



Comparative Effect of Newer Antihistamines on Psychomotor Functions in Indian Population

Vivek K. David, Dinesh K. Badyal, Ashish Varghese*, Emy Alexander**

Abstract

The purpose of the present study was to comparatively evaluate the effect of newer antihistamines on psychomotor functions in Indian population. Seventy five patient volunteers were included in the study. Volunteers were put into 5 groups based on the type of antihistamine prescribed. Group-1 volunteers included those who were prescribed no antihistamine, group-2 were prescribed first generation antihistamines, group 3, 4 & 5 were prescribed second generation antihistamines cetirizine, fexofenadine and loratadine respectively. A battery of four psychomotor function tests: critical flicker fusion threshold (CFFT), digit symbol substitution test (DSST), finger tapping (FT) and visual analogue scale (VAS) for day time sedation was used in the study. First generation antihistamines impaired psychomotor functions establishing the validity of psychomotor function tests chosen for the study. Second generation antihistamines did not significantly affect CFFT frequency, but DSST score was significantly reduced. Fexofenadine significantly reduced FT score. All antihistamines produced sedation except loratadine on VAS. Second generation antihistamines impaired psychomotor performance in Indian patients, however there were individual differences evident in respect to the effect of drugs.

Key Words

Antihistamines, Psychomotor, Sedation, Cetirizine, Fexofenadine, Loratadine

Introduction

Histamine is involved in a wide range of physiological functions such as regulation of the sleep-wake cycle, arousal, cognition and memory mainly through interactions with histamine H_1 receptors. H_1 antihistamines are among the most widely used medications in the world (1). However, the use of traditional antihistamines, labeled as first generation antihistamines (e.g. diphenhydramine, chlorpheniramine and promethazine), is often associated with a number of adverse effects, of which sedation is the most pronounced (2). These first-generation antihistamines readily cross the blood-brain barrier leading to significant drowsiness, altered mood, reduced wakefulness and impaired cognitive and psychomotor performance (3). These adverse effects can interfere with the performance of daytime activities and place the patient at risk of accidents in situations such as driving and operation of machinery (4). Newer antihistamines (e.g. loratadine, cetirizine, fexofenadine and acrivastine) also referred to as second generation H_1 antihistamines or non-sedating antihistamines are preferred over

conventional antihistamines for a number of indications. Unlike the classic antihistamines, the newer antihistamines do not block cholinergic or central H_1 receptors and produce fewer side effects, such as sedation and impaired psychomotor performance (5). However a few studies have reported impairment of psychomotor performance and sedation with second generation H_1 antihistamines as well (1,6,7).

There are no comparative studies in Indian population to best of our knowledge on the effect of newer antihistamines on psychomotor functions. Hence, this short term preliminary study was planned to evaluate the effect of newer antihistamines on psychomotor functions in Indian population.

Material & Methods

This prospective, comparative and open labeled study was conducted in patient visiting the OPDs of departments of otolaryngology and dermatology in CMC, Ludhiana. The study was approved by IEC. Patients were recruited by putting up a notice for patient volunteers in OPDs. A

From the Deptt. of Pharmacology, *Otolaryngology and **Dermatology, Christian Medical College & Hospital, Ludhiana, India

Correspondence to : Dr. Dinesh K. Badyal, Professor & Head Deptt. of Pharmacology Christian Medical College, Ludhiana Punjab-India



written informed consent was taken from all the patients.

Patients of both sexes between age group of 18-60 and who have taken prescribed antihistamines for atleast two days were included in the study. Patients taking any other medication, which can affect psychomotor functions and patients suffering from disease/disorder affecting psychomotor functions were excluded from the study. Patients consuming alcohol and cigarettes were also excluded.

Seventy five patient volunteers were included in the study. Patients were classified into 5 groups on the basis of drug being prescribed. Fifteen patients were enrolled into each group. Group 1 included controls i.e. patients who were not prescribed antihistamines. Group 2 (Positive control) included patients who were prescribed first generation antihistamines (promethazine-25mg/day or hydroxyzine-25mg/day). Group 3, 4 and 5 were prescribed second generation antihistamines cetirizine 10mg/day, fexofenadine 120 mg/day or loratadine 10 mg/day, respectively. The volunteers were asked to abstain from caffeine containing beverages from the morning of the day when tests were to be conducted.

