Research Article

Comparative study of psychomotor performance amongst fixed dose combinations of first and second generation H_1 antihistaminics in adult healthy volunteers

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ABSTRACT

Background: Fixed dose combination (FDC) of first and second generation H_1 antihistaminics with paracetamol and phenylephrine are widely used and are the most frequent form of self-medication. Though previous studies have shown that H_1 antihistaminics cause psychomotor and cognitive impairment, to the best of our knowledge, no studies have utilized the FDC of antihistaminics to evaluate their effect on psychomotor performance. This study was planned to observe the effects of such combinations on CNS. The mainstay of the study was to compare the psychomotor performance upon administration of fixed dose combination of 1st and 2nd generation H_1 antihistaminics along with paracetamol and phenylephrine in adult healthy volunteers.

Materials and Methods: This was double blind cross over study conducted in 12 adult healthy volunteers. Following single dose of FDC of the 1st (chlorpheniramine maleate) and 2nd (cetrizine) generation anti-histaminics with paracetamol and phenylephrine, volunteers were subjected to perform a battery of validated tests to evaluate their cognitive and psychomotor performance (simple reaction time, arithmetic ability test, digit substitution test, digit cancellation test, immediate and delayed recall rests and a Stanford drowsiness scale) 2 hrs post dose. Data was analysed using analysis of variance test with Tukey's Multiple Comparison Test. A p value of < 0.05 was considered statistically significant.

Results: FDC containing cetrizine did not show significant difference from the other FDC containing chlorpheniramine maleate in any of the tests which had been performed, except for a mildly sedative action of cetirizine containing FDC.

Conclusion: FDC of antihistaminics do not cause impairment of cognition and psychomotor performance. Also, 2nd generation antihistaminics are not free from adverse effect like sedation. The possible reasons behind the obtained results are addition of paracetamol and low doses of antihistaminics in FDCs, laxity of tests and single dose administration.

Key words: Anti-histaminics, cetrizine, chlorpheniramine, fixed dose combinations, psychometric test.

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INTRODUCTION

Histamine is involved in a wide range of physiological functions like regulation of the sleep-wake cycle, arousal, cognition and memory.[1] It mediates these actions through interactions with H_1 receptors.[2] H_1 antihistamines are known to be used extensively. However, the use of 1st generation antihistamines (e.g. diphenhydramine, chlorpheniramine), is linked with a number of adverse effects like drowsiness, altered mood, reduced wakefulness and impaired cognitive and psychomotor performance.[3,4] These adverse effects may have an impact on daytime activities and the patient may be prone to accidents in situations like machinery handling, driving.[5] Second generation antihistamines (cetirizine, fexofenadine) which have been claimed to be non-sedative, are safe and preferred over conventional antihistamines for several indications.[6]

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Different from the classic antihistamines, the newer antihistamines refrain from blocking cholinergic or central H_1 receptors thereby producing fewer side effects. Sedation and impairment of psychomotor performance are two of the side effects which are claimed to be absent on using 2nd generation antihistamines.[7] There are studies, though, which have reported sedation and an impairment in psychomotor performance with use of 2nd generation H_1 antihistamines.[1,6,8]

Fixed dose combination (FDC) of 1st and 2nd generation H_1 antihistaminic with paracetamol and phenylephrine obtained without prescription are the most frequent form of self-medication for allergic diseases, cough and cold viral fever, pharyngitis etc.[9] Paracetamol is a widely used drug for the treatment of pain, fever and has been used in FDC. Though, it is now generally accepted that it inhibits COX -enzyme, the analgesic effects of paracetamol is reduced by inhibitors of many endogenous neurotransmitter systems including serotonergic, opioid and cannabinoid systems.[10,11] Phenylephrine is α agonist used as a decongestant. This drug also has side effects related to CNS like dizziness, lightheadedness, headache, nervousness, trouble sleeping, shaking etc.[12]

Though previous studies have shown that H_1 antihistaminics cause psychomotor and cognitive impairment,[13] to the best of our knowledge no studies are available using FDC of antihistaminic on psychomotor performance. All these drugs, more or less, do have adverse effects on CNS. Treatment-related sedation and its effect on cognition are a major concern. It is worthwhile to study whether such combinations add on to CNS depressant action of antihistaminics.

