

An evaluation of the effects of high-dose fexofenadine on the central nervous system: a double-blind, placebo-controlled study in healthy volunteers

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Summary

Background As regards central nervous system (CNS) effects there are three types of antihistamines. Those that cross the blood-brain barrier and cause widespread impairment of cognitive and psychomotor function; those that cross into the brain and, although without much impairment at low clinical doses, have a dose-related relationship to impairment; and those that do not cross into the brain and therefore possess no intrinsic potential for impairing CNS function.

Objective To investigate the acute effects of fexofenadine (360 mg) on various aspects of cognitive and psychomotor function in comparison to placebo and promethazine (positive internal control), an antihistamine known to produce psychomotor and cognitive impairment.

Methods Fifteen healthy volunteers received fexofenadine 360 mg, promethazine 30 mg and placebo in a 3-way cross-over, double-blind study. For each treatment condition, subjects were required to perform a series of tests of cognitive function and psychomotor performance at baseline and 1, 3, 5 and 7 h post-dose. The test battery consisted of critical flicker fusion (CFF), choice reaction time (CRT), compensatory tracking task (CTT) and a subjective assessment of sedation (LARS).

Results Fexofenadine was not distinguishable from placebo in any of the objective and subjective tests for up to seven hours following drug administration. However, all measures were significantly impaired following the administration of promethazine, which confirms the sensitivity of the test battery for sedation. The effects of fexofenadine and placebo were not significantly different from one another, whereas promethazine caused an overall reduction in CFF thresholds when compared to placebo ($P < 0.05$). There was an overall significant increase (impairment) in recognition, motor and total reaction time ($P < 0.05$), and both the tracking accuracy and reaction time aspects of CTT were significantly impaired ($P < 0.05$) following the administration of promethazine. In contrast, the effects of fexofenadine could not be distinguished from the placebo condition. Subjective ratings of sedation were significantly higher with promethazine when compared to placebo ($P < 0.05$) and fexofenadine ($P < 0.05$).

Conclusions Fexofenadine at a dose of 360 mg is demonstrably 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.

The identification of an antihistamine (fexofenadine) devoid of central effects even at supra-clinical doses separates it from currently available first and second generation drugs with no objective evidence of CNS side-effects on cognition and psychomotor function, and highlights the need for the introduction of a third generation of non-sedative antihistamines.

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

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Introduction

The administration of second generation antihistamines within their therapeutic dose window has significantly reduced the incidence of adverse central nervous system (CNS) side-effects,

which are commonly reported following the use of traditional antihistamines [1–3]. However, evidence exists to support the notion that CNS side-effects do occur when, for example, doses in excess of 10 mg loratadine or 10 mg cetirizine are administered [4–6].

As a result of their wide-spread over-the-counter availability, it is extremely difficult to ensure that the recommended dose is not exceeded, either by accident or intent, especially in those patients who require higher doses to achieve optimal symptomatic relief from their allergy.

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As antihistamines are largely used by ambulant patients, it is essential that any treatment maintains the integrity of the cognitive system so as to protect the ambulant patient from drug-induced accidents, particularly in patients who may be driving motor vehicles and/or working in risk-prone domestic or industrial environments [7,8]. This concern becomes particularly important when it is considered that about 5% of drivers may take an antihistamine before driving [9]. In an investigation examining the incidence of drug use among individuals killed in road traffic accidents during a one year period, the adjusted culpability rate for drivers using antihistamines was 72% compared with 87% for those using alcohol and 97% for those using tranquillisers and antidepressants [10].

A survey of hayfever sufferers [11] found that more than half (54%) self-medicated with over-the-counter drugs and a third of these patients experienced drowsiness because of their therapies. Such findings highlight the need for the development of antihistamines, which are free of detrimental effects on cognitive and psychomotor function.

Fexofenadine is a selective histamine H_1 receptor antagonist which does not penetrate the blood brain barrier and thus allows an effective blockade of H_1 receptors in peripheral tissues without any central side-effects [12,13].

Following oral administration, fexofenadine is rapidly absorbed reaching maximum concentration within 1.5–2 h. Pharmacological effects occur within 2 h and are sustained over a period of 24 h [14].