All patients were evaluated using a test battery of four psychomotor function tests. Critical flicker fusion threshold (CFFT) test is a measure of central integration of psychomotor function. The response was determined by the mean of three ascending and three descending frequencies of flicker (8). Digit symbol substitution test (DSST) is a subset of Wechsler adult intelligent schedule involving coding skills (symbols are substituted for numbers). Sensory recognition and processing as altered by drugs can be quantified with this test. The subjects were given 90 seconds to complete as many substitutions as possible. The score in DSST was the number of correct substitutions in the given time (9). Finger tapping (FT) rate using index finger of the dominant hand was determined over 60 second on a calculator keyboard to compare motor activity (7). Visual analogue scale (VAS) for day time sedation was assessed using 10 cm visual analogue scale with the endpoints of "wide awake" and "nearly asleep" (10). *Fig 1.* Shows the CONSORT.

Statistical analysis

Data was analysed using analysis of variance (ANOVA) test with post hoc Bonferroni test for multiple comparisons. P value <0.05 was considered as statistically significant.

Results

Table 1 shows the demographic profile of patients. age and sex was comparable in various groups. *Table 2* shows changes in psychomotor tests in various groups. CFFT frequency decreased significantly ($p < 0.001$) with

first generation antihistamines (group2) as compared to control (group1). There was no significant difference in the threshold frequency with cetirizine (group 3) and fexofenadine (group 4) as compared to control group (group1). However, threshold frequency was significantly more with loratadine as compared to control group. On comparison between first and second generation antihistamines, threshold frequency was significantly less with first generation antihistamines as compared to second generation antihistamines, cetirizine and loratadine. Within second generation antihistamines there was significant difference in threshold frequency with cetirizine (group 3) and fexofenadine (group 4) as compared to loratadine (group 5). In DSST, score decreased significantly ($p < 0.001$) with all antihistamines (group 2, 3, 4 and 5) as compared to control (group 1). There was no significant difference in the threshold frequency between first and second generation antihistamines.

The count in finger tapping decreased significantly ($p < 0.05$) with first generation antihistamines (group2) and fexofenadine (group 4) as compared to control group (group1). There was no significant difference in the count with cetirizine (group 3) and loratadine (group 5) as compared to control (group1). On comparing various antihistamines, the count was significantly less with first generation antihistamines (group2) and fexofenadine (group 3) as compared to loratadine (group5). The patients on all antihistamines (group 2, 3 and4) except loratadine (group5) were significantly more sedated as compared to control (group1) in the VAS.

Discussion

A large number of trials with an even larger number of tests have been carried out to assess psychomotor performance and the sedative effect of the newer H1 antihistamines (8). There are no comparative studies in Indian population. Most of these earlier studies are from western literature. However, many of these tests lack validity and the results are not reproducible. Hence, inclusion of a positive control guarantees the sensitivity of the test battery (11,12). In the present study, the use of first generation antihistamines, hydroxyzine and promethazine in group 2 as positive control established the validity and sensitivity of the test battery.

A task, which often features in studies investigating the central effects of the antihistamines, is the critical flicker fusion threshold (CFFT). CFFT has consistently demonstrated the reduction in cognitive capacity following traditional antihistamines, as well as detecting changes with newer antihistamines, where other tests have failed to detect impairment (13). As expected, first generation antihistamines significantly decreased CFFT as compared