Thus, the objective of this study was to assess the degree of sedation and impairment in cognition, psychomotor functions (if any) upon administration of fixed drug combination of chlorpheniramine maleate 2 mg, phenylephrine 2.5 mg and Paracetamol l500 mg i.e. FDC1 (Tablet Chekold, Esquire) and fixed dose combination of cetrizine 5 mg, phenylephrine 5 mg and paracetamol l500 mg i.e. FDC2 (Tablet Cheston cold, Cipla Limited).

MATERIALS AND METHODS

The study was a double blind cross over study, conducted in the Department of Pharmacology, Bharati Vidyapeeth Deemed University Medical College, Pune, India, after the protocol was approved by the Institutional Ethics Committee (BVDU/MC/19).

Inclusion criteria

Adult healthy volunteers between the ages of 20-24 years were included in the study after obtaining written consent.

Exclusion criteria

Subjects with the history of consumption of any drug 14 days prior to the test, and history of drinking > 20 standard alcoholic units per week or > 5 beverages containing caffeine per day were excluded from the study. The consumption of alcohol and/or any other beverage containing nicotine, caffeine or any other stimulants was forbidden 24 hrs before the start of the test.

Drugs under investigation

FDC1 is the fixed dose combinations of chlorpheniramine maleate 2 mg, phenylephrine 2.5 mg and paracetamol 500 mg (Tablet Chekold, Esquire). FDC2 is the fixed dose combination of cetrizine 5mg, phenylephrine 5 mg and paracetamol 500 mg (Tablet Cheston cold, Cipla Limited).

Pre-requisites

The volunteers were instructed not to eat anything till the study was completed. They were only allowed to drink water.

Assessment of psychomotor performance

A battery of validated psychometric tests such as six digit cancellation test,[14] digit

symbol substitution test,[15] simple reaction time,[16] arithmetic ability test[15], memory free-recall,[17] and Stanford drowsiness scale[18] were conducted to assess the psychomotor performance of the volunteers.

Six digit cancellation test

Volunteers were given a sheet consisting of 1200 randomized digits arranged in 40 columns and asked to cancel as many target digits as possible in three minutes. The resulting score consists of the correctly crossed out numbers minus the incorrectly crossed out numbers.

Digit symbol substitution test

This test was used to assess recoding and recognition of sensory information. It consists of digit-symbol pairs (e.g. 1/-, 2/⊥, …, 7/Λ, 8/X, 9/=) followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (120 sec) was measured.

Simple reaction time

This is a simple tool to measure reaction time using computer screen. Subject were asked to click right button. Red spotlight appeared on screen and when the spotlight would turn green, subject were asked to click right button again. Average reaction time was calculated for six reading.

Arithmetic ability test

Central processing was assessed by arithmetic ability test in which the volunteers were asked to solve simple mathematical problems i.e. addition, subtraction, multiplication and division (five of each) within two minutes time.

Memory free recall

a) Word list memory task (immediate recall)

The task involves presenting the subject with a list of 10 words which was read to him at a constant rate of 1 word every 2 seconds. The word list was presented 3 times to the subject; the order of words was randomized for each trial. At the end of each of the three presentations, the subject was asked to recall the list of words; all responses were recorded.

b) Delayed word list memory task

It is to test the delayed recall of the list of 10 words presented earlier over 3 trials. A short distraction period was interpolated between the final list item, and the start of the recall period. Here, no additional cues were given; the subject must spontaneously recall as many of the 10 words as he can.

Stanford drowsiness scale

This is a quick way to assess how alert the subject is feeling. Volunteers were asked to tick one for the 7 below mentioned statements;

1. I feel active, vital, alert, and well awake.
2. I am at a high level, but not at top performance. I am able to concentrate.
3. Relaxed, awake but not completely alert, responsive.
4. Somewhat drowsy, slowed.
5. Drowsy, beginning to stop my activity, hard to stay awake.
6. Sleepy, I prefer to lie down.
7. Almost disconnected, cannot stay awake, about to fall asleep.

