SHORT ARTICLE

Effects of Fexofenadine, Cetirizine and Diphenhydramine on Psychomotor Performance in Adult Healthy Volunteer

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Abstract

The present study was conducted to assess and compare the cognitive and psychomotor effects of fexofenadine, a newer second generation antihistamine with cetirizine, diphenhydramine and placebo in 10 healthy adult volunteers in a double blind, randomized cross over study. Following single dose of each drug, the volunteers were subjected to perform a series of tests of cognitive and psychomotor performance at 1, 3 and 6 hours post dose. The test battery consisted of both subjective and objective tests which were further grouped into instrumental and non-instrumental. Instrumental tests included – Simple reaction time (SRT), Multiple Choice ReactionTime Task (MCRT) and Critical Flicker Fusion frequency threshold (CFFT). The tests used in the non instrumental group were- Stanford Sleepiness Scale (SSS), Digit Cancellation Task (DCT), Digit Symbol Substitution Task (DSST) and mental arithmetic tests. Fexofenadine at doses of 120 mg was not significantly different from placebo in any of the tests used. However, as expected for a verum, all the measures were significantly disrupted by diphenhydramine 25 mg upto 6 hours post dose. Cetirizine 10 mg has produced significant subjective somnolence at 3 & 6 hours post dose but without any impairment of objective tests. These results allow the conclusion that fexofenadine at its recommended therapeutic dose of 120 mg is free from impairment effects on aspects of psychomotor function and hence can be used safely. Cetirizine is mildly sedating though it did not impair any of the objective psychometric tests.

Key Words

Antihistamines, Fexofenadine, Sedation, Psychomotor performance

Introduction

Antihistamines are widely used for allergic disorders. First generation H_1receptor antagonists, though effective, have the disadvantage of causing CNS depressant effects such as drowsiness and impairment of cognitive and psychomotor skills (1). Second generation H_1receptor antagonists, being more lipophobic are nonsedating and do not impair the psychomotor performance (2). However, all non sedating antihistamines are not similar and do cause sedation or psychomotor impairment to some extent. Use of second generation antihistamines such as terfenadine and astemizole has been associated with serious drug interactions alongwith macrolide antibiotics and anti-fungal agents. This has been shown to result in QT interval prolongation on ECG and rare incidence of life threatening ventricular arrhythmias has been reported (3). Another second-generation antihistamine cetirizine is reported to produce drowsiness (4). Fexofenadine, a newer second-generation antihistamine an active metabolite of terfenadine and is a selective H_1 receptor antagonist. It offers nearly all the advantages of an ideal antihistamine including high clinical efficacy, lack of CNS and anticholinergic side effects, once a day administration and lack of propensity to cause QT interval prolongation or increased risk of ventricular arrhythmias (5). It is claimed to be non-sedating and having no psychomotor impairing effect (6-8).

The aim of the present study was to assess the effect of fexofenadine on psychomotor performance and to compare with cetirizine, another very commonly used second generation antihistamine in our setup. Diphenhydramine was taken as the positive control.

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Material and Methods

Ten normal healthy adult volunteers aged 21 to 39 years (27.4+2.39) fulfilling the relevant inclusion criteria were entered into the study. Associated disease or concomitant medications were ruled out. The use of alcohol or any beverage containing stimulants was forbidden from 18 hours on the evening proceeding the day of experiment. Smoking was prohibited on test days.The study was a randomized, double blind, cross over placebo and verum- controlled study in which subjects acted as their own controls. It was conducted in PG Deptt. of Pharmacology and Therapeutics, GMC, Jammu. The drugs under investigation were fexofenadin HCL (120 mg) from Hoechst Marion Roussel, diphenhydramine (25 mg) from Parke Davis (India) Ltd., cetirizine (10 mg) from Cipla Ltd. and placebo (Glucose D). All the study medications were supplied in identical capsules and each single oral dose was taken at 0930 hours with a wash over period of one week between each study session. The protocol was approved by the institutional ethics committee following informed consent and medical history, all the subjects underwent a medical examination (including haematology, urine/stool analysis, biochemistry and ophthalmic check-up for colour blindness). Subjects included in study were familiarized with the study procedures and were subjected to two pre study practice sessions not more than one week apart to remove any influence of learning effects on the study (9). On each of the test days, pre drug baseline recordings were made on each of the psychometric tests at 0900 hrs after which drugs were administered at 0930 hrs. and further testing was carried out at 1,3 and 6 hours post dose. Assessments of sedation using subjective rating scales were made at each time point prior to the performance of the psychometric test battery. **Instrumental tests** like simple reaction time task-SRT (10), multiple choice reaction time-MCRT (9), critical flicker fusion frequency threshold-CFFT (12) and **Non-instrumental tests** like stanford sleepiness scale-SSS (12,13) as a *subjective test* as well as digit cancellation test-DCT (14), digit symbol substitution test-DSST (15) and mental arithmetic tests (15), as *objective tests* were used in the present study.

