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COMPARATIVE CNS ACTIVITIES OF CLINICALLY EMPLOYED ANTIHISTAMINES (H_1 ANTAGONIST)

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ABSTRACT: Aim: H1 Antihistamines are classified into the first generation and second generation agents. The main differences between the first and second generations of drugs are their propensity to cause central nervous system (CNS) side effects. Therefore, the present study was aimed to analyze the effects of different H1 antihistamines (first and second generation) on CNS using different animal experimental models. **Materials and Methods:** H1 antihistamines such as pheniramine maleate (3 mg/kg, 6 mg/kg), cetirizine (0.6 mg/kg, 1.2 mg/kg), levocetirizine (0.6 mg/kg, 1.2 mg/kg), loratadine (1 mg/kg, 2 mg/kg) and desloratadine (0.6 mg/kg, 1.2 mg/kg) are evaluated and compared for their effects on CNS using experimental animal model (Pentobarbitone sleeping time, spontaneous motor activity, motor coordination) in *Swiss albino* mice. **Results and Discussion:** Desloratadine (0.6 mg/kg, 1.2 mg/kg) and loratadine (1 mg/kg, 2 mg/kg) did not produce significant ($P<0.05$) effect on sleeping time when compared to control. At 120 min time interval after treatment with cetirizine (1.2 mg/kg) and levocetirizine (1.2 mg/kg) was shown a reduction in locomotor activity and remaining three drugs such as pheniramine (6 mg/kg), loratadine (2 mg/kg) and desloratadine did produce any effect on locomotor activity. Treatment with a higher dose of pheniramine (6 mg/kg) and cetirizine (1.2 mg/kg) was shown significant ($P<0.05$) motor coordination while other drugs did not induce any motor in-coordination. First generation antihistamines were shown a significant effect on CNS activity at low and high dose while only some second-generation antihistamines showed a significant effect on CNS at the high dose. **Conclusion:** Numerous well-performed, sensitive measures of psychomotor and cognitive performances are needed to study to compare the effect of the first generation and second generation antihistamines on CNS to avoid serious impairment of CNS function.

INTRODUCTION: Antihistamines are broadly divided into first and second generation drugs based on their structural characteristics, pharmacokinetic, and adverse effects.

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The effects of antihistamines on the central nervous system are determined by their capability to cross the blood-brain barrier and capacity to bind with the H_1 receptor. The capability of drugs to cross blood-brain barrier depends on the lipophilic nature of the drug entity and its affinity towards P glycoprotein [1].

First generation drugs penetrate blood-brain barrier readily due to their lipophilicity/solubility ratios, relatively low molecular weight, and for some, lack of recognition by the P-glycoprotein reflux pump

expressed on the luminal surfaces of endothelial cells in the cerebral vasculature [2].

Second generation drugs are highly specific for histamine receptors. They penetrate poorly into the CNS due to their lipophilic nature, relatively high molecular weight, or recognition by the P-glycoprotein efflux pump expressed on the luminal surfaces of endothelial cells in the cerebral vasculature. Though second-generation drugs penetrate blood brain barrier to lesser extent but many of them have been found to produce dose related impairment of CNS functions [3, 4].

Epidemiologic studies have been done to establish the relationship between increased incidence of automobile accidents and the administration of antihistamines. The adverse effects of first-generation H_1 antihistamines are mainly on the CNS, including impaired driving performance, drowsiness, lassitude, fatigue, and dizziness. Although the new-generation antihistamines, do not exert serious CNS effects, a small number of individuals may experience sedation with these drugs [5, 6].

Therefore, the present study was aimed to analyze the effects of different antihistamines (first and second generation) on the central nervous system using different animal experimental models.

MATERIALS AND METHODS:

Animal: Swiss albino mice weighing 25-30 gm of either sex were procured from the departmental animal house for experimentation. Animals were divided into groups (n=8) and housed in poly-acrylic cages under standard laboratory conditions (temperature 25 ± 2 ºC and dark-light cycle 14-10 hrs) with an allowance of free access to standard dry pellet diet (Hindustan Lever, Kolkata, India) and water ad libitum. The animals were transferred to the laboratory at least one hour before experimentation. The experiments were performed during day time (08.00–16.00 h). The animals were cared for and maintained by CPCSEA guidelines.

Drugs and Other Chemicals: The pure form of powdered pheniramine maleate, cetirizine, levocetirizine, loratadine, and desloratadine were obtained from Cadila Pharmaceutical Ltd., India. Pentobarbitone Sodium (standard drug) was obtained from Ind-Swift Pvt. Ltd., India. A tween 80 (used as solvent and vehicle) was obtained from ACS Chemical Ltd, Ahmedabad, India. All other chemicals used in the experiments were of analytical grade.