Study procedure

Subjects in the study were familiarized with tests i.e. they were subjected to one pre-test practice session in order to remove any influence of learning effect on the study. The volunteers were subjected to the same battery of tests before administration of the FDC which served as control. This was followed by a single oral dose of study medication (FDC1 or FDC2) which was given at 12:30 pm (wash period of one week between each study session). The tests mentioned above were performed 2 hrs after consumption of the fixed drug combinations under study.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using Graph Pad Prism software version 5. Analysis of variance test with Tukey's Multiple Comparison was used and $p < 0.05$ was considered as statistically significant. Results were expressed as mean ± SEM.

RESULTS

There is no statistically significant difference in any of psychomotor performance test except Stanford drowsiness scale, where FDC containing cetrizine and chlorphenaramine, showed significant difference from baseline ($p < 0.0001$). There is also statistically significant difference between FDC1 and FDC2 ($p = 0.0116$) in the Stanford drowsiness scale (Table 1).

DISCUSSION

In the present study old as well as newer H_1 anti-histaminics were employed. The purpose of the study was to determine whether or not fixed drug combinations (FDCs) of 1st and 2nd generation anti-histaminics have psychomotor or cognitive-impairing effects, to determine if these FDCs have any subjective effects, including those that might be considered liability-related in nature i.e. sedation, drowsiness, calmness and tranquility which can thereby increase the risk of occupation related injuries and/or accidents.

Table 1: Effects of FDC of chlorpheniramine (FDC1) and cetirizine(FDC2) on different psychometric tests

Test	Baseline value (millisecond)	Post drug values (mean+SEM)	
		FDC1	FDC2
SRT	0.45 + 0.37	0.46 + 0.23	0.45 + 0.25
DST	91.58 + 5.12	95.16 + 1.72	92.08 + 2.62
DCT	4.83 + 0.39	5.41 + 0.36	5.33 + 0.36
AAT	66.33 + 4.05	61 + 3.43	61.33 + 3.27
IRT	7.66	7.75	7.58
DRT	6.83 + 0.38	6.58 + 0.30	6.75 + 0.31
SSC	1 + 0	2.92 + 0.19*	2.33 + 0.142*, †

SRT-Simple reaction time, DST-Digit symbol substitution Test, DCT- Six digit cancellation test,
AAT-Arithmetic ability test, IRT-Immediate memory recall test, DRT-Delay memory recall test,
SSC-Stanford drowsiness scale.
FDC1- Chlorpheniramine maleate +phenylephrine hydrochloride + paracetamol.
FDC2-Cetrizine dihydrochloride + phenyleprine hydrochloride + paracetamol.
*$p < 0.0001$ vs. baseline value, †$p = 0.0116$ vs. FDC1.

Surprisingly the present study, which engaged adult healthy volunteers, failed to detect any significant difference between sedative and psychomotor effects of 1st and 2nd generation H_1 anti-histamines except a statistically significant difference in Stanford drowsiness scale (Table1). As there are no studies available with FDCs, we compared our results with previous studies in which 1st and 2nd generation antihistaminics, alone, are used. Though there are controversial results in many studies, 1st generation antihistaminic usually cause impairment of cognition and psychomotor performance.[19-21]

One of the many possible reasons for no notable difference between sedative and psychomotor effects of 1st and 2nd generation H_1 anti-histamines can be directed to the low dose of the drugs. The present study used 5 mg cetrizine in one FDC while 2 mg chlorpheniramine in the other FDC, which did not produce subjective or objective impairment and/or effects indicative of sedation or psychomotor impairment. In many previous studies, the dose of cetirizine used is 10-20 mg and that of chlorpheniramine 4-12 mg.[22-24] Our results are consistent with other two comparative studies in Indian population, though, the studies did not use FDCs, they did utilize cetrizine 10 mg/day.[13,21] Apart from low dose we had given single dose, more sedation or psychomotor impairment were seen with repeated dosing.[25]

