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RESEARCH ARTICLE

The effect of fexofenadine, a newer second-generation antihistaminic, on phenobarbitone sleeping time and its comparison with terfenadine, astemizole and cetirizine in albino rats

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ABSTRACT

Background: The second-generation antihistaminic fexofenadine has been claimed to be superior to terfenadine and cetirizine, in possessing the negligible sedating property and can be safely given to pilots and drivers. Here, it is a study that compares the sedative property of fexofenadine to terfenadine, astemizole, and cetirizine by phenobarbitone induced sleeping time in albino rats. **Aims and Objectives:** To evaluate the nonsedative antihistaminic action of fexofenadine and comparing it with cetirizine, terfenadine, and astemizole. **Materials and Methods:** A total of 90 albino rats of either sex weighing 100-200 g were selected and randomly divided into nine equal groups. At 0 h phenobarbitone 40 mg/kg is injected intraperitoneal to the rats. The animals are placed on their backs, and duration of loss of righting reflex is measured. Each rat was pretreated at "−1" h with the drugs orally using orogastric tube. The different groups are as follows: Group 1 was given distilled water; Groups 2-9 were given with fexofenadine 20 mg and 40 mg/kg. Terfenadine 20 mg and 40 mg/kg, cetirizine 2 mg and 4 mg/kg, and astemizole 2 mg and 4 mg/kg body weight, respectively, and data are statistically analyzed by unpaired *t*-test and ANOVA. **Results:** The mean phenobarbitone sleep time duration of fexofenadine (20 mg and 40 mg) is comparable to placebo and is less sedative. This study shows cetirizine produces longer duration of sleep ($P < 0.01$) followed by astemizole ($P < 0.01$), terfenadine, and non-sedative fexofenadine. **Conclusion:** This study shows fexofenadine produces less sedation at both the lower and higher dose as compared to that of control and other groups.

KEY WORDS: Fexofenadine; Astemizole; Terfenadine; Cetrizine; Sleeping Time

INTRODUCTION

H_1-antihistamines are the mainstay of treatment for common cold, urticaria, allergy, motion sickness, and Parkinsonism, etc. The older first-generation H_1-antihistamines such as chlorpheniramine penetrate readily into the brain to cause sedation, drowsiness, fatigue and impaired concentration and memory causing detrimental effects on learning in children and also an impairment of the ability of adults to perform the work and drive. They should be cautiously used in such conditions.[1-3] This is because most drugs of this class are lipid soluble, cross the blood brain barrier, and affect the central nervous system (CNS), causing sedation and impaired laboratory indices of psychomotor function. Recently, newer the second-generation H_1 receptor antagonists such as cetirizine, fexofenadine, and loratadine have been introduced are safe, cause less sedation and are more efficacious. This is because they do not appear to be centrally active, either because of poor penetration of CNS or because of selective affinity for peripheral H_1 receptor sites. The major reason

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for the reduced penetration of the second-generation H_1-antihistamines into the brain is because their translocation across the blood–brain barrier is under the control of active transport proteins, of which the adenosine-5′-triphosphate-dependent efflux pumps, P-glycoprotein.[4,5]

Although fexofenadine is devoid of CNS effects, many other second-generation H_1-antihistamines still penetrate the brain to a small extent where they have the potential to cause some degree of drowsiness or somnolence, and particularly when used at the higher doses. Henceforth, this preclinical study was undertaken to compare the sedative property of fexofenadine, a newer the second-generation antihistaminic with terfenadine, astemizole, and cetirizine in albino rats using potentiation of phenobarbitone sleep time model.

MATERIALS AND METHODS

The study was conducted in Central Animal Laboratory, JJM Medical College and Research Institute Davangere. Adult healthy albino rats of either sex weighing between 100 and 200 g were housed in the air-cooled central animal house was included in the study. The pregnant female albino rats were excluded from the study.

They were allowed to get acclimatized to laboratory conditions (12:12 h dark/light, 25-2°C) for 7 days. They had free access to food and water *ad libitum*. This study was done after obtaining prior approval from the Institutional Animal Ethics Committee. All animals were handled according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments in Animals, Government of India.

Treatment Schedule

A total of 90 albino rats of either sex weighing 100-200 g were selected and randomly divided into nine equal groups containing 10 rats in each group. This was guess estimate sampling; no formal sample size was calculated. No animal was sacrificed in this study.