Statistical Analysis

The change in performance relative to the basal value at different time intervals has been analysed by paired 't' test for each drug. $P<0.05$ was considered significant. All the three study drugs were compared along with the placebo using the analysis of variance.

Results

The results are shown in (Table 1). For SRT, analysis of the results showed no significant change in post drug scores at any of the trial periods with fexofenadine whereas the effect of diphenhydramine was statistically significant at 1 hour ($P<0.001$), 3 hrs. ($P<0.01$) and 6 hrs. ($P< 0.05$). Cetirizine also did not produce any significant change in SRT scores. The results of MCRT showed that a significant treatment effect was evident with diphenhydramine causing an overall increase in the error index. Diphenhydramine caused an increase in mean error index at 1 hour ($P<0.05$), reached to maximum at 3 hours ($P<0.01$) and the index started declining at 6 hours post dose, but still significant statistically ($P<0.01$). Fexofenadine and cetirizine did not produce any significant change in the mean error index and the effect of both these drugs was found to be statistically similar when compared with the placebo.

Analysis of the results for CFFT showed that diphenhydramine had significant greater reduction than all other treatments at 1 hr, 3 hrs and 6 hrs with peak effect at 3 hrs. The significant effects of diphenhydramine used as internal control validated the sensitivity of CFFT as a measure of CNS impairment. There was no noticeable difference between the post dose Critical Flicker Fusion scores following fexofenadine, cetirizine and those found with placebo. Diphenhydramine produced highly significant results with peak effect at 3hrs on SSS. The effect with cetirizine on the scale though insignificant, started at 1 hour, became statistically significant at 3 hours and persisted upto 6 hours. Fexofenadine and placebo did not produce any significant effect on SSS at any of the trial periods as followed upto 6 hours.

Fexofenadine, cetirizine and placebo did not produce any significant change in the number of digits correctly substituted whereas with diphenhydramine the results were statistically significant on performing DSST. No significant change was observed in number of digits cancelled in DCT after giving fexofenadine, cetirizine and placebo as studied upto 6 hours. On the contrary, with diphenhydramine there was a significant decrease in the number of digits cancelled with maximum effect at 3 hrs.($P<0.001$).No change was observed either in the number of sums attempted or number of errors made in arithmetic tasks after administration of fexofenadine, cetirizine and placebo as investigated upto six hours.

Table.1 Effects of fexofenadine,Cetirizine, Diphenhydramine &Placebo on different psychomatric tests & their comparison.