H_1 antihistamines act as inverse agonists, and the distribution of the receptors is extensive in brain areas linked with the waking state and cognition. Therefore, the sedative effect is directly proportional to the lipid solubility of the drug and the drug's capability to cross the blood-brain barrier. Moreover, the colonization of these H_1 receptors could allow circulating

histamine to saturate other receptors, like the central H_3 receptors, which can also induce sedation.[26,27] The H_3 receptor functions as an auto- and hetero-receptor. Activation of H_3 autoreceptor primarily inhibits synthesis and release of histamine and causes impairment of cognition.

In high doses H_1 antihistaminics block H_1 receptors and allow circulating histamine to saturate H_3 receptors which decreases release of histamine and adds to its sedative effect. But in low doses, FDCs are not able to saturate and activate H_3 receptors.[26-28] This may be one of the possible reasons behind an insignificant difference between psychomotor performance of fixed dose combination of 1st and 2nd generation antihistaminics.

Another reason can be laxity or drawbacks in the tests which were implied to test the psychomotor performance of the volunteers. As all the volunteers have high and roughly the same intelligent quotient, it is probable that the tests designed were too simple and easy. It is imperative to state that the time allocated for every test may have been more than required. A fact to be highlighted is the interplay of memory in these tests. As three tests were taken (pre-training, pre-drug test, post-drug test) it is possible that the volunteers would have memorized the possible answers to the questions. Due to this drawback, though all subjects complained of drowsiness, none showed cognitive and psychomotor impairment.

An interesting factor noted was the development of somnolence (without objective impairment) upon administration of cetrizine. Though the difference in the sedating potential of cetrizine may be due to individual variation[29] it is imperative to state that almost 50% of the volunteers felt a higher pang of drowsiness upon administration of FDC containing cetirizine this show that the conventional 1st generation antihistamines and some of the 2nd generation antihistamine are also having adverse effects. Our results are similar to other study in Indian population.[13,21]

Another reason for the lack of difference in the results is the addition of paracetamol. Some researchers produced experimental data demonstrating that the analgesic effect of paracetamol is due to the indirect activation of cannabinoid cb1 receptors, opioid and serotonergic system.[11] So, paracetamol acts like a pro-drug, the active form being a cannabinoid. These findings finally explain the peculiarity of paracetamol's effects, including the behavioral ones like subjective effects of relaxation, and tranquility. May be serotonergic action of paracetamol interfere direct neurological effects of H_1 antihistaminics through cholinergic and serotoninergic block.[23]

Another possible reason is related to mechanism of H_1 antihistaminics is in contrast to the well- known sedative effects, a few studies also found mild stimulating effects on performance for the H_1-antagonists terfenadine, ebastine, fexofenadine and desloratadine. A proclaimed mechanism from animal studies states that some H_1-antagonists either directly or via GABA-ergic interneurons enhance dopaminergic activity.[30]

Other ingredient present in FDC is phenylephrine. It is α agonist used as decongestant. One of the many studies we went through revealed no true improvement in psychomotor performance upon administration of the combination of second generation antihistamines with pseudoephedrine.[31] Since the concentrations of pseudoephedrine accumulate over time, improvement would only appear after several days of administration.[32] An animal study demonstrated impairment in cognition due to stimulation of α-1 adrenoceptor in the prefrontal cortex. Whether there is any role of pseudoephedrine in FDCs on cognition and psychomotor behavior has to be explored.[33]

Limitation of our study was small sample size and selection bias with population as

adverse effects are more common in elderly. In future we have planned to conduct similar study with antihistaminics alone and FDCs. We also intend to perform such study in different population and elderly people.

Survey of literature has not revealed any report regarding the effects of fixed drug combinations containing cetrizine and chlorpheniramine with phenylephrine and paracetamol on these tests and hence our findings could not be compared. One has to consider probably above mentioned reasons are responsible for non-impairment of cognition and psychological behviour due to these drugs.

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