In patients with seasonal allergic rhinitis, 2 weeks' treatment with fexofenadine 120 mg or 180 mg once daily, produced significantly greater improvements in total symptom scores than placebo [15]. Significant improvements were also evident following the administration of fexofenadine 180 mg in patients with chronic idiopathic urticaria [16] and, when compared with loratadine in patients with seasonal allergic rhinitis, fexofenadine produced significant improvements in quality of life to an extent considered to be clinically meaningful [17].

With regards to its CNS profile, the effects of fexofenadine are not distinguishable from placebo at daily doses of up to 240 mg as results from a number of placebo and verum-controlled studies have demonstrated [18–21]. Vermeeren and O'Hanlon [18] demonstrated that fexofenadine 120 mg or 240 mg, either as a single dose or in divided doses, did not have any significant effects on aspects of 'on-the-road' driving ability. Furthermore, Hindmarch et al. [19] showed that the effects of fexofenadine (80–180 mg) were not distinguishable from placebo on a number of tests including the critical flicker fusion task and choice reaction time test, whereas the positive control produced significant impairments on both tasks at up to 12 h postdose. Similarly, Nicholson et al. [20] have demonstrated that at a dose of 240 mg/day, fexofenadine is without any central activity on a number of measures including reaction time, tracking ability and vigilance tasks. Weiler et al. [21] demonstrated the lack of impairment with fexofenadine (60 mg) on various aspects of car driving whereas diphenhydramine (50 mg) was shown to cause significant impairments in cognitive and psychomotor performance. Similarly, Bower et al. [22] investigated the effects of fexofenadine (180 mg) on various tests of psychomotor function and concluded that the effects of fexofenadine were not distinguishable from placebo, whereas significant impairments were evident following the administration of diphenhydramine.

The aim of this study was to assess the central profile of a supra-clinical dose of fexofenadine (360 mg/day) in comparison to placebo 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 and sensitivity of the psychometrics to sedation.

Methods

Subjects

Fifteen healthy volunteers (5 male, 10 female), aged 18–50 years (mean age 34.5 years) with a mean weight of 69 kg, fulfilling the relevant inclusion/exclusion criteria, 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 were taking any concomitant medication (except oral contraceptives) likely to interfere with the study measures. The use of alcohol and nicotine were 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, 3-way cross-over 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 360 mg, promethazine 30 mg (as a verum) and placebo. All treatments were supplied in identical capsules and each single oral dose was taken at 09.30 h. Each treatment day was separated by a washout period of 6 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 [23].

On each of the test days, subjects attended the study centre where a breath alcohol reading was taken. 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, 3, 5 and 7 h post-dose. Assessments of sedation were made at each time-point prior to the performance of the objective test battery.

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 pre-medication nights.

Assessments

Critical Flicker Fusion threshold (CFF) The CFF task assesses CNS arousal and, more specifically, the ability to

discriminate discrete 'bits' of sensory information [24,25]. Subjects were required to discriminate flicker from fusion, and vice versa, in a set of four light emitting diodes arranged in a one centimetre square. The diodes are held in foveal fixation when viewed at a distance of one metre. Individual thresholds are determined by the psychophysical method of limits on four ascending and four descending scales [26]. The means of these four ascending and four descending presentations gives the threshold frequency in hertz (Hz). CFF has been shown to be sensitive to a variety of psychoactive compounds [19,27]. A lowering of the CFF threshold is indicative of a reduction in the overall integrity of the CNS [28].

Choice Reaction Time (CRT) CRT is used as a valid, reliable and sensitive measure [29] of drug-induced changes in psychomotor speed [25,28]. From a central starting position subjects were required to extinguish 1 of the 6 red lights, illuminated at random, by touching the appropriate response button. Using this arrangement it was possible to measure 3 components of reaction time: the total reaction time (TRT) from stimulus onset to completion of response, the movement time (MRT) measures the time to move the finger between the start and the response buttons, and the processing or recognition reaction time (RRT), obtained from subtracting MRT from TRT. The mean reaction time for 50 stimulus presentations was recorded.

Compensatory Tracking Task (CTT) This sensitive, valid and reliable interactive task of psychomotor function entails tracking a moving arrow on a visual display unit (VDU) screen using a mouse [29]. The response measure (RMS) is the mean deviation from the track programme over the one minute trial period, with lower scores indicative of more accurate tracking. A peripheral awareness task (PRT) was included in which the subjects were required to respond to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking task. The mean reaction time to these stimuli over the trial period was taken as the response measure for this component of the divided attention task.