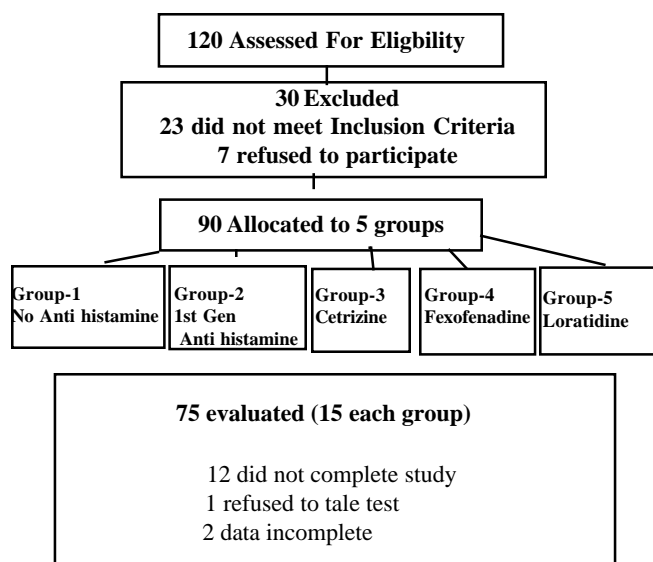


Fig. 1 CONSORT Diagram of Study

Table 1. Demographic Profile of Patients in Various Groups

Groups	Group 1	Group 2	Group 3	Group 4
Age (Years) (Mean±SE)	35±2.5	36±2.9	35±3.0	35±1.6
Sex (M:F)	47:53	53:47	47:53	47:53

Table 2. Changes (mean±SE) in Psychomotor Tests in Various Groups

Groups	CFFT (Frequency per second)	DSST (Score in 90 seconds)	FT (Count per minute)	VAS (Percentage)
1 (Control)	24.89±0.49	56.93±2.54	280.67±8.21	7.33±4.08
2 (Positive control- First generation antihistamines)	22.37±0.24*	29.40±2.51*	250.20±9.34*	36±3.59*
3 (Cetirizine)	24.79±0.42# ^φ	34.20±2.20*	275.33±6.95	35.67±3.74* ^φ
4 (Fexofenadine)	23.81±0.20 ^φ	28.40±1.88*	248.60±1.89* ^φ	27±1.68*
5 (Loratidine)	26.58±0.37*#	29.80±2.13*	282.80±5.42#	16±4.45#

*p<0.05 as compared to group1(Control)
p<0.05 as compared to group 2
φ p<0.05 as compared to group 5

CFFT: Critical flicker fusion threshold
DSST: Digit symbol substitution test
FT: Finger tapping
VAS: Visual analogue scale

to control group, indicating impairment of psychomotor functions. Second generation antihistamines (cetirizine, fexofenadine and loratidine) did not significantly affect the psychomotor functions as shown by changes in CFFT.

Earlier studies also documented no significant change in CFFT with second generation antihistamines (3,13). The mean CFFT with loratadine increased significantly as compared to control. However, this does not indicate that loratadine improves psychomotor function because highest individual values in both groups have reached 28 per second. Hence this statistical difference here was not clinically significant.

Sensory recognition and processing was affected by all antihistamines as indicated by highly significant decrease in the mean score in DSST as compared to control. The decrease in score in DSST was comparable with all antihistamines, indicating that first and second generation antihistamines produces same level of impairment in sensory recognition and processing. The count in FT decreased significantly with first generation antihistamines and fexofenadine as compared to control. First generation antihistamines are known to decrease motor activity, however fexofenadine is not reported to significantly affect motor activity (13-15). Loratadine slightly increased the FT count, but this was not statistically

significant. Within second generation antihistamines the FT count difference was significant between loratadine as compared to fexofenadine and first generation antihistamines. All antihistamines produced significant day time sedation as compared to control group on VAS. The sole exception was loratadine, which did not significantly produce sedation on VAS as compared to control group.



The increasing order of sedation with the various antihistamines used in the present study was; first generation antihistamines > cetirizine > fexofenadine.

Sedative effect of cetirizine has been a subject to ongoing controversy. Results of the studies done with single dosing regimens as well as with repeated doses have been reported as being contradicting (16,17). A thorough literature review showed, that well designed studies demonstrated either no impairment of objective parameters of CNS function at all or showed mild impairment at higher doses on sensitive tests, such as the sleep latency, tracking speed, critical fusion and divided attention (18). In one of the well designed studies there was evidence of minor impairment in the driving test (19).

