A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function

I. Hindmarch, Z. Shamsi, N. Stanley & D. B. Fairweather

HPRU Medical Research Centre, Egerton Road, Guildford, GU2 5XP, United Kingdom

Aims To assess whether fexofenadine in a range of doses from 80 to 180 mg has any disruptive effects on aspects of psychomotor and cognitive function in comparison with placebo, loratadine and promethazine, an antihistamine known to produce psychomotor and cognitive impairment.

Methods Twenty-four healthy volunteers received fexofenadine 80 mg, 120 mg and 180 mg, loratadine 10 mg, promethazine 30 mg (as a positive internal control) and placebo in a six-way crossover, double-blind study. Following each dose, subjects were required to perform a series of tests of cognitive function and psychomotor performance at 1.5, 3, 6, 9, 12 and 24 h post dose. The test battery included critical flicker fusion (CFF), choice reaction time (CRT) and assessment of subjective sedation (LARS). Overall levels of activity were monitored by means of wrist mounted actigraphs throughout each of the 24 h experimental periods.

Results Fexofenadine at all doses tested was not statistically different from placebo in any of the tests used and loratadine did not cause any significant impairment of cognitive function. Significant impairments were found following promethazine. Promethazine caused a significant reduction in CFF threshold and this effect was evident up to 12 h post dose ($P<0.05$). There was a significant increase in recognition reaction time at 3 and 6 h post promethazine administration, and the drug caused a significant ($P<0.002$) increase in the percentage of 'sleep-like' activity from actigraph records during the daytime.

Conclusions Fexofenadine at doses up to 180 mg appears free from disruptive effects on aspects of psychomotor and cognitive function in a study where the psychometric assessments have been shown to be sensitive to impairment, as evidenced by the effects of the verum control promethazine 30 mg.

Keywords: antihistamines, cognitive function, fexofenadine, loratadine, promethazine, psychomotor performance

Introduction

Antihistamines are the drugs of choice in the symptomatic treatment of various allergic disorders such as seasonal and perennial allergic rhinitis and chronic urticaria [1, 2]. However, the use of traditional antihistamines such as diphenhydramine, chlorpheniramine, triprolidine and promethazine is often associated with a number of unwanted side-effects of which sedation is the most pronounced [3–5]. These side-effects can interfere with the performance of daytime activities and not only place the patient at an increased risk of accidents in situations such as driving and operation of machinery, where high levels of alertness are required [5–7], but also reduce compliance with treatment regimens due to excessive fatigue and malaise.

Adverse effects experienced with older drugs with sedative effects resulted in the development of a second generation of antihistamines with equipotent antiallergic action. Clinical trials have consistently demonstrated that the second generation antihistamines have a much more favourable therapeutic index and a significantly lower incidence of sedative effects than have their predecessors and so represent a major advance in antihistamine therapy [2, 8, 9]. Unlike the classical antihistamines, the newer agents do not readily cross the blood brain barrier and

Correspondence: Dr Z. Shamsi, HPRU Medical Research Centre, Egerton Road, Guildford GU2 5XP, UK.

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have a greater affinity to bind to peripheral H_1-receptors and are thus relatively devoid of undesirable central effects such as sedation, fatigue, etc. [9].

Fexofenadine is the active metabolite of terfenadine and has been shown to possess potent antihistaminic activity in experimental animals and in man [personal communication, Hoechst Marion Roussel 1995]. Animal studies have shown that fexofenadine does not penetrate the blood brain barrier and thus allows an effective blockade of H_1-receptors in peripheral tissues without significant central side-effects [personal communication, Hoechst Marion Roussel 1995].

Following oral administration, fexofenadine is rapidly absorbed reaching maximum concentration within 1–2 h. Pharmacological effects occur within 1–2 h and are sustained over a period of 24 h [10].

In healthy human volunteers, fexofenadine produced a dose related reduction of histamine induced weal and flares at single oral doses of 40 mg to 130 mg with maximal effect being obtained at 130 mg. Increasing the dose of fexofenadine to 800 mg was well tolerated with no increases in treatment related adverse events [personal communication, Hoechst Marion Roussel 1995]. In a number of double-blind controlled trials, fexofenadine (40 mg–240 mg twice daily) was significantly superior to placebo in providing relief from symptoms of seasonal allergic rhinitis (SAR) [11]. The most commonly reported adverse event associated with fexofenadine was headache, and the incidence of fatigue and drowsiness was comparable with those found in patients receiving placebo treatment [11].

