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Original Research Article

One-time use of Second-Generation Anti Histaminics on Healthy Human Volunteers' Cognitive and Psychomotor Function

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Abstract

Aim: study of effect of a single dose of second generation antihistaminics on cognitive and psychomotor function in healthy human volunteers. **Methods:** A single blind prospective, case control study was conducted in the Department of Pharmacology Darbhanga Medical College, Darbhanga Bihar India for 14 months (1 August 2020 – 31 September 2021). A pilot study was conducted to test feasibility and operational efficiency of certain procedure or unknown effect. 100 healthy human volunteers of both sexes between 18-25 years were registered. Subjects were divided in five groups from A to E (20 subjects in each group). Participants of group A served as control group; that is no antihistaminics was given to them (placebo, Tab. folvite 5 mg, wythe). Participants of group B were given first generation antihistaminic, promethazine 25 mg (Tab. avomine 25 mg, nicholas piramal) and this group was taken as positive control group. Rests of three groups were given second generation antihistaminics. **Results:** Total 100 volunteers were registered, among them 30were male and 70 were female. Mean age of volunteers was 20.46±1.06 years. Results were described in table. Significance of difference was analyzed by paired t-test p value less than 0.05 considered as significant. We observed no statistically significant difference on various test parameters both predose mean and post dose mean with placebo (p value>0.05) There was statistically significant difference observed on perceptual speed test (p value=0.013 and t-value=2.845, 95% confidence interval 1.378-9.822),Stanford Sleeping Scale (p value 0.001and t value- 4.063, 95% confidence interval 2.546 to 0.787) and BVRT (p value=0.004 and t value=3.5, 95% confidence interval 0.181 to 0.753) while no statistically significant effect has been observed in other tests variable (p>0.05). Predose and post dose mean of SSS is expressed in number. In female (p value<0.008) highly significant. In group C there was a statistically significant difference observed in DSST (P value=0.046, t value=2.84, 95% confidence of interval 0.093 to 10.174) and FTT (P value 0.001, t value 4.075, 95% confidence of interval 10.675 to 34.392) while no statistically significant effect was observed in other test variable (p value>0.05)

There was no statistically significant effect was observe in any test parameter (group D) p value>0.05 for all parameters. Statistically significant difference in DSST was observed with loratadine (p value=0.034, t-value=2.348, 95% confidence interval range 0.404 to 8.929) while no statistically significant effect was been observe in other test variable (p-value>0.05). **Conclusion:** The sedative effect of promethazine and alteration in cognitive and psychomotor function. Cetirizine and loratadine with a single dose there was no sedation but they alter the some parameter of psychomotor function. Cetirizine altered the DSST and FTT score. Loratadine altered the DSST only**.**

Keywords: promethazine, Cetirizine, antihistaminics , cognitive function

Introduction:

The incidence of allergic diseases such as allergic rhinitis (AR), allergic asthma (AA), chronic idiopathic urticaria (CIU) and atopic dermatitis (AD) has continued to rise over the past several decades, affecting a large number of people worldwide.[1] Symptoms such as itching, sneezing, rhinorrhea and rhino by on caused by allergic diseases usually lower the quality of life.[2] In fact, millions of people have been reported to experience physical impairments and reductions in quality of life, as well as economic bur- dens, derived from allergic diseases and its associated co-morbidities.[3] Antihistamines have been widely used as a first-line drug in the treatment of allergic diseases. The first-generation antihistamines were no longer recommended because of their side effects including hepatotoxicity, cardiotoxicity, sedative effects, anticholinergic effects and lack of selectivity for the H1-receptor.[4] The second-generation antihistamines have replaced the first-generation antihistamines as commonly used drug in the treatment of allergic diseases because of their modest sedative effects and more significant and persistent curative effect compared with the first-generation antihistamines.[4] However, some of the second-generation antihistamines, such as terfenadine and as temizole, are rarely used because of their apparent cardiotoxicity.[5] As a new generation antihistamine and an active metabolite of terfenadine - a highly selective H1 antagonist, fexofenadine has positive antihistamine effects.[6] In addition, fexofenadine has no cardiotoxicity and minimal adverse effects on liver because only about 5% dosage of fexofenadine is metabolized by liver. As the substrate of P-glycoprotein, fexofenadine that is difficult to pass the blood-brain barrier may have no sedative effect and other central nervous functions.[7] A large number of studies have been carried out to assess psychomotor performance and the sedative effect of the H1 antihistamines.[8-9] There are very few studies in Indian population. This study was therefore carried out to evaluate the effect of a single dose of second generation antihistaminic (fexofenadine, cetirizine, loratadine) in comparison to first generation antihistaminic (promethazine) on cognitive and psychomotor function in normal human volunteers. Normal healthy human volunteers were chosen because in the patients single dose of antihistaminic is not sufficient to treat the problem, as most of the allergic condition required 5 to 7 days of treatment and so we should not deprive them of treatment as it is irrational to use single dose in patients and our result may alter if patient is on any other medication due to drug- drug interaction.