Preparation of Drug and Mode of Treatment: The treatment drugs such as loratadine and desloratadine were suspended 1% Tween 80, and all other drugs were suspended in Sterile Physiological Saline (SPS) containing 0.5% Carboxy Methyl Cellulose (CMC). All animals were treated *via* the intraperitoneal route of administration. In the present study, we have taken one control group as tween 80 is impermeable so it cannot alter the activity of the central nerves system (CNS) [7].

Treatment Schedule: The animals were divided into the following groups (n=8)

Group I: The animals of this group received 0.5 ml/kg, 1% Tween 80 suspended in SPS i.p.

Group II: The animals of this group received Pheniramine (3 mg/kg).

Group III: The animals of this group received Pheniramine (6 mg/kg).

Group IV: The animals of this group received Cetirizine (0.6 mg/kg).

Group V: The animals of this group received Cetirizine (1.2 mg/kg).

Group VI: The animals of this group received Levocetirizine (0.6 mg/kg).

Group VII: The animals of this group received Levocetirizine (1.2 mg/kg).

Group VIII: The animals of this group received Loratadine (1 mg/kg).

Group IX: The animals of this group received Loratadine (2 mg/kg).

Group X: The animals of this group received Desloratadine (0.6 mg/kg).

Group XI: The animals of this group received Desloratadine (1.2 mg/kg).

Pentobarbitone Sleeping Time: Pentobarbitone Sodium (30 mg/kg, i.p.) was injected 30 minutes after administration of test drug and vehicle in all groups for the screening of centrally acting compounds [8, 9]. The time elapsed between loss and

recovery of the righting reflex was noted and taken as sleeping time. This reflex was considered positive when the animal placed on its side recovers from this position within one minute. It was considered lost when the recovery requires a longer period. This time has been expressed in min. Sleeping time was expressed as Mean ± SEM.

Spontaneous Motor Activity: Spontaneous motor activity was measured by Actophotometer (Techno lab. Lucknow). The actophotometer is an instrument designed for registering walking and running movement of mice by recording the number of times; they interrupt a beam of light [10]. The instrument consists of a chamber of 30 × 30 × 24 cm in size with a soundproof lid on its top. The floor of the chamber is covered by six photo cell beams, and each time the animal crosses the beam, it is counted and shown on the LCD unit. Thirty minutes after administration of test drug and vehicle i.p., the activity was measured for each group by placing them in actophotometer for 10 minutes at 30 min interval for 120 min (2 h).

Motor Co-Ordination: Skeletal muscle relaxation was induced by a test compound could be evaluated by testing the ability of mice or rats to remain on a rotating rod [11]. For this purpose, a group of mice was trained to remain on the rotarod for 3 min at 25 r.p.m. The animals were discarded and replaced if they failed to do so. Ninety animals were considered and trained on rotarod in eleven groups (n=8). On next day both vehicle or test compound was introduced, and the ability of animals to remain on the rotarod was assessed before and 30 minutes after i.p. administration. The falloff time from the rotarod was noted for each animal during the scheduled time (3 min) and was compared with the control group.

Statistical Analysis: All the values were expressed as mean ± SEM or mean ± SD. Statistical analysis was carried out using SAS 9.1 version. Statistical significance of the difference between two means was assessed by one-way ANOVA followed by Dunnets' Test. A probability level of $P<0.05$ was considered significant.

RESULT:

Pentobarbitone Induced Sleeping Time: Results of present study showed lower dose treatment with pheniramine maleate (3 mg/kg) and cetirizine (0.6 mg/kg) significantly ($P<0.05$) potentiated sleeping time while lower dose treatments with levocetirizine (0.6 mg/kg), loratadine (1 mg/kg) and desloratadine (0.6 mg/kg) had no significant effect on sleeping time **Table 1**. Higher dose treatment with pheniramine maleate (6 mg/kg), levocetirizine (1.2 mg/kg) and cetirizine (1.2 mg/kg) were significantly ($P<0.05$) potentiated sleeping time whereas higher dose of loratadine (2 mg/kg) and desloratadine (1.2 mg /kg) had not shown significant effect on sleeping time when compared to control **Table 1**.

TABLE 1: EFFECT OF ANTIHISTAMINES ON PENTOBARBITONE SLEEPING TIME IN MICE (N=8)

Treatment	Dose	Sleeping Time (min)
Control	0.2 ml	13.62 ± 0.52
Pheniramine	3 mg/kg	27.00 ± 1.07*
Pheniramine	6 mg/kg	32.00 ± 4.04*
Cetirizine	0.6 mg/kg	23.75 ± 1.04*
Cetirizine	1.2 mg/kg	25.36 ± 0.74*
Levocetirizine	0.6 mg/kg	13.88 ± 0.64
Levocetirizne	1.2 mg/kg	17.00 ± 1.06*
Loratadine	1 mg/kg	13.88 ± 0.83
Loratadine	2 mg/kg	13.75 ± 0.71
Desloratadine	0.6 mg/kg	14.00 ± 0.76
Desloratadine	1.2 mg/kg	13.75 ± 0.71