The aim of this study was to assess whether fexofenadine in a range of doses from 80–180 mg has any disruptive effects on aspects of psychomotor and cognitive function in comparison with placebo, loratadine and promethazine, an antihistamine known to produce psychomotor and cognitive impairment and included in this study as a positive internal control to establish the validity of the psychometrics used in this particular instance.

Methods

Subjects

Twenty-four healthy volunteers (15 male, 9 female), aged 19–58 years (mean age 32.6), were entered into the study. All subjects were in good health without a significant clinical history of physical or mental illness. None of the subjects was taking any concomitant medication (except oral contraceptives) likely to interfere with the study measures. The use of alcohol and nicotine was forbidden and products containing caffeine were prohibited on test days. Food consumption was strictly controlled and only allowed at the specified times. Written informed consent was obtained from all subjects and their GPs. The study was approved by the Ethics Committees of the South-West Surrey Health Authority and the University of Surrey.

Design

The study was a randomised, double-blind, placebo controlled, six way crossover study where each subject acted as their own control. The treatment sequence was balanced for residual effects using a Latin Square design. The drugs under investigation were fexofenadine 80 mg, 120 mg and 180 mg; promethazine 30 mg (as a verum), loratadine 10 mg and placebo. All treatments were supplied in identical capsules and each of the doses was taken as a single oral dose at 08.30 h. Each treatment day was separated by a washout period of 4 days or more.

Procedure

Following informed consent, medical history and GP approval, all subjects underwent a medical examination (including 12 lead electrocardiogram, urinalysis, haematology, biochemistry and drugs of abuse screen). If subjects fulfilled the inclusion/exclusion criteria they were entered into the study and familiarized with the study procedures and trained on the battery of psychometric tests in order to preclude learning effects [12].

On each of the test days subjects attended the study centre where a breath alcohol reading was taken. Subjects were then given an actigraph to be worn on the nondominant wrist for 24 h. Pre-treatment baseline recordings were then made on each of the psychometrics (described below) after which medications were administered and further testing carried out at 1.5, 3, 6, 9, 12 and 24 h post dose (subjects were required to sleep at the test centre overnight). Adverse events and concomitant medication were recorded at each visit.

Caffeine, nicotine and alcohol were prohibited on study days and light meals given to subjects whilst on the study. Subjects were instructed to avoid late-nights and go to bed at their usual bedtime (minimum of 6–8 h sleep) on all premedication nights. Subjects were prevented from napping during the day by vigilant members of staff and were encouraged to stay mentally alert.

Assessments

Critical Flicker Fusion Threshold (CFF) CFF is a means of measuring the ability to distinguish discrete sensory data and is taken as an index of overall CNS activity (13–15]. The subjects were required to discriminate flicker/fusion in a set of four light emitting diodes held in foveal fixation at 1 m. Individual thresholds were determined

by the psychophysical methods of limits on three ascending and three descending scales [16] and the mean of these values was then recorded. A lowering of the CFF threshold is indicative of a reduction in the capacity to process information.

Choice Reaction Time (CRT) CRT was used as a sensitive measure of drug-induced changes in psychomotor speed [13, 14]. From a central starting position subjects were required to extinguish one of the six red lights, illuminated at random, by touching the appropriate response button. Using this arrangement it was possible to measure three components of reaction time: the total reaction time (TRT) from stimulus onset to completion of response; the movement time (MRT) between the start and response buttons and the processing or recognition time (RRT), obtained from subtracting MRT from TRT. The mean reaction time for 20 stimulus presentations was recorded.

Line Analogue Rating Scales for sedation (LARS) The LARS is employed as a measure of the subjective effects of psychoactive drugs. Subjects mark a series of 10 cm line analogue scales, indicating their present feeling with regards to a mid-point, which represents their normal state of mind before treatment began. The mean scores of ratings of 'tiredness', 'drowsiness', and 'alertness', presented among several distracter scales, are taken as a measurement of perceived sedation [17]. The higher the score (in mm), the less alert and more tired and drowsy the subject feels.

