SOME CLINICAL PHARMACOLOGICAL STUDIES WITH TERFENADINE, A NEW ANTIHISTAMINE DRUG

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- 1 A double-blind cross-over trial between placebo, chlorpheniramine, and terfenadine, a new antihistamine drug, was performed in healthy male volunteers to determine and compare their CNS and autonomic effects.
- 2 Terfenadine and chlorpheniramine were administered orally in therapeutic doses.
- 3 In objective tests of critical flicker frequency, pursuit rotor, reaction time, salivary volume and pupillary diameter, no statistically significant difference was observed between the treatments.
- 4 On analogue rating scales, chlorpheniramine produced a statistically significant ($P < 0.05$) degree of sedation and impaired concentration as compared to placebo and terfenadine.
- 5 The results obtained in analogue rating scales were not normally distributed and, therefore, use of non-parametric statistical methods for analysis of such data is strongly advocated.

Introduction

Terfenadine (RMI 9918), α -(4-*tert*-butylphenyl)-4-(α -hydroxy- α -phenylbenzyl)-1-piperidine butanol (Figure 1), is a newly synthesized compound, which has been found to possess antihistaminic activity in animal experiments. Unlike other antihistamines it is devoid of central nervous system (CNS) effects up to a dose of 100 mg/kg in mice, rats, guinea pigs, dogs and monkeys. It has also been investigated for antihistaminic activity in man. In normal human volunteers terfenadine produced a dose-related reduction of histamine wheals at single oral doses of 20 mg to 200 mg with maximum effect being obtained at 60 mg. In a double-blind controlled trial terfenadine compared well with chlorpheniramine in providing relief in symptoms of allergic rhinitis. The incidence of sedative effects, as recorded by patients in these trials,

was similar with placebo, terfenadine and chlorpheniramine (Merrell-National Laboratories, 1977).

Since the CNS and autonomic effects of terfenadine in man have not been systematically investigated, a double-blind cross-over trial was done to determine and compare these effects of single and multiple doses of terfenadine with chlorpheniramine and placebo, using a battery of objective and subjective tests. The sensitivity of the tests employed to detect CNS activity was then compared.

Methods

Twelve healthy male volunteers, aged 21-25 years and weighing 60-80 kg, participated in the study.

Figure 1 The structural formula of terfenadine.

They received the following treatments in random order based on a 3×4 latin square design with an interval of at least 5 days between each: (1) terfenadine (60 mg — 3 tablets of 20 mg each — twice daily) and chlorpheniramine placebo (one capsule thrice daily); (2) chlorpheniramine capsules (4 mg thrice daily) and terfenadine placebo (3 tablets twice daily); (3) chlorpheniramine placebo (one capsule thrice daily) and terfenadine placebo (3 tablets twice daily). The first dose was given in the morning of day 1 and the final dose at a similar time on day 3. The subjects were instructed to abstain from nicotine, tea, coffee or alcohol from a day prior to the test day and throughout the test period and no other medications were allowed during the test period.

The following tests were performed just before (0 h) and at 2 h and 4 h after taking the first dose. All the tests were repeated 4 h after the last dose on day 3. In addition the subjects were required to complete the analogue rating scales at 4 h on day 2.

Objective tests

Critical flicker frequency (CFF) The method of Turner (1964), as modified by Ogle & Turner (1974), was used to determine the CFF. The threshold frequency expressed in Hz was taken as the mean of the frequencies at which, to conditioned subjects, a flickering light source appeared to change from flickering to steady and *vice versa*. Subjects, initially dark adapted for 3 min, were conditioned to flickering light (20 Hz) for 1 min. The rate of flickering was gradually increased in steps until it appeared fused to the subject (threshold CFF). The process was then reversed, i.e. from fused to flickering after conditioning to 20 Hz. A similar procedure was followed for determining the threshold CFF after conditioning to fused light (50 Hz). Following every measurement of threshold CFF, the subjects were required to look away from the light source for 1 min before being conditioned to a flickering or fused light again. Four threshold measurements were made at each test session in the following order:

- (a) ascending threshold from 20 Hz after conditioning to 20 Hz;
- (b) descending threshold from 50 Hz after conditioning to 20 Hz;
- (c) ascending threshold from 20 Hz after conditioning to 50 Hz;
- (d) descending threshold from 50 Hz after conditioning to 50 Hz.

The mean of the values of the four threshold measurements thus obtained was taken as the threshold CFF value.