At "0" h phenobarbitone 40 mg/kg was injected intraperitoneally to the albino rats. The animals were placed on their backs on warmed (37°) pad and duration of loss of lighting reflex (starting at the time of hexobarbital injection) was measured until they regain their righting reflex. If there was any doubt as to the reappearance of the righting reflex, the subject was placed gently on its back again and if it rights itself within 1 min, this time is considered as the endpoint. The test used was "potentiation of phenobarbital sleeping time." The test is used to elucidate CNS-active properties of the drugs such as hypnotics, sedatives, and tranquilizers. At the high doses are known to prolong hexobarbital-induced sleeping time after a single dose of hexobarbital.

Each rat was pretreated at "−1" h (1 h before) with the drugs given orally using the albino rats were allocated into different groups as follows. Details of treatment schedule are shown in Table 1.

Statistical Analysis

The data were presented as mean ± standard error of the mean. Student's *t*-test (unpaired) was used for comparison between two groups. One-way ANOVA was used for multiple group comparison followed by Newman-Keuls range test for pairwise comparison. $P = 0.05$ or less was considered for statistical significance. The Statistical Package for Social Sciences Version 18 was used for the analysis of data.

RESULTS

Table 1 shows the mean phenobarbitone sleep time duration of all the nine groups. The sleeping duration data is comparable among the groups. Table 2 compares phenobarbitone sleep time between the control and antihistamine pretreated groups. Tables 3 and 4 shows high and low dose wise comparisons.

DISCUSSION

Mattila and Paakaari[6] reported in their study of newer non-sedating antihistamines fexofenadine, loratadine, acrivastine,

Table 1: Baseline characteristics of various groups - phenobarbitone sleep time

Groups	Test drugs with dosage	Sleeping time in minutes (mean±SD)
1	Pretreated with 2 ml of distilled water PO.+phenobarbitone 40 mg/kg BW IP (control)	160.4±20.8
2	Pretreated with fexofenadine 20 mg/kg BW, PO. 1 h prior+post-treated with phenobarbitone	157.52±12.6
3	Pretreated with fexofenadine 40 mg/kg BW, PO. 1 h prior+post-treated with Phenobarbitone	159.2±19.5
4	Pretreated with terfenadine 20 mg/kg BW, PO. 1 h prior+post-treated with Phenobarbitone	177.2±28.0
5	Pretreated with terfenadine 40 mg/kg BW, PO. 1 h prior+post-treated with Phenobarbitone	254.7±44.9
6	Pretreated with astemizole 2 mg/kg BW, PO. 1 h prior+post-treated with Phenobarbitone	254.7±44.9
7	Pretreated with astemizole 4 mg/kg BW, PO. 1 h prior+post-treated with phenobarbitone	216.2±48.2
8	Pretreated with cetirizine 2 mg/kg BW, PO. 1 h prior+post-treated with phenobarbitone	208.4±48.2
9	Pretreated with cetirizine 4 mg/kg BW, PO. 1 h prior+post-treated with phenobarbitone	317.0±40.6

PO: Per orally, BW: Body weight, IP: Intraperitoneally, SD: Standard deviation

Table 2: Comparison of duration of sleep with control and anti-histamine pretreated groups

Control Group 1	Group no	Mean±SEM	Diff. from control	Significance	
				*t***	*P*
Distilled water 160.4±20.8	Fexofenadine 20 mg/kg BW (2)	157.5±1.52	2.9	0.38	0.71
	Fexofenadine 40 mg/kg BW (3)	159.2±2.18	1.2	0.13	0.90
	Terfenadine 20 mg/kg BW (4)	177.2±3.12	16.8	1.52	0.15
	Terfenadine 40 mg/kg BW (5)	169.9±3.93	9.5	0.80	0.44
	Astemizole 2 mg/kg BW (6)	254.7±4.92	94.3	6.02	<0.001*
	Astemizole 4 mg/kg BW (7)	216.2±5.32	55.8	3.36	<0.01*
	Cetirizine 2 mg/kg (8)	308.4±5.18	148.0	8.92	<0.001*
	Cetirizine 4 mg/kg (9)	317.0±4.85	156.6	10.87	<0.001*

**Unpaired *t*-test, *Significance, <0.01 Significant, SEM: Standard error of mean, BW: Body weight

Table 3: Comparison of sleep time duration between low-doses antihistamine pretreated groups

Group no.	Mean±SEM	Difference between groups		
		Groups compared	Mean difference	*P* value
Fexofenadine 20 mg/kg BW (2)	157.5±1.52	2-4 (fexofenadine v/s terfenadine)	19.8	NS
		2-6 (fexofenadine v/s astemizole)	97.3	<0.01 S
Terfenadine 20 mg/kg BW (4)	177.2±3.12	2-8 (fexofenadine v/s cetirizine)	151.0	<0.01 S
		4-6 (terfenadine v/s astemizole)	77.5	<0.01 S
Astemizole 2 mg/kg BW (6)	254.7±4.92	4-8 (terfenadine v/s cetirizine)	131.2	<0.01 S
Cetirizine 2 mg/kg (8)	308.4±5.18	6-8 (astemizole v/s cetirizine)	53.7	<0.05 S