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 [30]. The higher the score (in millimetres), the less alert and more tired and drowsy the subject feels. This scale has been shown to correlate well with various objective measures of arousal/sedation [31] and has been used extensively to detect subjective sedation with many different classes of compounds [30,32].

Analysis

For all primary and secondary variables (CFF, CRT, CTT and LARS), the change from baseline (time 0) was used in the analyses.

The measurements to assess cognitive and psychomotor effects of the three treatments were analysed using an analysis of variance (anova) model with factors for treatment and time, as a repeated measure, if applicable. In the event of a significant

treatment effect, an adjusted least squares means procedure was used for pair-wise treatment comparisons. All the statistical tests were performed two-tailed at the 5% level of significance (Bonferroni adjusted).

Results

Of the 15 subjects enrolled onto this trial, 14 volunteers completed the study. One subject withdrew from the trial for reasons unrelated to any aspect of the study. The mean scores ($\pm$ SEM) for all treatments on all psychomotor and cognitive tests are presented in Table 1.

There was a significant main effect of treatment on CFF threshold ($F(2, 132) = 12.89$, $P < 0.0001$) and time of testing ($F(3, 56.9) = 4.95$, $P < 0.005$). The treatment-time interaction was also significant ($F(6, 56.9) = 4.26$, $P < 0.005$). The results for promethazine 30 mg showed a very different pattern from the other two treatment regimens, with a marked decrease in the CFF threshold for up to seven hours post-dose. The comparison of the treatment means showed a significant overall difference between promethazine and placebo (mean difference of 1.63 Hz with 95% confidence limits (CL) -2.49 , -0.76). There was also an overall significant difference between promethazine and fexofenadine (mean difference of 1.42 Hz with 95% CL -2.28 , -0.55) (Fig. 1).

The analysis of the results for the RRT showed a significant main effect of treatment ($F(2, 146) = 13.30$, $P < 0.001$) and time of testing ($F(3, 23.1) = 3.08$, $P < 0.05$), with an increase in reaction time from 1–7 h following the administration of promethazine (Fig. 2), although the treatment-time interaction was not significant ($F(6, 23.1) = 1.45$, $P = 0.238$). The comparison of the treatment means demonstrated a significant difference between promethazine and placebo (mean difference of 48.97 ms with 95% CL 19.71, 78.23). Similarly, promethazine was significantly different from fexofenadine 360 mg when the treatment means were compared (mean difference of 55.99 ms with 95% CL 26.74, 85.23).

An overall significant treatment effect was evident for the MRT ($F(2, 146) = 3.41$, $P < 0.05$) with promethazine causing significant increases in MRT at every time-point. There was

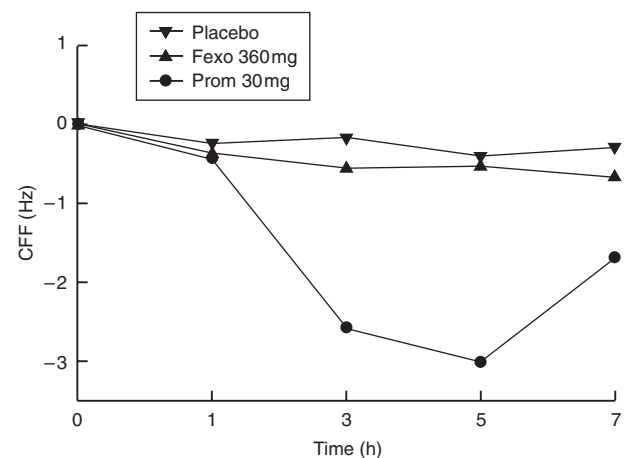


Fig. 1. Critical flicker fusion thresholds (Hz). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine 30 mg (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

Table 1. Mean Scores (+ SEM) for all psychomotor and cognitive tests with all treatments