Pursuit rotor The performance of subjects on a standard pursuit rotor (Forth Instruments) were measured following the method described by Berry & Grubb (1974) and Ogle, Turner & Markomihelakis (1976). The subjects were required to follow and keep

a light-sensitive probe in contact with a rotating light source on a turntable beneath a frosted glass top. The light source with an area of 15×20 mm followed a snowflake pattern at a fixed speed of 10 rev/min. The readings were taken every 10 s and were expressed as a percentage. Subjects were required to follow the moving light source for twelve consecutive rounds. The contact times for the last six rounds were meaned. **Reaction time** Reaction time was measured with a digital counter (Southern Techniques Electronics Ltd) which was started by the same switch button which initiated the stimulus, a green light 15 mm in diameter. The subject registered his response by pressing a button which switched off the light and stopped the counter. A total of twenty-three stimuli were given at randomized intervals, the first three being discarded. The twenty readings were meaned.

Anticholinergic effects: (a) *Salivary volume* Salivary volume was measured according to the procedure described by Kingsley & Turner (1974). Subjects were instructed to suck an acid drop over a period of 2 min without swallowing and then to spit out all saliva, together with the remaining acid drop, into a measuring cylinder through a funnel. (b) *Pupil diameter* This was measured by scale and by the photographic method of Sneddon & Turner (1967).

Subjective tests

Analogue rating scales On a linear scale, measuring 100 mm, subjects were required to mark the point which represented their feeling in relation to sedation, concentration and mood. The extremes of the scale were 'as alert as I have ever been' and 'I cannot keep awake' for sedation; for concentration the extremes were 'I cannot concentrate because of the rush of ideas' and 'my mind is as sluggish as it has ever been'. The extremes for mood were 'I have never been happier' and 'life is just not worth living'.

In addition, volunteers were asked to write down subjective feelings of any side-effects.

Subjects did not have access to their previous assessments at the time of filling in the rating scales.

Statistics

Analysis of variance was used to compare the results of the objective tests and Wilcoxon's matched pair signed ranks test was used to compare the results of the rating scales.

Results

Objective tests

Terfenadine and chlorpheniramine did not produce any significant effect ($P > 0.05$) on threshold CFF, pursuit rotor, reaction time, salivary volume and

Figure 2 Frequency-distribution histogram of scores on analogue rating scales for (a) sedation, (b) mood and (c) concentration as observed at 0 h day 1 at three different test periods ($n=36$ for each test). Distribution is clearly not normal in sedation and mood scores, and the distribution of concentration scores is skewed.

pupillary size at 2 and 4 h on day 1 and at 4 h on day 3 in comparison to placebo (Table 1).

Subjective tests

The frequency distributions of the scores on the analogue rating scales are shown in Figure 2. The distribution of scores for sedation and mood show no similarity to a normal distribution, and the distribution of scores for mood is markedly skewed. Therefore, it seemed preferable to use a non-parametric statistical technique to examine within subject differences between drugs, particularly in this study where the actual size of the differences on the analogue rating scales were of less interest than the direction of the changes. A Wilcoxon's matched pairs signed ranks test was used at each time point to examine the

differences in the three analogue rating scales for each subject between the two drugs and placebo. On the sedation rating scale (Figure 3), chlorpheniramine shows a consistent effect compared with placebo and at least seven out of the ten subjects were more sedated on chlorpheniramine than placebo at all times after treatment except at 4 h on day 1. Chlorpheniramine produced significant sedation ($P < 0.05$) at 2 h on day 1 and at 4 h on day 2 in comparison to placebo and at 4 h on day 3 in comparison with placebo as well as terfenadine. Chlorpheniramine also impaired concentration at 4 h on day 3 ($P < 0.01$) (Table 3). Terfenadine did not produce any significant alteration in concentration, mood or alertness.

Five subjects receiving chlorpheniramine felt tired or sleepy at one or more test periods, whereas only one subject each on placebo or terfenadine had similar complaints.

Table 1 Mean $\pm$ s.e. mean ($n=12$) effect of placebo, chlorpheniramine and terfenadine on CFF, pursuit rotor, reaction time and salivary volume