Also in normal healthy human volunteers only single dose was given to prevent unnecessary exposure to antihistaminics and to prevent the side effects of drugs because antihistaminics can cause many adverse effects or can hamper the normal routine of volunteers.

Materials and Methods

A single blind prospective, case control study was conducted in the Department of Pharmacology Darbhanga Medical College , Darbhanga Bihar India for 14 months (1 August 2020 – 31 September 2021), after taking the approval of the protocol review committee and institutional ethics committee.

A pilot study was conducted to test feasibility and operational efficiency of certain procedure or unknown effect. 100 healthy human volunteers of both sexes between 18-25 years were registered.

Inclusion criteria

Healthy human volunteers of both sexes between 18-25 years of age, after taking written informed consent.

Exclusion criteria

Suffering from any disease or illness, on any medication, gives history of consuming alcohol or tobacco and who had taken caffeinated drink on the day of study were excluded from our study.

Methodology

Subjects were divided in five groups from A to E (20 subjects in each group). Participants of group A served as control group; that is no antihistaminics was given to them (placebo, Tab. folvite 5 mg, wythe). Participants of group B were given first generation antihistaminic, promethazine 25 mg (Tab. avomine 25 mg, nicholas piramal) and this group was taken as positive control group. Rests of three groups were given second generation antihistaminics. Participants of group C were given cetirizine 10 mg (Tab. cetzine 10 mg GSK). Participants of group D were given fexofenadine 120 mg (Tab. allegra 120 mg Sanofi, aventis). Participants of group E were given loratadine 10 mg (Tab. lorfast 10 mg cipla).

The participants were informed about protocol of study. The written informed consent obtained in proforma prescribed by Institutional Ethics Committee. Cognitive and psychomotor functions of all the subjects from each group were assessed pretreatment and 60 minutes after taking single dose of drug (post treatment), sequence of tests were same as in case of predose. By using a battery of simple tests, which are easy to perform, less time consuming and do not require any complicated instrument. Which are as follows: This test measures attention and vigilance as described by Gelfman et al.[10] In this test subject is required to mark the same digit in the row as the one circled at the beginning of the row in 60 seconds the number of correct responses serves as the score. It is a test of psychomotor performance in this test the subject is given a key grid of numbers and matching symbols and a test section with numbers and empty boxes.[11] The test consists of filling as many empty boxes as possible with a symbol matching each number in 90 seconds.

This is an introspective measure of sleepiness. Subjects were given a printed sheet having a seven point scale mentioning degree of sleepiness and scale rating from 1 to 7. The participants were instructed to listen carefully as investigator says some numbers and repeat them. Count maximum correct digit span forward until two consecutive failures on same length. The participants were instructed to listen carefully as investigator says some numbers and repeat them the participants were instructed to count maximum correct digit span backward until two consecutive failure on same length. Subjects are asked to make trail by connecting numbers and time noted the

participants were instructed to listen carefully as investigator says some numbers and repeat them.