Wrist actigraphy (activity monitoring) The subjects wore a wrist actigraph (Ambulatory Monitoring Inc. AMA-32C Mini Motionlogger, Ardsley, New York) on their nondominant wrist for the duration of each treatment period. Actigraphy has been shown to be capable of measuring reductions in behavioural activity (sedation) caused by psychoactive compounds [18, 19]. These small wrist watch sized devices contain a piezoelectric transducer that detects motion and generates a signal voltage. In zero crossing mode the signal voltage is compared with a reference voltage for a change in state. The device records the number of changes in state per epoch. Automatic sleep/wake detection algorithms have been developed and refined until they now correlate well with traditional sleep EEG in their measurement of sleep time [20–24] and these have been incorporated into proprietary ACTION3 software. Percentage sleep/wake for the duration of each visit and for the day (0830–2300) were scored automatically using the ACTION3 software.

Analysis

The data were analysed as changes from baseline using a 2 factor repeated measures ANOVA. The factors were treatment (6 levels: fexofenadine 80 mg, 120 mg and 180 mg; promethazine 30 mg, loratadine 10 mg and placebo) and time (6 levels: 1.5, 3, 6, 9, 12 and 24 h). *Post hoc* pairwise comparisons between the treatment means were performed using Newman-Keuls tests. All the statistical tests were performed two tailed at the 5% level.

Results

For CFF, analysis of the changes from baseline showed significant main effects of treatment ($F(5,85)=3.51$; $P<0.01$) and time of testing ($F(5,85)=2.69$; $P<0.05$). The results for promethazine 30 mg showed a very different pattern from all other treatment regimens, with a marked decrease in the CFF threshold, throughout the 24 h period, the lowest mean thresholds being from 3 –9 h post medication. *Post hoc* analysis revealed that overall, promethazine scores were significantly different from placebo, fexofenadine 80 mg and loratadine 10 mg. Examination of the results of the drug × interaction showed a consistent reduction in the CFF threshold following the administration of promethazine at 3 h [mean reduction (m.r.) of 2.28 Hz, 95% CI of the difference −3.19, −1.38], 6 h [m.r. −2.15 Hz, 95% CI of −3.18, −1.12], 9 h [m.r. −2.30 Hz, 95% CI of −3.44, −1.15] and 12 h [m.r. −1.54 Hz, 95% CI of −2.55, −0.53] when compared with placebo. Promethazine was also significantly ($P<0.05$) different from fexofenadine 80 mg at 3, 6, 9 and 12 h post medication, from fexofenadine 120 mg and loratadine 10 mg at 3, 6 and 9 h and from fexofenadine 180 mg at 3 and 9 h post medication. None of the other treatments could be distinguished from placebo (Figure 1).

The results for recognition reaction time (RRT, a component of the total reaction time task), showed no significant main effects of treatment, but there was a significant effect of time ($F(5, 100)=11.05$; $P<0.001$) with an increase in reaction time from 1 to 9 h following the administration of promethazine. Pairwise comparisons revealed that promethazine 30 mg was significantly different from placebo at 3 h [mean increase of 38.4 msec, 95% CI of the difference 15.69, 61.10] and 6 h [mean increase of 35.45 ms, 95% CI of the difference, 13.87, 57.04], and from fexofenadine 80 mg, 120 mg and 180 mg and loratadine 10 mg at 3 h, with promethazine having higher mean increases and thus slower reaction times, than the other treatment regimens. MRT was similar with all drugs. The results for total reaction time (TRT) showed that there was a significant time effect

Table 1 Confidence intervals (95%) for all significant (s) and nonsignificant (ns) differences of all treatments at all time points, when compared with placebo. Figures in brackets indicate

i) mean change in CFF (Hz), negative values indicating a reduction of CFF scores and hence an impairment.

ii) mean change in RRT (ms)—higher scores indicate impairment (increase in recognition reaction time).

iii) mean change in TRT (ms)—higher scores indicate impairment (increase in total reaction time).

iv) mean change in LARS (mm)—Higher scores indicate impairment/sedation.