	Drug	- 1 h	+ 1 h	+ 3 h	+ 5 h	+ 7 h
CFF (Hz)	Placebo	32.09 (1.23)	31.83 (1.35)	31.93 (1.40)	31.69 (1.26)	31.80 (1.43)
	Fexo 360 mg	32.27 (1.32)	31.93 (1.22)	31.76 (1.29)	31.82 (1.23)	31.66 (1.27)
	Prom 30 mg	32.32 (1.36)	31.93 (1.24)	29.75 (1.41)	29.32 (1.36)	30.66 (1.40)
RRT (ms)	Placebo	343.82 (11.04)	345.19 (12.87)	353.96 (12.27)	359.59 (14.10)	344.58 (10.34)
	Fexo 360 mg	352.66 (11.21)	357.80 (10.49)	353.46 (12.06)	350.98 (11.59)	346.53 (11.16)
	Prom 30 mg	337.42 (8.65)	364.93 (14.13)	407.40 (21.58)	408.30 (25.87)	392.99 (20.71)
MRT (ms)	Placebo	260.51 (15.93)	255.90 (17.86)	251.19 (16.34)	245.70 (17.32)	257.01 (14.29)
	Fexo 360 mg	254.99 (14.08)	254.68 (17.49)	256.32 (17.46)	257.47 (17.40)	248.06 (13.57)
	Prom 30 mg	251.07 (19.04)	268.21 (16.84)	275.86 (13.26)	268.29 (18.05)	262.71 (15.38)
TRT (ms)	Placebo	604.33 (18.88)	601.10 (17.37)	605.15 (14.33)	605.29 (17.74)	601.59 (16.89)
	Fexo 360 mg	607.65 (14.49)	612.48 (16.58)	609.78 (17.54)	608.45 (18.90)	594.58 (14.11)
	Prom 30 mg	588.49 (19.16)	633.13 (10.92)	683.26 (22.56)	676.60 (32.73)	655.71 (25.02)
CTT-ERR (pixels)	Placebo	22.51 (3.79)	21.91 (2.34)	22.37 (2.42)	23.09 (2.56)	23.85 (3.32)
	Fexo 360 mg	17.05 (0.90)	18.37 (1.42)	22.32 (2.84)	24.41 (2.50)	20.38 (2.17)
	Prom 30 mg	19.25 (1.91)	26.55 (2.92)	52.93 (8.39)	55.96 (6.78)	41.88 (7.25)
CTT-RT (ms)	Placebo	574.49 (23.23)	621.90 (34.67)	616.41 (29.29)	658.91 (43.32)	640.58 (36.27)
	Fexo 360 mg	547.41 (20.89)	589.74 (24.40)	609.25 (26.53)	674.46 (38.73)	613.77 (28.48)
	Prom 30 mg	564.67 (22.92)	665.64 (45.80)	852.33 (75.74)	914.37 (78.40)	787.65 (78.71)
LARS (mm)	Placebo	49.68 (2.55)	53.46 (2.30)	52.85 (1.07)	48.62 (2.06)	51.33 (2.29)
	Fexo 360 mg	53.46 (2.26)	50.28 (2.53)	52.40 (2.69)	53.22 (1.99)	53.19 (2.11)
	Prom 30 mg	51.96 (1.76)	54.99 (2.79)	66.47 (3.91)	62.99 (3.65)	58.89 (4.26)

CFF, critical flicker fusion; CTT-ERR, compensatory tracking task-accuracy; CTT-RT, compensatory tracking task-recognition time; Fexo, fexofenadine; LARS, line analogue rating scales; MRT, movement reaction time; Prom, promethazine; RRT, recognition reaction time; TRT, total reaction time.

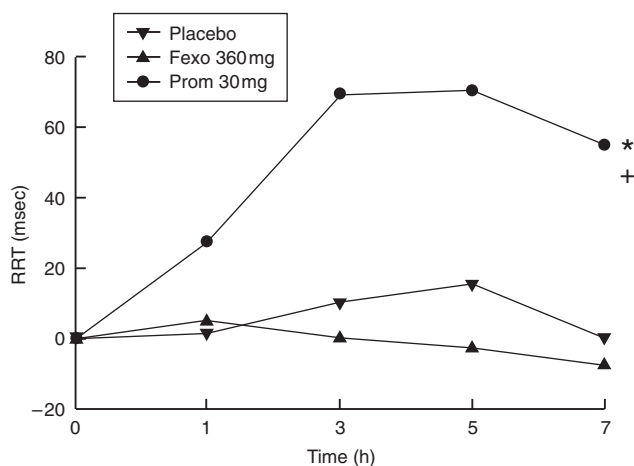


Fig. 2. Recognition reaction time (ms). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