Subjects are asked to make trail by connecting numbers and alphabets and time noted. Subject is asked to listen and repeat list of word as many as possible. To assess the motor function. Participants were instructed to tap on 'Tab key' of lap top by index finger of dominant hand as rapidly as possible for 30 seconds and duration is noted by using stop watch. Participants were shown a card for 10 seconds carrying test image followed by another card having one response image and two distractors same test was repeated with another set of cards one hour after administration of test drugs to assess visual memory.

Statistical analysis

All mentioned tests were done predose and postdose in each groups and all data was analyzed by using statistical software SPSS-21.0 version and Microsoft excel 2010. Data was analyzed by applying paired t test, ANOVA test followed by Tukey's post hoc test for all multiple comparisons.

Results

Total 100 volunteers were registered, among them 30were male and 70 were female. Mean age of volunteers was 20.46±1.06 years. Results were described in table. Significance of difference was analyzed by paired 't- test' p value less than 0.05 considered as significant.

Group A effect of placebo

We observed no statistically significant difference on various test parameters both predose mean and postdose mean with placebo (p value>0.05) (Table 1).

Table 1: Effect of placebo on various test parameters

Tests	Pre-dose mean	Pre-dose SD	Post-dose mean	Post-dose SD	P value
PST	46.33	6.15	44.2	7.29	0.14
DSST	68.27	7.12	71.53	9.05	0.061
FDST	8.8	1.01	9.2	1.08	0.054
BDST	6.87	1.77	7.4	1.3	0.164
SSS	1.6	0.63	1.67	0.72	0.582
TMT- A	22.2	7.08	22.07	9.62	0.935
TMT-B	45.33	14.16	45.07	12.16	0.912
WMT-1	6.93	1.71	7.2	1.42	0.499
WMT-2	8.33	1.4	8.6	1.4	0.433
FTT	161.07	35.06	162.73	30.29	0.641
BVRT	4.8	0.41	5	0	0.082

Tests (PST, DSST, FDST, BDST, SSS, WMT-I, WMT-2, FTT, BVRT) are expressed as in numbers and Tests TMT-A and TMT-B are expressed as time duration in seconds.

Table 2: Effect of promethazine on various test parameters.

Tests	Pre-dose mean	Pre-dose SD	Post-dose mean	Post-dose SD	P value
PST	45.33	5.05	39.73	7.35	0.013*
DSST	63.2	8.17	60.47	9.67	0.318
FDST	8.73	1.67	8.6	1.35	0.61
BDST	7	1.96	6.93	1.98	0.879
SSS	1.8	1.01	3.47	1.73	0.001**
TMT- A	25.2	7.75	24.33	6.82	0.65
TMT-B	51.73	14.94	50.73	11.74	0.812
WMT-1	6.93	1.67	6.47	1.64	0.363
WMT-2	8.33	1.54	8.13	1.13	0.619
FTT	133	45.38	125.4	27.84	0.474
BVRT	4.87	0.35	4.4	0.63	0.004***

Test (PST, DSST, FDST, BDST, SSS, WMT-I, WMT-2, FTT, BVRT) are expressed in numbers and Tests TMT-A and TMT-B are express time duration in seconds. (P value<0.05) for PST, SSS and BVRT)

Table 3: Difference in the effect of promethazine between female and male on stanford sleepiness scale.

Females			**Males**	
Pre-dose		**Post-dose**	**Pre-Dose**	**Post-dose**
Mean	2	4.25	1.57	2.57
SD	1.195	1.982	0.787	0.787
P value	0.008		0.061	

Group (B) effect of promethazine

There was statistically significant difference observed on * perceptual speed test (p value=0.013 and t-value=2.845, 95% confidence interval 1.378-9.822),**Stanford Sleeping Scale (p value 0.001and t value-4.063, 95% confidence interval 2.546 to 0.787) and ***BVRT (p value=0.004 and t value=3.5, 95% confidence interval 0.181 to 0.753) while no statistically significant effect has been observed in other tests variable (p>0.05) (Table 2). Predose and postdose mean of SSS is expressed in number. In female (p value<0.008) highly significant (Table 3

Group (C) effect of cetirizine

In group C there was a statistically significant difference observed in *DSST (P value=0.046, t value=2.84, 95% confidence of interval 0.093 to 10.174) and **FTT (P value 0.001, t value 4.075, 95% confidence of interval 10.675 to 34.392) while no statistically significant effect was observed in other test variable (p value>0.05) (Table 4).