Test	Day	Time (h)	Placebo	Chlorpheniramine	Terfenadine
Critical flicker frequency (Hz)	1	0	28.8 $\pm$ 0.7	29.6 $\pm$ 0.8	29.3 $\pm$ 0.7
	1	2	28.9 $\pm$ 0.7	28.8 $\pm$ 0.8	28.7 $\pm$ 0.6
	1	4	29.4 $\pm$ 0.7	28.4 $\pm$ 0.8	28.4 $\pm$ 0.7
	3	4	29.2 $\pm$ 0.6	28.7 $\pm$ 0.9	29.0 $\pm$ 0.8
Pursuit rotor (% efficiency)	1	0	74.8 $\pm$ 4.4	72.5 $\pm$ 4.2	76.2 $\pm$ 3.3
	1	2	76.4 $\pm$ 3.8	77.0 $\pm$ 4.2	80.7 $\pm$ 2.9
	1	4	78.8 $\pm$ 3.7	77.3 $\pm$ 3.3	81.2 $\pm$ 2.8
	3	4	78.9 $\pm$ 3.5	74.5 $\pm$ 4.9	80.5 $\pm$ 2.4
Reaction time (ms)	1	0	326 $\pm$ 19.3	319 $\pm$ 17.5	310 $\pm$ 17.9
	1	2	326 $\pm$ 21.6	326 $\pm$ 18.1	309 $\pm$ 19.9
	1	4	327 $\pm$ 19.3	317 $\pm$ 15.2	315 $\pm$ 18.0
	3	4	328 $\pm$ 16.4	311 $\pm$ 16.4	308 $\pm$ 18.5
Salivary volume (ml)	1	0	13.6 $\pm$ 1.0	15.3 $\pm$ 1.1	15.8 $\pm$ 1.4
	1	2	15.1 $\pm$ 0.8	16.1 $\pm$ 1.2	15.3 $\pm$ 1.3
	1	4	14.8 $\pm$ 1.3	15.2 $\pm$ 1.0	15.5 $\pm$ 1.3
	3	4	15.7 $\pm$ 1.3	14.8 $\pm$ 0.8	14.8 $\pm$ 1.4

Figure 3 Median scores on rating scales for (a) mood, (b) concentration, and (c) sedation at 2 h and 4 h on day 1 and 4 h on days 2 and 3 after placebo (○), chlorpheniramine (●) and terfenadine (△) in twelve subjects. The extremes of the scales are given in the test. (*) indicates significant difference from placebo and/or terfenadine ($P < 0.05$).

Discussion

Terfenadine, a new antihistaminic drug, has been compared with chlorpheniramine and placebo in its CNS and autonomic effects in normal healthy male volunteers. Chlorpheniramine was administered in a dose of 4 mg three times daily and terfenadine was

given in a dose of 60 mg twice daily, the doses of both drugs being within the therapeutic range.

In what we may call objective tests, i.e. critical flicker frequency, pursuit rotor or reaction time, none of the drugs produced any significant change as compared to placebo at the times tested. Out of these objective tests the CFF test has been very commonly employed and is probably the most sensitive for detecting central depressant activity from tranquilizers and sedatives (Turner, 1968; Hedges, Turner & Harry, 1971; Ogle & Turner, 1974). It appears that, when CNS depression is a prominent pharmacological property of a drug, therapeutic doses will produce detectable changes in performance of subjects in objective tests. On the other hand, with drugs which produce only minor CNS depression as a side-effect, these objective tests may fail to detect it unless the dose is sufficiently increased beyond the therapeutic range to impair performance. Thus, Ogle *et al.* (1976) observed a significant decrease in efficiency of subjects on pursuit rotor tests after a high dose (240 mg) of propranolol. Chlorpheniramine however, though known to produce some sedation in therapeutic doses in some subjects, did not affect the performance of our subjects in any of the objective tests employed. This is in agreement with earlier studies (Turner, 1968) which did not find any change in CFF with chlorpheniramine 4 mg.

On the analogue scales, however, chlorpheniramine produced a significant degree of sedation ($P < 0.05$) at 2 h after the first dose as well as at 4 h on day 2 and at 4 h after the last dose on day 3. Chlorpheniramine at 4 h on day 3 also significantly ($P < 0.01$) impaired concentration (see Figure 3). Terfenadine, on the other hand, appeared to be devoid of sedative effects at these times because the effect of terfenadine was indistinguishable from placebo on analogue rating scales.

The frequency distribution of scores in the linear rating scales appeared not to be normally distributed (see Figure 2). While it is probable that parametric statistical tests would show apparent significant differences between treatments, the use of such tests assumes a distribution of data which does not differ substantially from normality. When the distribution is not normal, however, as in the present experiment, the results of parametric tests are open to question. It therefore seemed more appropriate to use a non-parametric statistical test which makes no assumption about the underlying distribution of data to compare these results. With such a test, namely the Wilcoxon's matched pairs signed ranks test, there were significant differences between chlorpheniramine and placebo in the rating scales for sedation and reduction in concentration but not in the more objective tests. This suggests that the tests may be of potential value in investigations designed to screen the CNS effects of pharmacologically active substances. In this

connection Farhoumand, Harrison & Wadsworth (1977) detected sedative effects of a high dose of oxprenolol (480 mg) on rating scales but not on more objective tests such as reaction time and CFF.

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