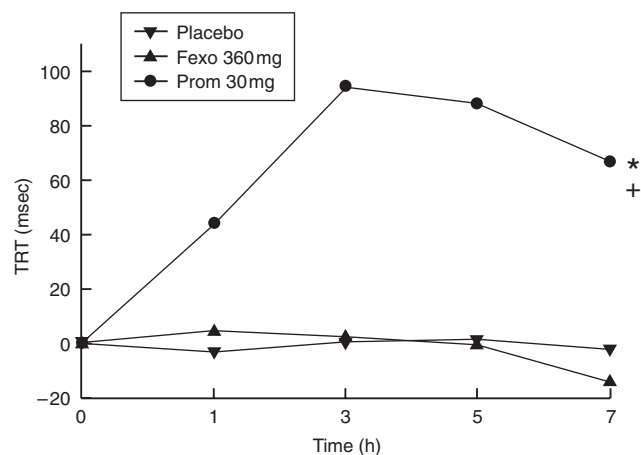


Fig. 3. Total reaction time (ms). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine 30 mg (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

no significant effect of time ($F(3, 10.5) = 0.17$, $P = 0.91$] or treatment-time interaction ($F(6, 10.5) = 0.99$, $P = 0.48$). Comparison of the treatment means revealed a significant difference between promethazine and placebo (mean difference of 25.77 ms with 95% CL 0.70, 50.84). The results for TRT mirrored the observed results for both the RRT and MRT, in that a significant treatment effect was evident [$F(2, 146) = 15.31$, $P < 0.0001$] with promethazine causing an overall increase in total reaction time at all time-points (Fig. 3). There were no significant effects of time ($F(3, 19.3) = 2.45$, $P = 0.095$) or treatment-time interaction ($F(6, 19.3) = 1.31$, $P = 0.298$). Comparison of the treatment means revealed a significant

difference between promethazine and placebo (mean difference of 74.74 ms with 95% CL 36.30, 113.17). Similarly, the effects of promethazine were significantly different to fexofenadine (mean difference of 74.17 ms with 95% CL 35.76, 112.59).

The analysis of variance of the change in tracking ability from baseline revealed a significant treatment effect at 0.01% level ($F(2, 146) = 19.13$, $P < 0.0001$) and time of testing ($F(3, 11.3) = 11.03$, $P < 0.01$). The treatment-time interaction was also significant ($F(6, 11.3) = 6.37$, $P < 0.005$). The results for promethazine 30 mg showed a very different pattern from the other treatment regimens, with a marked decrease in tracking ability (Fig. 4). The comparison of the treatment means showed

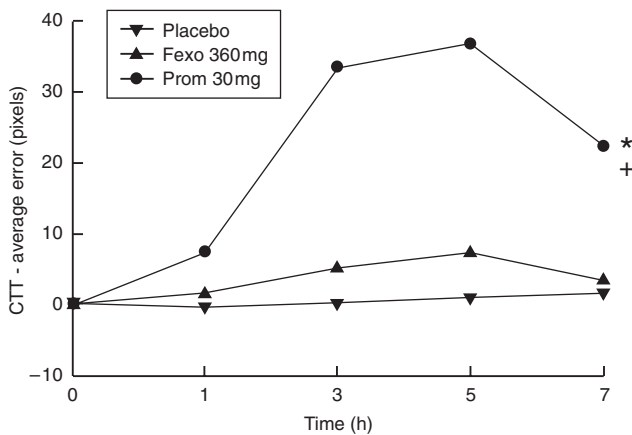


Fig. 4. Compensatory tracking task – tracking ability (pixels). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine 30 mg (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

that overall, promethazine scores were significantly different from placebo (mean difference of 24.79 pixels with 95% CL 14.15, 35.42) and fexofenadine 360 mg (mean difference of 20.74 pixels with 95% CL 10.11, 31.36).

Significant treatment effects were evident on the reaction time component of the CTT ($F(2, 146) = 14.92$, $P < 0.0001$) as well as significant time-effects ($F(3, 22.8) = 9.60$, $P < 0.001$). The treatment–time interaction was also significant ($F(6, 22.8) = 3.41$, $P < 0.05$). The results for promethazine were significantly different from the other two treatment conditions, with promethazine causing a consistent increase in reaction time for up to seven hours post-dose (Fig. 5). Comparison of the treatment means revealed the difference to be due to an overall significant increase in reaction time to the peripheral stimulus following promethazine administration when compared to placebo (mean difference of 180.38 ms with 95% CL 89.78, 270.98) and fexofenadine 360 mg (mean difference of 165.23 ms with 95% CL 74.68, 255.79).

