $P<0.01$). Finally, Shur & Checkley (1982) have shown that desipramine administered as an antidepressant to six patients did not modify the miosis induced by pilocarpine at the beginning of treatment but increased it after 6 weeks.

Several hypotheses can be put forward to explain the lack of effect of atropine on basal pupil diameter and pilocarpine-induced miosis when administered as a single 1 mg oral dose, knowing that an antagonistic effect cannot be excluded with higher oral doses or local applications. The first one is insufficient diffusion of atropine to the eye as compared with its wide diffusion in the salivary glands. This is supported by the study of Lazenby *et al.* (1968) who observed that atropine increased intraocular pressure in 14 patients when administered as eyedrops but not when administered orally in two 0.6 mg doses at 4 h intervals. Similarly, Longmore *et al.* (1985) have shown that atropine had a greater antagonistic effect on sweat gland response to carbachol in man when applied into the skin than when given by mouth.

Another explanation could be that the concentration of pilocarpine in our eyedrops was too high, giving supra-maximal responses. Against this assumption is the fact that in experiments carried out by Szabadi *et al.* (1980) in which the effects of pilocarpine were inhibited by amitriptyline, the pilocarpine concentration in eyedrops was 0.07 M or 1.7% as opposed to 0.25% in our own experiments. However, one cannot exclude the possibility that in the Szabadi *et al.* (1980) study the pilocarpine-induced miosis was inhibited by amitriptyline through mechanisms other than antagonism at muscarinic receptors of the eye.

In our study the antihistaminic agents were devoid of anticholinergic effects, notably on heart rate and salivary secretion. With regard to terfenadine, our results are in agreement with those of Kulshresta *et al.* (1978) who administered the drug in exactly the same doses as ours to 12 volunteers and also found no anticholinergic effect. As for mequitazine, it must be noted that undesired anticholinergic effects (dry mouth, visual disorders, retention of urine) have been reported with this drug in patients on long-term treatment (Dry *et al.*, 1980; Demaubeuge *et al.*, 1982; Richards *et al.*, 1984; Beaumont *et al.*, 1986). The lack of anticholinergic activity of mequitazine in our study might be due to the small number of subjects and/or the short duration of treatment.

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(Received 7 July 1987, accepted 10 August 1987)