S.No	Test	Drugs(S)	Baseline value (Mean (±SEM)	Post drug (Mean ± SEM) +1hr	+3hrs	+6hrs
1.	SRT(Millisec)	FEX	504.4±17.57	504.4±16.94	504.4±16.25	504.4±16.71
		CET	501.9±27.11	503.9±27.31 ¶	501.9±27.21 ¶	504.9±26.25 ¶
		DPH	503.8±18.93	589.2±20.55**	608.3±25.32*	589.10±27.54**
		PLA	503.2±19.67	504.2±18.88	504.2±19.12	504.2±18.73
2.	+MCRT	FEX	137.2±7.20	137.4±7.22	137.1±7.15	137.1±7.19
	(Error Index)	CET	136..2±6.89	138.00±6.50 ¶	136.6±6.78 ¶	136.5±6.84 ¶
		DPH	135.2±6.83	177.6±17.32**	206.7±18.98**	178.00±16.75
		PLA	135.2±7.21	137.2±6.56	134.9±7.28	135.4±7.18
3.	CFFT	FEX	38.02±0.49	38.02±0.49	38.02±0.49	37.99±0.48
	(Hertz)	CET	38.74±0.56	38.74±0.56 ¶	38.75±0.55 ¶	38.7±0.56 ¶
		DPH	37.95±0.43	36.70±0.50*	35.890.51*	36.77±0.44*
		PLA	38.67±0.45	38.65±0.43	38.66±0.45	38.70±0.47
4.	DSST	FEX	84.5±4.87	84.3±4.87	84.3±4.85	84.20±4.86
		CET	81.8±3.71	82.2±3.64 ¶	82.2±3.87 ¶	82.1±3.70 ¶
		DPH	81.6±3.83	68.6±2.75**	66.6±2.33***	68.40±2.73***
		PLA	79.3±3.60	79.3±3.48	79.0±3.58	79.3±3.55
5.	DCT (C/Min)	FEX	47.5±0.41	47.5±0.47	47.5±0.45	47.60±0.42
		CET	47.8±0.97	47.4±0.07 ¶	47.3±0.94 ¶	47.5±0.99 ¶
		DPH	47.8±0.86	42.7±0.64***	40.8±0.46***	42.70±0.76***
		PLA	47.9±0.92	47.6±0.94	47.9±0.83	47.9±0.92
6.	ADD(A/W)	FEX	15.6 ± 1.14 0.7 ± 0.20	15.8 ± 1.19 0.50 ± 0.15	16.00 ± 1.20 0.70 ± 0.20	15.80 ± 1.15 0.60 ± 0.20
		CET	15.3 ± 1.02 0.6 ± 0.20	15.5 ± 0.99 ¶ 0.4 ± 0.15	15.5 ± 0.99 ¶ 0.6 ± 0.25	15.4 ± 0.98 ¶ 0.4 ± 0.20
		DPH	15.6 ± 0.91 0.7 ± 0.20	12.00 ± 0.62** 1.3 ± 0.28	11.1 ± 0.49 107 ± 0.42	12.2 ± 0.59*** 1.4 ± 0.32
		PLA	15.7 ± 0.97 0.7 ± 0.20	15.7 ± 1.03 0.4 ± 0.15	15.6 ± 1.06 0.7 ± 0.20	15.8 ± 0.94 0.94 ± 0.20
7.	SUBT (A/W)	FEX	17.5 ± 1.35 0.9 ± 0.22	17.7 ± 1.33 0.6 ± 0.21	17.6 ± 1.29 0.8 ± 0.27	17.60 ± 1.40 0.9 ± 0.20
		CET	17.5 ± 1.44 0.9 ± 0.22	17.5 ± 1.45 ¶ 0.7 ± 0.21	17.5 ± 1.45 ¶ 0.8 ± 0.18	17.5 ± 1.46 ¶ 0.6 ± 0.20
		DPH	17.5 ± 17.31 0.99 ± 0.22	12.4 ± 1.07*** 1.8 ± 0.23	11.9 ± 0.88*** 2.1 ± 0.26***	12.6 ± 1.06*** 1.9 ± 0.29
		PLA	17.5 ± 1.38 0.9 ± 0.26	17.7 ± 1.40 0.9 ± 0.26	17.7 ± 1.53 0.9 ± 0.38	17.6 ± 1.32 0.9 ± 0.26
8.	SSS	FEX	1.1±0.09	1.3±0.14	1.4±0.15	1.30±0.14
		CET	1.00±0.00	1.20±0.12	1.6±0.15** ¶	1.5±0.15* ¶
		DPH	1.00±0.00	1.4±0.12*	2.2±0.18***	2.20±0.27**
		PLA	1.00±0.00	1.2±0.12	1.2±0.12	1.4±0.20

FEX: Fexofenadine, CET: Cetirizine, DPH: Diphenhydramine, PLA: PlaceboC/Min : Digits cancelled/Minute,A/W: Attempted/Wrong Sums. Paired t-tests * = p <0.05** = p <0.01*** = p<0.001 in comparison to basal value.¶ Computed F ratio >2.86 was considered significant.

Diphenhydramine led to statistically significant decrease in the number of sums attempted. As far as number of errors is concerned, the effect was significant at 3 and 6 hrs. in case of addition sums while in case of subtraction sums, there was significant increase in the number of errors made at all the times of trial period.