		Time (h)					
	Drug	*1.5*	*3.0*	*6.0*	*9.0*	*12.0*	*24.0*
CFF	Fex 80 mg	(0.14), −0.55, 0.84 NS	(−0.17), −1.16, 0.83 NS	(−0.08), −1.05, 0.88 NS	(−0.29), −1.27, 0.68 NS	(0.75), −1.68, 0.18 NS	(0.08), −1.02, 1.19 NS
	Fex 120 mg	(−0.57), −1.24, 0.09 NS	(−0.62), −1.17, −0.75 NS	(−0.31), −1.07, 0.45 NS	(−0.63), −1.49, 0.23 NS	(−0.94), −1.84, −0.05 NS	(−0.45), −1.31, 0.42 NS
	Fex 180 mg	(−0.74), −1.64, 0.16 NS	(−0.74), −1.56, 0.087 NS	(−1.39), −2.35, −0.43 NS	(−0.85), −1.81, 0.11 NS	(−1.25), −2.22, −0.28 NS	(−0.85), −1.88, 0.19 NS
	Lor 10 mg	(−0.29), −0.99, 0.41 NS	(−0.41), −0.98, 0.16 NS	(−0.68), −1.47, 0.11 NS	(−0.67), −1.81, 0.48 NS	(−0.99), −2.09, 0.12 NS	(−0.67), −1.57, 0.23 NS
	Prom 30 mg	(−0.97), −1.76, −0.20 NS	(−2.28), −3.19, −1.38 S	(−2.15), −3.18, −1.12 S	(−2.30), −3.44, −1.16 S	(−1.54), −2.55, −0.54 S	(−0.80), −1.84, 0.24 S
RRT	Fex 80 mg	(7.15), −9.77, 24.08 NS	(7.38), −13.79, 28.55 NS	(11.26), −1.62, 24.14 NS	(18.53), 1.68, 35.38 NS	(4.37), −16.44, 25.18 NS	(−6.43), −21.95, 9.08 NS
	Fex 120 mg	(18.55), −1.63, 38.73 NS	(8.37), −5.51, 22.24 NS	(19.30), 1.87, 36.73 NS	(9.30), −8.40, 27.01 NS	(−3.69), −21.25, 13.86 NS	(−2.37), −20.15, 15.42 NS
	Fex 180 mg	(−0.93), 13.57, 11.71 NS	(9.52), −8.74, 27.78 NS	(9.09), −10.78, 28.95 NS	(0.04), −18.34, 18.43 NS	(−2.52), −21.51, 16.46 NS	(−5.95), −26.75, 14.86 NS
	Lor 10 mg	(1.99), −16.97, 20.94 NS	(3.15), −12.22, 18.52 NS	(8.00), −4.97 20.98 NS	(7.40), −14.06, 28.85 NS	(−4.00), 22.76, 14.75 NS	(−9.27), −28.52, 9.99 NS
	Prom 30 mg	(10.00), −2.11, 22.12 NS	(38.40), 15.69, 61.10 S	(35.45), 13.87, 57.04 S	(15.84), −1.91, 33.58 NS	(0.75), −17.64, 19.14 NS	(−8.11), −26.10, 9.87 NS
TRT	Fex 80 mg	(3.41), −25.18, 32.01 NS	(0.76), −23.08, 24.59 NS	(7.99), −13.23, 29.21 NS	(22.59), 3.32, 41.86 NS	(7.49), −18.05, 33.03 NS	(−1.57), −22.91, 19.78 NS
	Fex 120 mg	(9.78), −13.20, 32.76 NS	(5.93), −17.39, 29.25 NS	(14.37), −8.93, 37.67 NS	(8.46), −20.71, 37.63 NS	(−11.59), −34.44, 11.27 NS	(0.97), −25.66, 27.59 NS
	Fex 180 mg	(8.41), −11.64, 28.47 NS	(22.05), −2.06, 46.16 NS	(9.40), −15.30, 34.09 NS	(−1.63), −22.71, 19.45 NS	(−7.31), −29.01, 14.39 NS	(−4.81), −30.98, 21.35 NS
	Lor 10 mg	(7.10), −9.24, 23.44 NS	(10.39), −15.46, 36.24 NS	(10.97), −6.40, 28.34 NS	(25.92), 3.60, 48.25 NS	(−0.61), −21.75, 20.53 NS	(−5.16), −30.45, 20.13 NS
	Prom 30 mg	(15.38), −1.07, 31.83 NS	(44.02), 11.26, 76.79 NS	(46.79), 21.29, 72.28 NS	(21.70), 0.41, 42.99 NS	(−4.93), −28.73, 18.87 NS	(−18.37), −38.84, 2.10 NS
LARS	Fex 80 mg	(−0.97), −2.78, 0.85 NS	(2.25), −0.58, 5.08 NS	(1.80), −1.35, 4.997 NS	(1.16), −0.83, 3.14 NS	(1.37), −0.61, 3.35 NS	(0.11), −1.31, 1.52 NS
	Fex 120 mg	(0.79), −2.00, 3.59 NS	(0.57), −2.49, 3.62 NS	(0.23), −2.45, 2.90 NS	(1.70), −1.93, 533 NS	(0.55), −1.59, 2.69 NS	(0.49), −4.16, 3.18 NS
	Fex 180 mg	(1.76), −0.55 4.07 NS	(3.89), 0.86, 6.92 NS	(6.33), 2.46, 10.20 NS	(5.62), 2.07, 9.16 NS	(2.92), −0.69, 5.90 NS	(2.13), −1.29, 5.54 NS
	Lor 10 mg	(0.95), −1.13, 3.16 NS	(1.76), −1.33, 4.84 NS	(0.98), −2.31, 4.26 NS	(1.80), −1.42, 5.04 NS	(0.67), −1.44, 2.77 NS	(−1.74), −4.41, 0.92 NS
	Prom 30 mg	(1.69, −2.00, 5.38 NS	(3.26), −0.95, 7.46 NS	(4.06), −1.25, 9.37 NS	(2.19), −3.51, 7.88 NS	(−1.16), −5.18, 2.86 NS	(−6.13), −10.41, 2.05 S