Data are expressed in minutes as the Mean ± SD, n=8; *p < 0.05 & p < 0.01 when compared to control group

Spontaneous Motor Activity: Spontaneous motor activity assessment was done at different time intervals, *i.e.* at 30, 60, 90, and 120 min after administration of drug using rotarod actophotometer for ten minutes. At first 30 min assessment showed no significant ($P<0.05$) reduction in locomotors activity with treatment of lower dose of pheniramine maleate (3 mg/kg), cetirizine (0.6 mg/kg), levocetirizine (0.6 mg/kg), loratadine (1 mg/kg) and desloratadine (0.6 mg/kg). At 60 min three out of five drugs such as pheniramine (3 mg/kg), cetirizine (0.6 mg/kg) and levocetirizine (0.6 mg/kg) were shown significant ($P<0.05$) reduction in locomotor activity when compared to control **Table 2**. At 90 minutes loratadine (1 mg/kg), pheniramine (3 mg/kg), cetirizine (0.6 mg/kg) and levocetirizine (0.6 mg/kg) also showed significant ($P<0.05$) reduction in locomotors count when compared to control. However, in the entire group, no effect on locomotor counts was noted at 120 min after lower dose treatment.

Locomotor count assessed at 30 min was shown no significant effect on counts with any of the drugs at a higher dose. At 60 min interval pheniramine (6 mg/kg), cetirizine (0.6 mg/kg) and levocetirizine (0.6 mg/kg) were shown significant (P<0.05) reduction in locomotor count when compared to control. Loratadine (2 mg/kg) was shown a significant reduction in the count at 90 min and a similar trend was noted for three drugs such as pheniramine (6 mg/kg), cetirizine (1.2 mg/kg) and levocetirizine (1.2 mg/kg). At 120 min time interval cetirizine (1.2 mg/kg) and levocetirizine (1.2 mg/kg) showed a reduction in locomotor activity and remaining three drugs such as pheniramine (6 mg/kg), loratadine (2 mg/kg) and desloratadine did not produce any effect on locomotor activity **Table 2**.

TABLE 2: EFFECT OF ANTIHISTAMINES ON SPONTANEOUS LOCOMOTOR ACTIVITY IN MICE

Treatment	Dose	30 min	60 min	90 min	120 min
Control	0.2 ml	216.25 ± 139.39	153.50 ± 60.85	149.50 ± 53.94	144.75 ± 55.36
Pheniramine	3 mg/kg	108.50 ± 5.32	71.00 ± 6.68*	73.50 ± 6.03*	74.50 ± 3.56
Pheniramine	6 mg/kg	195.00 ± 7.39	94.25 ± 5.74*	149.50 ± 53.94*	100.00 ± 5.72
Cetirizine	0.6 mg/kg	110.75 ± 9.22	73.25 ± 4.03*	81.00 ± 4.76*	77.00 ± 3.56
Cetirizine	1.2 mg/kg	131.00 ± 28.40	76.50 ± 9.33*	75.75 ± 7.37*	73.75 ± 8.22*
Levocetirizine	0.6 mg/kg	111.50 ± 9.47	77.50 ± 7.42*	74.25 ± 7.09*	244.25 ± 342.61
Levocetirizine	1.2 mg/kg	113.75 ± 5.74	68.25 ±5.12*	62.25 ± 2.87*	54.50 ± 15.67*
Loratadine	1 mg/kg	114.00 ± 35.24	111.00 ± 40.78	90.75 ± 33.09*	101.25 ± 32.94
Loratadine	2 mg/kg	111.00 ± 26.44	103.75 ± 26.09	98.25 ± 24.76*	102.75 ± 23.47
Desloratadine	0.6 mg/kg	124.25 ± 20.11	114.00 ± 20.54	118.75 ± 21.61	112.50 ± 19.21
Desloratadine	1.2 mg/kg	122.50 ± 10.47	119.75 ± 10.69	118.75 ± 4.35	114.75 ± 5.91

Data are expressed as activity counts for 10 minutes (Mean ± SEM; n=8) at different time intervals (minutes) after administration of the drug. One way ANOVA followed by Dunnet's test was used for statistical analysis and *p < 0.05 & p < 0.01 when compared to the control group.

Motor Coordination: The animals treated with different antihistamines (lower and higher dose) were tested on a rotating rod for 3 min at 25 r.p.m to evaluate motor coordination. Only pheniramine at a lower dose (3 mg/kg) was shown significant (P<0.05) effect on motor coordination while the remaining drug did not affect motor coordination when compared to control **Table 3**. On treatment with higher dose only pheniramine (6 mg/kg) and cetirizine (1.2 mg/kg) shown significant (P<0.05) effect on motor coordination while other drugs did not induce any motor in-coordination when compared to control **Table 3**.