One-way ANOVA, *F*=37.0, *P*<0.01, S: Significant, Newman-Keul's range test, least emizole significant difference, LSD=44.0, *P*<0.05; 54.7, *P*<0.05, BW: Body weight, NS: Non-significant

Table 4: Comparison of sleep time duration between high doses antihistamine pretreated groups

Group no.	Mean±SEM	Difference between groups		
		Groups compared	Mean diff.	*P*-value
Fexofenadine 40 mg/kg BW (3)	159.2±2.18	3-5 (fexofenadine v/s terfenadine)	10.7	NS
		3-7 (fexofenadine v/s astemizole)	57.0	<0.01 S
Terfenadine 40 mg/kg BW (5)	169.9±3.93	3-9 (fexofenadine v/s cetirizine)	157.8	<0.01 S
		5-7 (terfenadine v/s astemizole)	46.3	<0.05 S
Astemizole 4 mg/kg BW (7)	216.2±5.32	5-9 (terfenadine v/s astemizole)	147.1	<0.01 S
Cetirizine 4 mg/kg (9)	317.0±4.85	7-9 (astemizole v/s cetirizine)	100.8	<0.01 S

One-way ANOVA, *F*=37.0, *P*<0.01, S: Significant, Newman-Keul's range test, least significant difference, LSD=44.3, *P*<0.05; 55.0, *P*<0.01, SEM: Standard error of the mean, BW: Body weight, NS: Non-significant

astemizole, cetirizine, astemizole and terfenadine however not entirely free from central effects and there at astemizole quantitative differences between them psychomotor and sleep studies in the healthy subjects in laboratory may predict that antihistamine does not cause drowsiness; but the safety margin is narrow enough to cause a central sedating effect during actual treatment. This might result from a patient individual sensitivity, disease induced sedation or drug dosages that are various reasons relatively or absolutely larger. In this study, phenobarbitone sleep duration potentiation by fexofenadine (20 and 40 mg); new agent is compared with relative phenobarbitone sleep time of terfenadine (20 and 40 mg), astemizole (2 and 4 mg), and cetirizine (2 and 4 mg). This study depicts the mean sleep time duration of fexofenadine (20 and 40 mg) doses similar to that of control.

Mason J et al.[7] reported that fexofenadine is highly specific H_1 receptor antagonist with safety profile similar to that of control and does not impair performance in test of driving or psychomotor performance and has been shown to improve the quality of life in patient treated with season allergic rhinitis. This study also shows no dose-related sedation even at the higher doses.

Rousell et al.[7] also reported fexofenadine is truly sedating, showing no dose related increase in sedation even at the higher doses. In this study, comparison of mean phenobarbitone sleep duration of all the low dose groups and high dose groups of antihistamine pre-treated animal shows fexofenadine and terfenadine have shorter duration of sleep compared with that of astemizole and cetirizine groups.

O'Hanlon and Ramaekers[8-10] reported that the second-generation antihistamine such as fexofenadine and its parent compound, terfenadine, did not impair the performance of automobile drivers or no central nervous depression. This study shows phenobarbitone sleep time in albino rats shows that cetirizine is most potent followed by astemizole, terfenadine, and fexofenadine, whereas fexofenadine was indistinguishable from placebo.

Philpot[11] reported that cetirizine, at recommended doses, has been shown to impair the performance and cognition, in several studies, although to a much lesser degree than older antihistamines. Cetirizine has safety profile of only fair to good because in astemizole to other nonsedating antihistamine, the incidence of sedation has been slightly higher in patients treated with cetirizine, compared with dose receiving placebo. Hence, cetirizine should be described as mildly sedative rather than nonsedating. This sedation terfenadine is particularly important for patients whose mental alertness is critical (students and operation of machinery and motor vehicle) and for whom classic antihistamines might cause troublesome sedation.

Limitation of Study

The only parameter studied was potentiation of phenobarbitone sleep time. The other aspects of sedation parameters such as electroencephalogram, electromyogram, and electro-oculographic not evaluated. Owing to nonavailability of other analytical methods, other parameters could not be studied. Also need for clinical study, in healthy human volunteers.

CONCLUSION

This study shows fexofenadine produces less sedation at both the lower and higher dose as compared to that of control and other groups of antihistamines.

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