A factor analysis was carried out on the LARS data to obtain factors and their loading to allow the different treatments to be differentiated. Factor 1 contained alert (loading: 0.99), clumsy (loading: 0.72), drowsy (loading: -0.56), energetic (loading: -0.68) and tired (loading: 0.86). Factor 2 contained depressed (loading: 0.95), happy (loading: 0.55) and sad (loading: 0.94). Analysis of variance using factor 1 as the dependent variable demonstrated a significant treatment effect ($F(2, 152) = 5.87$, $P < 0.01$). There were no significant effects of time ($F(3, 25.6) = 1.79$, $P = 0.175$) or treatment–time interaction ($F(6, 25.6) = 2.20$, $P = 0.076$).

There were no significant effects of treatment, time or treatment–time interaction when using factor 2 as the dependent variable.

Comparison of the treatment means using factor 1 as the dependent variable revealed an overall increase in sedation scores following promethazine administration when compared to placebo (mean difference of 28.39 mm, $P = 0.055$) and fexofenadine 360 mg (mean difference of 38.87 mm ($P < 0.01$)) (Fig. 6).

Analysis of variance using factor 1 as the dependent variable at one hour post-dose did not reveal a significant treatment effect. However, a similar analysis at 3 h post-dose showed a

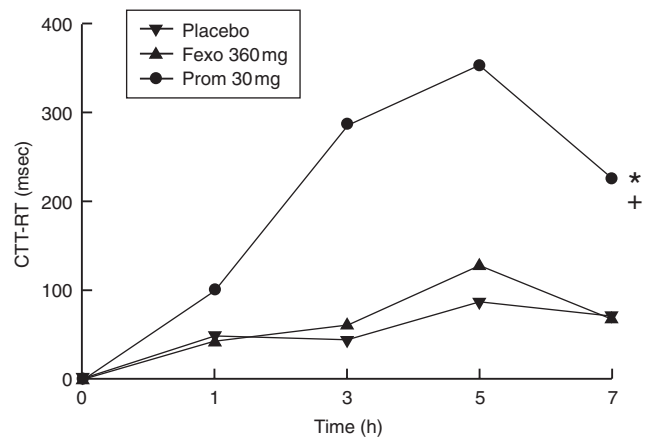


Fig. 5. Compensatory tracking task – reaction time (ms). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine 30 mg (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

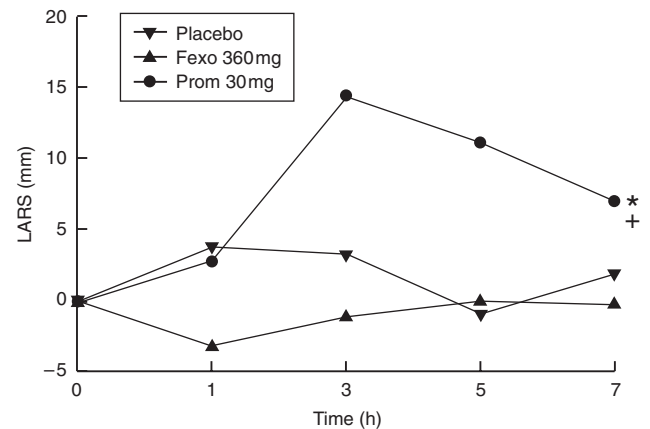


Fig. 6. Line analogue rating scale for sedation (mm). Mean change from baseline following the administration of fexofenadine 360 mg (filled triangle), promethazine (filled circle) and placebo (filled wedge). * $P < 0.05$ when compared to placebo. + $P < 0.05$ when compared to fexofenadine.

significant treatment effect ($F(2, 24) = 7.85$, $P < 0.01$), with higher scores at 3 h post-dose following the administration of promethazine when compared to both placebo ($P < 0.05$) and fexofenadine ($P < 0.01$).

Similarly, performance of an anova at the 5 h post-dose revealed a significant treatment effect ($F(2, 24) = 8.77$, $P < 0.01$), with an increase in sedation scores following the administration of promethazine in comparison to both placebo ($P < 0.01$) and fexofenadine ($P < 0.01$). The effects of promethazine failed to reach significance at 7 h post-drug administration.