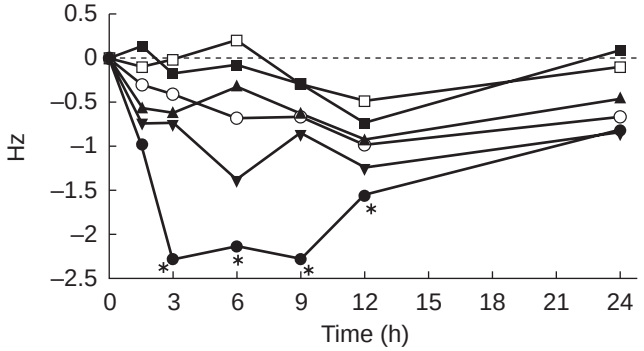

Figure 1 Critical flicker fusion thresholds (Hz). Mean change from baseline following the administration of fexofenadine 80 mg (filled square), 120 mg (filled triangle), 180 mg (filled wedge), loratadine (clear circle), promethazine (filled circle) and placebo (open square). $\star P < 0.05$ when compared with placebo.

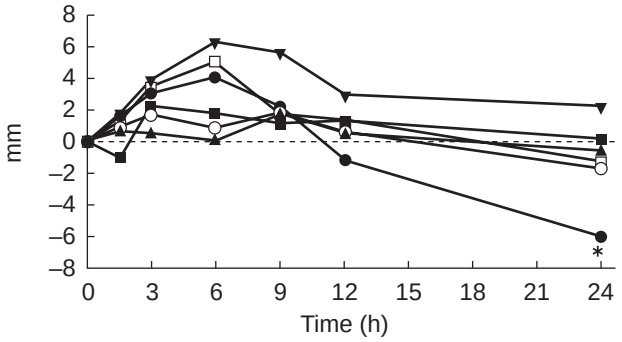

Figure 3 Line Analogue Rating Scale for Sedation (mm). Mean change from baseline following the administration of fexofenadine 80 mg (filled square), 120 mg (filled triangle), 180 mg (filled wedge), loratadine (clear circle), promethazine (filled circle) and placebo (open square). $\star P < 0.05$ when compared with placebo.