Group (D) effect of fexofenadine

There was no statistically significant effect was observe in any test parameter (group D) p value>0.05 for all parameters (Table 5).

Group (E) effect of loratadine

Statistically significant difference in *DSST was observed with loratadine (p value=0.034, t-value=2.348, 95% confidence interval range 0.404 to 8.929) while no statistically significant effect was been observe in other test variable (p-value>0.05) (Table 6). ANOVA test was done to know any variation in within the group and between the groups for individual test analysis.

Table 4: Effect of cetirizine on various test parameters.

Test	Pre-dose mean	Pre-dose SD	Post-dose mean	Post-dose SD	P value
PST	46	6.44	43.2	7.35	0.12
DSST	67.2	10.06	62.07	11.23	***0.046**
FDST	9.13	1.06	9.27	1.03	0.546
BDST	7.47	1.46	7.93	1.83	0.169
SSS	1.6	0.63	1.53	0.64	0.774
TMT- A	23.67	7.67	22.33	3.33	0.462
TMT-B	54.73	9.48	51.2	10.24	0.22
WMT-1	6.8	1.42	7.27	1.44	0.204
WMT-2	8.4	1.35	8.33	1.11	0.872
FTT	163.27	37.94	140.73	41.82	****0.001**
BVRT	4.8	0.41	4.87	0.52	0.719

Test (PST, DSST, FDST, BDST, SSS, WMT-1, WMT-2, FTT, BVRT) scores are expressed as numbers and Tests TMT-A and TMT-B are expressed time duration in seconds. For DSST and FTT (p value < 0.05 using paired‘t test’)

Table 5: Effect of fexofenadine on various test parameters.

Test	Pre-dose mean	Pre-dose SD	Post-dose mean	Post-dose SD	P value
PST	45.4	5.93	42.93	6.71	0.08
DSST	62	9.008	64	8.619	0.39
FDST	9.733	0.594	9.667	0.488	0.582
BDST	8.333	1.234	8.667	1.543	0.43
SSS	1.267	0.594	1.467	0.64	0.334
TMT- A	22.667	4.909	22	5.332	0.585
TMT-B	54.333	8.756	51.8	7.683	0.416
WMT-1	7.067	1.033	7.2	1.146	0.546
WMT-2	9	0.926	8.867	1.246	0.737
FTT	169	23.746	172.533	17.25	0.564
BVRT	4.6	0.828	4.933	0.258	0.173

Test (PST, DSST, FDST, BDST, SSS, WMT-I, WMT-2, FTT, BVRT) are express in numbers and Tests TMT-A and TMT-B are express time duration in seconds (p value>0.05) for all tests parameters

Table 6: Effect of loratadine on various test parameters.

Test	Pre-dose mean	Pre-dose SD	Post-dose mean	Post-dose SD	P value
PST	45.2	9.03	42.8	6.43	0.18
DSST	64.73	11.74	60.07	7.12	***0.034**
FDST	9.6	0.91	9.4	1.24	0.51
BDST	8.27	1.75	8.13	1.92	0.737
SSS	1.67	0.62	1.87	0.83	0.334
TMT- A	20	3.89	20.2	3.9	0.874
TMT-B	45.13	9.94	48.6	10.03	0.181
WMT-1	7	1.81	7.47	1.81	0.396
WMT-2	8.6	1.45	9.13	1.19	0.056
FTT	130.67	49.99	153.27	32.47	0.089
BVRT	4.4	0.91	4.8	0.41	0.111

Test (PST, DSST, FDST, BDST, SSS, WMT-I, WMT-2, FTT, BVRT) are express in numbers and Tests TMT-A and TMT-B are express time duration in seconds.

Table 7: P-value of all tested drugs on various test parameters.