TABLE 3: EFFECT OF ANTIHISTAMINES ON MOTOR CO-ORDINATION BY ROTAROD TEST IN MICE

Treatment	Dose	Fall of counts in 3 min	% increase in fall off counts
Control	0.2 ml	7.88 ± 0.64	-
Pheniramine	3 mg/kg	15.13 ± 1.23*	92.0
Pheniramine	6 mg/kg	11.00 ± 1.31*	39.6
Cetirizine	0.6 mg/kg	8.75 1.04	11.0
Cetirizine	1.2 mg/kg	10.88 ± 1.25*	38.1
Levocetirizine	0.6 mg/kg	8.75 ± 0.71	11.0
Levocetirizine	1.2 mg/kg	8.13 ± 1.13	3.8
Loratadine	1 mg/kg	8.00 ± 0.76	1.5
Loratadine	2 mg/kg	8.00 ± 0.76	1.5
Desloratadine	0.6 mg/kg	8.75 ± 1.49	11.0
Desloratadine	1.2 mg/kg	8.00 ± 0.76	1.5

Data are expressed in minutes as the Mean ± SD and percentage, n=8; *p < 0.05 when compared to the control group

DISCUSSION: Antihistamines are among the most widely used medication in the world for the symptomatic treatment of allergic disorder such as chronic urticaria, various skin allergy, and perennial allergic rhinitis. The histamine exerts some effect on CNS, which includes a cycle of sleep and waking, thermal regulation, food intake, aggressive and emotion behavior, memory, learning, and locomotion [12]. First generation antihistamines such as hydroxyzine, promethazine, diphenhydramine, and chlorphenamine readily penetrate brain which is responsible for sedative

action on CNS. The second generation of antihistamine penetrate poorly in CNS and thus does not produce sedating effects. In previous studies, it's reported that the cetirizine may be slightly more sedating then placebo even at recommended doses. Major therapeutic effects of antihistamines are seen in the suppression of the early response to allergen challenge in the conjunctiva, nose, skin, and lower airway [13].

The results of our study are congruent with Patel *et al.*, (2000) who reported that the cetirizine (2 mg/kg & 4 mg/kg dose) treated (i.p) rats showed significant dose dependent increase in sleeping time. Cetirizine (0.6 mg/kg & 1.2 mg/kg) potentiated sleeping time in this paradigm. McLeod RL in 1998 has reported sedating activity of cetrazine at 30 mg/kg p.o in mice [14]. I.C.V. treatment of cetirizine (0.03-0.3 microg/mouse) dose-dependently increased the duration of pentobarbitone induced loss of righting reflex in both nondiabetic and diabetic mice [15].

It has been reviewed in experimental as well as in clinical studies the first generation antihistamines are associated with CNS side effects like sedation and the secondary effects like psychomotor impairment. Although second-generation H_1 antihistamine claim to be "non-sedating," some agents still cause CNS side effects, though findings are conflicting with one and another.

The present experimental study was undertaken in mice to evaluate the CNS effects of first and second generation H_1 antihistamine by subjecting animals to i.p. administration of Pheniramine maleate, Cetirizine, Levocetirizine, Loratadine, and Desloratadine (at the low and the high doses, the ratio being 1:2). The CNS effects were evaluated by evaluating CNS parameter like Pentobarbitone induced sleeping time, spontaneous motor activity, and motor coordination, using appropriate statistical methods. Only Pheniramine and Cetirizine potentiated sleeping time at both lower and higher dose while levocetirizine at higher dose potentiated sleeping time. Pheniramine at higher and lower dose induced motor incoordination and cetirizine at higher dose induced motor incoordination significantly. Desloratadine was free from CNS effect in all three CNS parameters in both at lower and at a higher dose. No correlation between the lower and higher dose of any antihistamine drugs was found, and the intensity to produce CNS effect could be established following statistical analysis [16, 17].

Some results correlate with the findings of the earlier research work as reviewed herein. Further species difference is likely to influence the results as the study has been carried out in experimental animals. Therefore these observations cannot be made directly applicable to clinical cases. With the introduction of more and more novel antihistamines, the need for practical guidelines on switching medications is likely to become more acute. Switching between drugs with a different mode of action, which in turn are associated with different dosing requirements, side effect profiles and requires careful handling. The principle of individualization should be illuminated.

CONCLUSION: In the light of the reported serious CNS side effects of H_1 antihistamines drug usage and the results obtained herein, it is concluded that, initial choice should be made based on particular basis such as patient's medical and socioeconomic status, and the clinicians should be proactive about warning their patients about the potential CNS side effects such as sedation, psychomotor impairment, and motor incoordination, *etc*.

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CONFLICT OF INTEREST: Nil

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