($F(5,100) = 7.13$, $P < 0.001$) but no significant treatment effect. The *post hoc* pairwise comparisons did not show any significant differences between the six drugs at any one time point, however, the pattern of results show that there was a trend for promethazine to slow reaction times at 3 and 6 h post dose.

No main effects of drug were evident in the subjective ratings of sedation (LARS), but there were significant effects of time ($F(5,95) = 5.70$; $P < 0.001$) and the treatment–time interaction was significant ($F(25, 475) = 192$; $P < 0.01$). Ratings of sedation were lower with promethazine than with placebo at 12 h post dose, and this difference was significant at 24 h post dose [95% CI of the difference -10.41, -1.85] (Figure 3).

An analysis of percentage sleep measured by actigraphy revealed a significant increase in the percentage of sleep with promethazine across the study period as compared with all other treatments ($F(5,70) = 2.59$; ($P < 0.05$). There was a significant increase in the percentage of epochs staged as 'sleep' during the day ($F(5,75) = 4.46$; $P < 0.002$) with promethazine, however, there was no significant difference in the amount of sleep during the night. There was a highly significant main effect of time which undoubtedly represented the normal circadian and ultradian rhythms.

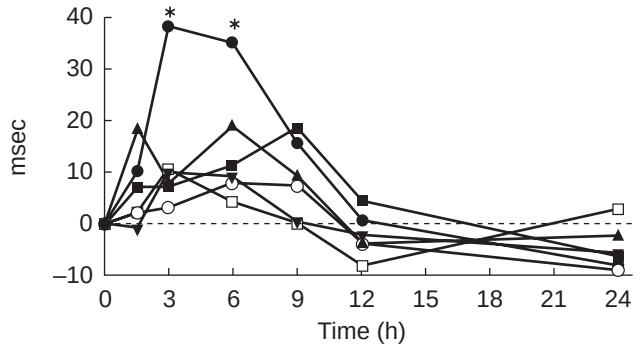

Figure 2 Recognition reaction time (ms). Mean change from baseline following the administration of fexofenadine 80 mg (filled square), 120 mg (filled triangle), 180 mg (filled wedge), loratadine (clear circle), promethazine (filled circle) and placebo (open square). $\star P < 0.05$ when compared with placebo.

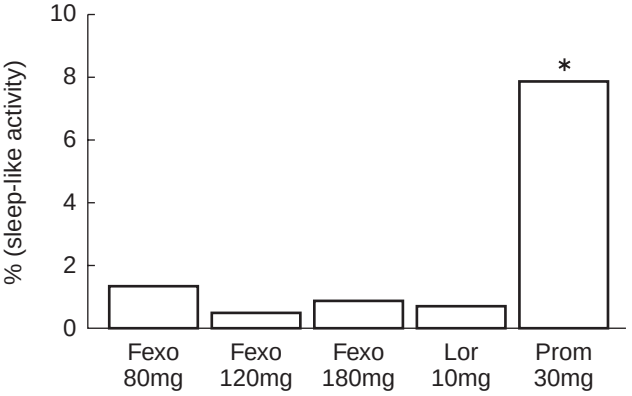

Figure 4 Percent daytime 'sleep-like' activity. Mean change from placebo where $\star P < 0.05$.

There were no reports of serious adverse events and no subject withdrew due to drug intolerance or any drug related event. Twenty-two subjects experienced at least one clinical adverse event, of which 19 were regarded as possibly, probably or definitely drug related. Five subjects experienced a related adverse event on placebo, five on fexofenadine 80 mg, seven on fexofenadine 120 mg, four on fexofenadine 180 mg, four on loratadine 10 mg and nine on promethazine 30 mg. The most frequently reported adverse events were drowsiness (18), headache (12) and nausea (4). There was a higher incidence of sedation and drowsiness reported among the promethazine group, however, all other reported adverse events such as nausea were evenly distributed among the treatment groups. Fourteen subjects took concomitant medication, the most frequently taken medication being paracetamol.