Tests	Placebo	Promethazine	Cetirizine	Fexofenadine	Loratadine
PST	0.14	0.013	0.12	0.08	0.18
DSST	0.061	0.318	0.046	0.39	0.034
FDST	0.054	0.61	0.546	0.582	0.51
BDST	0.164	0.879	0.169	0.43	0.737
SSS	0.582	0.001	0.774	0.334	0.334
TMT-A	0.935	0.65	0.462	0.585	0.874
TMT-B	0.912	0.812	0.22	0.416	0.181
WMT-1	0.499	0.363	0.204	0.546	0.396
WMT-2	0.433	0.619	0.872	0.737	0.056
FTT	0.641	0.474	0.001	0.564	0.089
BVRT	0.082	0.004	0.719	0.173	0.111

Table 8: Post hoc analysis of effect of antihistaminics on post dose DSST.

Groups	P value
Promethazine and placebo	0.01
Promethazine and cetirizine	0.988
Promethazine and fexofenadine	0.816
Promethazine and loratadine	1

(p value<0.05) in between promethazine and placebo.

When variation in amongst the antihistaminics was compared in PST, FDST, BDST, TMT-A, TMT-B, WML- 1and WML-2. There was no statistically significant variation between the groups and within the groups, (p- value>0.05). DSST- When variation in amongst the antihistaminics in DSST was compared there was statistically significant difference in between the groups and within group (p value=0.005, F value=4.096). After application of post hoc test for multiple variable comparisons we observed there was significant variation between placebo, promethazine, cetirizine and loratadine (Table 8).

SSS- on comparison of variation amongst the antihistaminics in Standford sleepiness scale we observed that there was statistically significant difference in between group and within group (p value=0.000 and F value= 10.394) (Figure 1). Results are expressed as Mean±SD. FTT- On comparison of variation amongst the antihistaminics in FTT there was statistically significant difference was observed between the groups and within the groups (p value=0.001, F value=5.348). After application of post hoc test on FTT, we observed there was statically significant variation between placebo and promethazine, cetirizine and fexofenadine and highly significant variation is seen when we compared fexofenadine and promethazine (p value=0.001) (Table 9).

Table 9: Post hoc analysis of effect of antihistaminics on FTT.

Groups	P value
Promethazine and placebo	0.013
Promethazine and cetirizine	0.657
Promethazine and fexofenadine	0.001
Promethazine and loratadine	0.111

FTT expressed in numbers.

BVRT- when we compared the variation amongst the antihistaminics in BVRT there was statistically significant difference in between group and inter groups (p value=0.002, F value=4.605). Highly significant difference observed in placebo and promethazine (p-value=0.002) (Table 10).

Table 10: Post hoc analysis of effect of antihistaminics on BVRT.

Groups	P value
Promethazine and placebo	0.002
Promethazine and cetirizine	0.029
Promethazine and fexofenadine	0.009
Promethazine and loratadine	0.086

BVRT scores are expressed in numbers

Discussion

Antihistamine effects that assessed by the inhibition rate of histamine-induced wheal and flare are important measurements to evaluate the efficacy of antihistamines in the treatment of allergic diseases. In our study in promethazine group (positive control) there was significant change in PST, Stanford Sleepiness Scale and BVRT (p-value<0.05) while there was no significant effect is seen in other parameters but in the study by Hind march et al promethazine taken as positive control group showed significantly reduced Critical flicker fusion threshold (CFFT).[12] David et al observed promethazine significantly decrease in finger tapping count (FT) and Critical flicker fusion threshold (CFFT) observed (p<0.001) as compared to control group which demonstrated decline in cognitive functions.[13] Jauregui et al observed that classic antihistamines increased day time sleepiness and decreased the sleep quality scores.[14] Kamei et al concluded that fexofenadine did not cause any cognitive or psychomotor dysfunction when administered at the therapeutic doses, in contrast to the sedative effect of promethazine (p value<0.05), Rapid Visual Information Processing test (RVIP) also done to assess attention performance and it was observed that promethazine significantly decreases correct response.[15] Promethazine is potent histamine and acetylcholine receptor antagonist that is why having more sedative effect in comparison with second generation antihistaminics. Valk et al studied the adverse effects of H1 antihistaminics (mainly first generation) 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.[7]