When all the three study drugs were compared with the placebo, using the analysis of variance, the computed

F-ratio was found to be more than the table F-ratio (2.86). This indicates that the results are statistically significant and significance is because of higher mean values of diphenhydramine (Table 1).

Discussion

Conventional H_1 receptor antagonists ,first generation antihistamines and some of the second generation antihistamines are not free from limitations. This led to the discovery of fexofenadine, a metabolite of terfenadine, with similar clinical efficacy , nonsedating properties and it is not associated with serious arrhythmias (16,17).

In the present study old as well as newer antihistamines were employed.Overall, the scores obtained on the psychometric test battery following diphenhydramine were impaired significantly upto 6 hours post dose. This shows the sensitivity of the current set of tests to untoward CNS activity. In contrast fexofenadine at doses 120 mg. was not significantly different from the placebo in its effects on psychomotor performance.

For measuring subjective symptoms of sleepiness, SSS was employed in the present study. Diphenhydramine as expected produced somnolence on SSS to a great extent. In our study, fexofenadine has been found to be non-sedating because it did not affect SSS at any time. This finding is in conformity with the earlier results (18,19). The sedative effect of cetirizine has been widely studied but the reports have been conflicting. While studying the effect of cetirizine 10 mg in the present study, it was observed that it produced a significant degree of somnolence. These findings are consistent and similar to those reported by other researchers (19). In fact, US FDA has classified cetirizine into sedating antihistaminics (20). However, other workers have not reported somnolence more than the placebo with cetirizine (21,22). The difference in the sedating potential of cetirizine may be due to inter individual variation (22).

There has been a lack of correlation between subjective & objective effects of H_1 receptor antagonists. Objective impairment has been found in asymptomatic subjects (23) and conversely in other studies, although subjects have complained of somnolence, no objective impairment has been found (24). This phenomenon has been observed with cetirizine in the present study as well where cetirizine has produced significant subjective somnolence without any impairment of objective tests.

One of the most popular measures of sensorimotor performance is reaction time to a critical stimulus. In the present study, fexofenadine did not produce any significant effect on reaction time of both types and these findings are in similarity with earlier report (7). Cetirizine produced no significant change in simple and multiple-choice reaction time and these results are consistent with the earlier literature (21). The CFFT is very sensitive test of the changes in the capacity of an individual to process information and one of the basic tests used in the psychometric testing because the task of information processing is essential to all daily activities. In this test fexofenadine did not significantly impair performance in our study. It shows that this drug can be given for a longer period of time without affecting the daily activity of the individual. Hindmarch (1998) found similar results in his study on fexofenadine (25). Cetirizine also did not impair CFFT in the present study as reported by other workers as well (26). However, diphenhydramine produced significant change in this test at different time intervals as expected.

The DSST, a simple pencil and paper test is reported to measure integration speed and accuracy of visual and fine motor skills. In the present study neither fexofenadine nor cetirizine significantly altered the number of digits correctly substituted from that of the pre drug values. Similar findings have also been reported by Barbara and co-workers with fexofenadine 120, 180 or 240 mg. OD (27). However, diphenhydramine significantly impaired this test. Gengo *et.al* also found that diphenhydramine acutely causes more compromise in cognition than either placebo, cetirizine or terfenadine (28). However, Gengo *et.al.* found significant difference in performance on D.S.S.T scores at 6 and 8 hours after 20 mg dose of cetirizine (21).

Fexofenadine and cetirizine have not shown any impairing effect on remaining objective tests used in the present study i.e. DCT and arithmetic task. The scan of literature has not revealed any report regarding the effects of these drugs on these tests and hence our findings could not be compared. This study again shows that fexofenadine and cetirizine do not interfere with the concentration and fine motor skills which may be beneficial in driving, class room activities and for the pilots. However, diphenhydramine in the study greatly impaired performance by affecting DCT and arithmetic tasks as reported in the literature.Fexofenadine, like its precursor terfenadine, does

not penetrate the blood brain barrier to a clinically important extent and selectively binds to peripheral H_1 receptors (5,6).

Conclusion

It is quite evident from the present study that fexofenadine is totally nonsedating and free of disruptive effects on psychomotor performance. Fexofenadine is a promising drug, and is also effective for the treatment of allergy specially in those involved in skilled activity.

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