Drowsiness was reported with fexofenadine in 1% patients in earlier studies. This incidence is similar to that for placebo. Most of the studies have reported no significant change in psychomotor performance with fexofenadine (20). However, in the present study, fexofenadine impaired score in DSST, decreased finger count and also produced significant sedation in Indian patients. Loratadine was non-sedating antihistamines in this study. Our results for loratadine are in agreement with earlier studies. Studies employing self-report measures, such as diary cards, visual analogue scales, rating scales and mood inventories have shown that the effect of loratadine on somnolence, fatigue and mood was comparable to those found with placebo. In studies exploring physiological indices of CNS functioning, such as EEG-evoked potentials and sleep latency tests, loratadine has been shown to be free of CNS effects. In addition, studies have investigated the effects of loratadine on actual driving performance and on tests of cognitive and psychomotor functioning. On all of these performance measures, loratadine has been shown to have effects comparable to placebo (3,13,14,17,18).

Conclusion

On the basis of these results, we can conclude that results of this study in Indian population do not show a clear and consistent distinction between so called sedating and non-sedating antihistamines. Loratadine was the only second generation antihistamines which did not affect psychomotor functions and was non-sedating in the Indian patients. We therefore believe that warnings about antihistamines' possible adverse effects on driving and other potentially dangerous activities should not be waived even for the second generation drugs.

Acknowledgment

The authors thanks the ICMR, New Delhi, for providing financial support for current research.

References

1. Keller GA, Di Girolamo G. Antihistamines: past answers and present questions. *Curr Drug Saf* 2010; 5(1): 58-64
2. Welch MJ, Meltzer EO, Simons FE. H1-antihistamines and the central nervous system. *Clin Allergy Immunol* 2002; 17: 337-88.
3. Tashiro M, Mochizuki H, Iwabuchi K, et al. Roles of histamine in regulation of arousal and cognition: functional neuroimaging of histamine H1 receptors in human brain. *Life Sci* 2002; 72: 409-14.
4. Valk PJ, Simons M. Effects of loratadine/montelukast on vigilance and alertness task performance in a simulated cabin environment. *Adv Ther* 2009; 26(1):89-98
5. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann Allergy Asthma Immunol* 2004; 92: 294-303.
6. Simons FER, Simons KJ. The pharmacology and use of H1-receptor antagonist drugs. *N Engl J Med* 1994; 330: 1663-70.
7. Rathi SK. Comparison of levocetirizine and cetirizine in chronic idiopathic urticaria. *Indian J Dermatol* 2004; 49: 130-31.
8. Hindmarch I. Psychomotor function and psychoactive drugs. *Br J Pharmacol* 1980; 10: 189-209.
9. Wechsler D. 4 manuals for the Wechsler adult intelligence scale. New York: Psychological Corporation; 1955.
10. MacPhee GJ, Goldie C, Roulston D, et al. Effect of carbamazepine on psychomotor performance in naive subjects. *Eur J Clin Pharmacol* 1986; 30: 37-42.
11. Nicholson AN, Stone BM, Turner C, Mills SL. Antihistamines and aircrew: usefulness of fexofenadine. *Aviat Space Environ Med* 2000; 71: 2-6.
12. Walsh JK, Muehlbach MJ, Schweitzer PK. Simulated assembly line performance following ingestion of cetirizine or hydroxyzine. *Ann Allergy* 1992; 69: 195-200.
13. Hindmarch I, Shamsi Z. Antihistamines: models to assess sedative properties, assessment of sedation, safety and other side-effects. *Clin Exp Allergy* 1999; 29 Suppl 3: 133-42.
14. Witek TJ, Canestrari DA, Miller RD, Yang JY, Riker DK. Characterisation of daytime sleepiness and psychomotor performance following H1 receptor antagonists. *Ann Allergy Asthma Immunol* 1995; 74: 419-26.
15. Markham A, Wagstaff AJ. Fexofenadine. *Drugs* 1998; 55: 269-74.
16. Takahashi H, Ishida-Yamamoto A, Iizuka H. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. *Clin Exp Dermatol* 2004; 29: 526-32.
17. Philpot EE. Safety of second generation antihistamines. *Allergy Asthma Proc* 2000; 21:15-20.
18. Campoli-Richards DM, Buckley MM, Fitton A. Cetirizine: a review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma and chronic urticaria. *Drugs* 1990; 40: 762-81.
19. Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance and EEG during driving. *Eur J Clin Pharmacol* 1992; 42: 363-69.
20. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J Allergy Clin Immunol* 2003; 111: 770-76.