Church et al studied effects of first-generation H1 antihistamines on the CNS are similar to an additive with those produced by ethanol or other CNS-sedatives, such as benzodiazepines.[16] Sen et al examined The Civil Aerospace Medical Institute's (CAMI's) Toxicology database for the presence of the

first-generation antihistamines in pilot fatalities of civil aircraft accidents that occurred during a 16-year (1990-2005) period.[17]

In our study we observed that cetirizine significantly affects DSST and FTT (p value<0.05 and 0.001 respectively). Gango et al also observed change in DSST and Trail making task B (TMT B).[18]

Hind march et al observed that cetirizine does not cause any change in DSST and do not affect SSS which is different from our study. They also observed and does not make any significant change in simple reaction task (SRT) score.[12]

In study by Gupta et al it was observed that 10 mg of cetrizine produced significant degree of sedation but do not affect DSST and digit cancellation test (DCT).[19] These finding are similar with study of Tashiro et al.[3] However Gango et al and Simons observed that cetrizine is non- sedating antihistaminic.[18,20] Kamei et al revealed that cetrizine penetrate brain may result in dose related cognitive impairment.[15] Gupta et al observed that Cetrizine and Fexofenadine not alter the DSST which is similar in our study with Fexofenadine but cetrizine shows significant effect on DSST (p value-0.004).[19]

We observed no change in any parameter with fexofenadine which is similar with placebo. Hindmarch et al showed that fexofenadine does not affects psychomotor function and causes sedation even in high dose up to 180 mg.[12] Gupta et al was observed that fexofenadine do not interfere with psychomotor functions and fine skills; finding of these two studies are similar to our study. Same result seen in other study done by Bender et al.[19,21]

Kamel et al also found same results and no effect on psychomotor functions but David et al observed that fexofenadine causes a decrease in DSST, FT count and causes sedation.[13,15] The findings of study of Gupta et al were also similar with study of Vermeen and O'Hanlon.[19,22] In present study no significant change observed in finger tapping. Other study done by David et al observed that fexofenadine decrease finger tapping count.[13] In our study we observed significant change in DSST with loratadine (p value=0.03) while there was no change in other parameters but in study done by David et al an increased in finger tapping count was observed but no change in DSST was observed. Both of the studies concluded that loratidine is non-sedating antihistaminic. David et al observe loratadine was only antihistaminic which affects the psychomotor functions but does not cause sedation. Loratadine does not alter the performance at therapeutic doses of 10 mg/day that all antihistaminics causes sedation except loratidine and second generation antihistaminics also affects psychomotor functions in Indian population.[13]

In study done by Hindmarch et al loratidine is taken as negative internal control and promethazine as positive controlled they used CFFT, choice reaction time (CRT), line analogue rating scale for sedation and noted that it is a non- sedative antihistaminic and does not cause CNS side effects following 10 mg dose.[12]

Valk et al concluded that loratadine is similar to placebo in effects on daytime somnolence and psychomotor performance. Loratadine treatment resulted in significantly less sleepiness and impairment of vigilance and tracking than diphenhydramine.[10]

Conclusion

Second generation antihistaminics are supposed to be non- sedating however they may cause sedation , some studied have shown alteration in psychomotor function by second generation antihistaminics, so these drugs are unsafe and even single dose may be hazardous in subjects whose job requires alertness.

Our study has confirmed the sedative effect of promethazine and alteration in cognitive and psychomotor function. Cetirizine and loratadine with a single dose there was no sedation but they alter the some parameter of psychomotor function. Cetirizine altered the DSST and FTT score. Loratadine altered the DSST only.

On the contrary, the fexofenadine did not produced sedation and no effect on any cognitive and psychomotor functions. Thus, based on the present study it may be concluded that cetirizine and loratadine should not be used by the person performing the job that requires alertness, such as driving vehicles and machinery, while fexofenadine can safely be used.

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