Discussion

Fexofenadine, at all three doses tested, was not significantly different from placebo in its effects on psychomotor performance and cognitive function. This is in contrast to the positive control, promethazine, which produced significant impairment of cognitive and psychomotor function as measured by CFF and CRT, for up to 12 h after drug intake. Loratadine included in this study as a negative internal control and as a comparator, is a nonsedating antihistamine and the present results are in agreement with previous studies [25, 26], demonstrating the lack of CNS effects following a 10 mg dose of this drug.

These present results are commensurate with the findings of Vermeeren *et al.* [27], in which they report a lack of CNS effects with fexofenadine at doses up to 240 mg on tests of choice reaction time and sustained attention. However, the authors also report an impairment on a critical tracking task with fexofenadine. This observed effect is not consistent as it appears following single daily doses of 120 mg and 240 mg but not after a divided dose of 120 mg twice daily.

Vermeeren *et al.* [27] also claim to have evidence of the activating effects of fexofenadine in that the administration of the higher divided dose reduced the mean SDLP on day 4 compared with placebo and that the combined effects of alcohol and the higher divided dose was significantly less impairing than that of alcohol alone. These present data from our study are contrary to the findings of Vermeeren *et al.* [27] as CFF thresholds, an objective measure of CNS arousal, show a non significant but dose related trend in the opposite direction to that needed to support notions of intrinsic activation. Present RRT scores also show no evidence of any dose related activation and thus, speculations regarding the possible activating properties of fexofenadine are not confirmed in this study.

Promethazine, the positive internal control, significantly reduced the CFF threshold by 2.5 Hz up to 9 h post dose and also increased the recognition reaction time by 40 ms at 3 and 6 h post dose when compared with placebo. These impairments are greater than those seen with 50 mg percentage of alcohol [28], which is the legal limit of alcohol in many countries.

Promethazine has previously been shown to cause a reduction in daytime behavioural activity for up to 6 h post dose [18]. Periods of very low behavioural activity are scored as sleep by the ACTION3 algorithm, so a reduction in activity is mirrored in an increase in 'sleep like' behaviour. In this, and our previous study [18], we have demonstrated that reduced behavioural activity, here expressed as an increase in daytime 'sleep like' behaviour, is reflected as a reduction in psychomotor performance and can thus be regarded as a measure of sedation.

There were no subjective reports of sedation as measured by LARS with any of the treatments including promethazine. Ratings of sedation were lower with promethazine than with placebo at 24 h post dose and given the overall pattern of results, this is likely to be a type I error.

It is of concern that a 30 mg dose of promethazine, reduced the CFF threshold by 2.5 Hz up to 12 h post dose and yet subjects reported themselves as being mentally alert throughout the 24 h test period. This implies that although subjects feel alert, they are objectively compromised as far as their ability to process information is concerned. Such discrepancies have important implications for the use of antihistamines in practice where patients are warned not to operate machinery or drive if they feel sedated [29].

The aim of this study was to investigate the effects of fexofenadine on a widely validated test battery known to be sensitive to the effects of psychoactive drugs on cognitive and psychomotor performance. The general conclusion that can be drawn from the present study is that there were no subjective or objective effects on psychomotor performance following the administration of fexofenadine. Fexofenadine at doses up to 180 mg appears to be free from disruptive effects on the central nervous system.

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References

1 Janssens MM, Howarth PH. The antihistamines of the nineties. *Clin Rev Allergy* 1993; **11**: 111–153.
2 Simons FER. The therapeutic index of newer H1-receptor antagonists. *Clin Exp Allergy* 1994; **24**: 707–723.
3 Mattila MJ, Matilla M, Konno K. Acute and sub acute actions on human performance and interactions with diazepam of temelastine and diphenhydramine. *Eur J Clin Pharmacol* 1986; **31**: 291–298.
4 Goetz DW, Jacobson MM, Apaliski SJ, Repperger DW, Martin ME. Objective antihistamine side effects are mitigated by evening dosing of hydroxyzine. *Ann Allergy* 1991; **67**: 448–454.
5 Brookhuis KA, de Vries G, de Waard D. Acute and subchronic effects of histamine (H1) receptor antagonist ebastine in 10, 20 and 30mg dose, and triprolidine 10mg on car driving performance. *Br J Clin Pharmacol* 1993; **36**: 67–70.
6 Seppala T, Savolainen K. Effects of astemizole on human psychomotor performance. *Curr Ther Res* 1982; **31**: 638–344.
7 Rombaut NE, Bhatti JZ, Alford C, Curran S, Hindmarch I. Psychopharmacological aspects of antihistamines. *Pharmacopsychoecologica* 1989; **2**: 21–30.