There were no reports of serious adverse events and no subject withdrew due to drug intolerance.

Discussion

Fexofenadine at a daily dose of 360 mg was not significantly different from placebo in its effects on psychomotor performance and cognitive function. In contrast, promethazine

produced significant impairments of CNS function as measured by CFF, CRT, CTT and LARS for up to 7 h after drug intake. These present results are commensurate with the findings of Nicholson et al. [20], in which they report a lack of CNS effects with fexofenadine at doses up to 240 mg/day on tests of reaction time, vigilance and sustained attention and are also in agreement with findings of Vermeeren and O'Hanlon [18] in which fexofenadine 120 mg or 240 mg, either as a single dose or as divided doses, did not have any significant impairing effects on aspects of 'on-the-road' driving ability. Similarly, Hindmarch et al. [19] showed that the effects of fexofenadine (80–180 mg) were not distinguishable from placebo on a number of tests including the CFF and CRT tasks, whereas the positive control produced significant impairments on both tasks at up to 12 h post-dose.

Promethazine, the positive internal control, significantly reduced the CFF threshold by 2.5 Hz up to 3 and 5 h post-dose and also increased the recognition, motor and total reaction time by 40 ms for up to 7 h post-dose when compared to placebo. Tracking ability was significantly impaired following promethazine administration and this impairment was sustained throughout the day. Peripheral reaction time was also significantly impaired following the administration of promethazine at every time-point. These impairments with promethazine are greater than those seen with 50 mg percentage blood alcohol concentration [33], which is the legal limit of alcohol in many countries.

Subjective reports of sedation were in agreement with the observed objective findings, with subjects reporting significantly higher scores of sedation with promethazine when compared to the other two treatment regimens.

The lack of objectively and subjectively measured CNS effects with fexofenadine at doses up to 360 mg/day suggests that its CNS profile differs from that of the second generation antihistamines (e.g. cetirizine, loratadine). It is claimed that these second generation antihistamines are non-sedating [34–36] due to their inability to cross the blood brain barrier. However, if no penetration to the CNS occurs, then drugs must necessarily be free of sedation regardless of the dose administered and so show no significant impairments on any tests of cognitive and psychomotor function. Indeed, the lack of objective evidence of impairment with lower doses (10 mg) of loratadine or cetirizine, for example [13,35–37], may be due to the fact that the concentrations achieved in the CNS are below those required to cause detrimental effects on cognitive and psychomotor abilities. Both loratadine and cetirizine cause psychomotor and cognitive impairment when taken at doses greater than 10 mg, which many patients need for symptomatic control of allergic conditions – particularly chronic idiopathic urticaria. Such drugs cannot be referred to as 'non-sedating' as this does not take into account the impairments which occur with the administration of higher doses. It would be better to regard them as possessing a 'window' of non-impairment, and according to the classification proposed by Howarth [38], cetirizine and loratadine are classified as category 2b antihistamines, implying that some sedation may occur when higher doses, demanded by an individual patient's clinical condition, are administered.

This study clearly demonstrates that there is no evidence of sedation following fexofenadine 360 mg; a dose up to three times that commonly used for seasonal allergic rhinitis and double that used for chronic idiopathic urticaria.

Such a lack of sedation is obviously, and statistically, significantly distinct from the effects of promethazine, but also quite different from the dose-related impairment demonstrated by loratadine and cetirizine [32]. Such a differentiation of demonstrable CNS effects between different antihistamines, leads to the conclusion that a classification of third generation of intrinsically non-sedating antihistamines, featuring fexofenadine, would be warranted.

Studies of placebo and verum-controlled studies using cross-over designs have shown significant sedation on a variety of psychometric tests at 20 and 40 mg loratadine [4–6] and 20 mg cetirizine [39]. The argument relating to crossing the blood brain barrier [40] implies that the molecule itself is not able to penetrate the vascular system and so not enter the CNS and cause sedation. Clearly, as these drugs penetrate the CNS, they cannot be regarded as non-sedative if the totality of dose regimens encountered in common clinical practice is to be taken into account.

The aim of this study was to investigate the effects of a supra-clinical dose 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 a daily dose of 360 mg appears to be free from disruptive effects on the central nervous system.

The identification of an antihistamine devoid of central side-effects even at supra-clinical doses generates the need for the introduction of a third generation of non-sedative antihistamines.

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