8 Meltzer EO. Comparative safety of H_1 antihistamines. *Ann Allergy* 1991; **67**: 625–633.

9 Simons FER. A new classification of H_1 receptor antagonists. *Allergy* 1995; **50**: 7–11.

10 Simons FER, Simons K. Peripheral H1 blockade effect of fexofenadine. *Ann Allergy, Asthma Immunol* 1997; **79**: 530–532.

11 Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy, Asthma Immunol* 1997; **79**: 443–532.

12 Parkin C, Kerr JS, Hindmarch I. The effects of practice on choice reaction time and critical flicker fusion threshold. *Human Psychopharmacol* 1997; **12**: 65–70.

13 Hindmarch I. A 1, 4 benzodiazepine, temazepam, its effect on some psychological limit of sleep and behaviour. *Arzneimittel Forschung (Drug Res)* 1975; **11**: 1836–1839.

14 Hindmarch I, Parrot AC. The effect of sub-chronic administration of three dose levels of 1,4-benzodiazepine derivative, clobazam, on subjective assessment of sleep and aspects of psychomotor performance the morning following night time medication. *Arzneimittel Forsch (Drug Res)* 1978; **28**: 2169–2172.

15 Hindmarch I, Subhan Z, Stoker MJ. The effects of zimeldine and amitriptyline on car driving and psychomotor performance. *Acta Psychiat Scand* 1983; **68**: 141–146.

16 Woodworth RS, Schlosberg H. *Experimental Psychology*, Methuen, London, 1958.

17 Hindmarch I, Gudgeon AC. The effects of clobazam and lorazepam on aspects of psychomotor performance and car handling ability. *Br J Clin Pharmacol* 1980; **10**: 145–150.

18 Stanley N. Actigraphy in psychopharmacology. In *Human Psychopharmacology, Methods and Measures, Vol 6* eds Hindmarch I, Stonier PD. John Wiley & Sons, Chichester., 1997: 67–93.

19 Stanley N, Hindmarch I. Actigraphy can measure antidepressant induced daytime sedation in healthy volunteers. *Human Psychopharmacol* 1997; **12**: 437–443.

20 Mullaney DJ, Kripke DF, Messin S. Wrist-actigraphic estimation of sleep time. *Sleep* 1980; **3**: 83–92.

21 Cole RJ, Kripke DF. Progress in automatic scoring by wrist actigraph. *Sleep Res* 1988; **19**: 331.

22 Sadeh A, Alster J, Urbach D, Lavie P. Actigraphically based automatic bedtime sleep-wake scoring: validity and clinical applications. *J Ambulatory Monitoring* 1989; **2**: 209–216.

23 Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep-wake identification. An empirical test of methodological issues. *Sleep* 1994; **17**: 201–207.

24 Cole RJ, Kripke DF, Greun W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist actigraphy. *Sleep* 1992; **15**: 461–469.

25 Mann KV, Crowe JP, Tietze K. Non sedating histamine receptor antagonists. *Clin Pharm* 1989; **8**: 331–344.

26 Belaich S, Bruttmann G, DeGreef H, *et al*. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Annals Allergy* 1990; **64**: 191–194.

27 Vermeeren A, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. *J Allergy Clin Immunol* 1997; **101**: 306–311.

28 Kerr JS, Dunmore C, Hindmarch I. The psychomotor and cognitive effects of a new antihistamine, mizolastine, compared to terfenadine, triprolidine and placebo in healthy volunteers. *Eur J Clin Pharmacol* 1994; **47**: 331–335.

29 Hindmarch I. It's all in the mind: Measuring somnolence and CNS drug side effects. *Human Psychopharmacol, Clin Exp* 1988; **13**: 385–387.