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Research Article

Comparative evaluation of H_1 receptor blocking activity and safety of newer H_1antagonist mizolastine with loratadine and placebo: a randomized double blind three way crossover study

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ABSTRACT

Background: Histamine is a naturally occurring body constituent synthesized from L-histidine by histidine decarboxylase enzyme that is expressed throughout the body including central nervous system neurons, gastric mucosa, mast cells and basophils. The objective of this study was to compare the pharmacological activity and safety of 10 mg mizolastine, 10 mg loratadine and placebo in healthy human volunteers.
Methods: After randomly allocating the 3 drugs, a battery of psychometric tests was done. Histamine prick test for wheal and flare reaction, VAS for sedation and itch followed by salivary flow test were done. Vitals were recorded. The subjects were randomized to receive either of the treatment in a cross-over manner with washout period of 7 days. The wheal and flare areas were recorded before and after 1,2,4,8, and 24 hours.
Results: Mean inhibition on histamine induced wheal and flare response with mizolastine was highly significant as compared to placebo from 1 hour onwards ($p<0.001$) with maximum inhibition of 98.1±1.8% at 4 hours and of 85.1±24.8percent at 8 hours, for wheal and flare, respectively. The mean inhibition on histamine induced response with loratadine was significant from 2 hours ($p<0.05$) for wheal area and 1 hour onwards up to 24 hours ($P<0.01$) for flare area with the maximum inhibition of 56.2±31.6 percent and 60.1±14.2percent at 8hours, respectively. Mean inhibition on histamine induced itch with mizolastine was also significant from 4 hours onwards and persisted up to 24 hours ($p<0.05$) with maximum inhibition of 58.6±54.2% at 8 hours for the itch response, unlike loratidine. There was no significant change in mean effect on sedation assessed on a VAS of 0-100 mm. There was no significant change in psychomotor functions, salivary flow or vital parameters. All were well tolerated.
Conclusions: Mizolastine has good antihistaminic activity than loratadine. Neither drug causes any psychomotor impairment or has anti-cholinergic action.

Keywords: Mizolastine, Loratadine, Placebo, Psychometric tests, Histamine prick test.

INTRODUCTION

Histamine is a naturally occurring body constituent synthesized from L-histidine by histidine decarboxylase enzyme that is expressed throughout the body including central nervous system neurons, gastric mucosa, mast cells and basophils.[1] It causes hypersensitivity reactions. In 1927, Best and his colleagues isolated it from liver and lung tissue and named it after Greek word 'histos'which means 'tissue'. It acts through H1,H2,H3 and H4 receptors.[2]

The triphasic response to the firm stroking of the skin is characterized sharply by demarcated erythema, a brief blanching of skin and release of histamine from the mast cells followed by arteriolar dilatation causing an intense red flare that extends beyond the margins of line of pressure and ends with appearance of wheal having the configuration of original stroking.[3] We've compared the pharmacodynamic profile of second generation anti-histamines, mizolastine and loratadine with placebo.

Table 1: Type of histamine receptor.

Type of histamine receptor	Location	Function
H1	Found on smooth muscle endothelium, and central nervous system tissue.	Causes vasodilatation, bronco constriction, smooth muscle activation, separation of endothelial cells and pain and itching due to insect stings, primary receptors involved in allergic rhinitis symptoms and motion sickness.
H2	Located on parietal cells	Primarily stimulates gastric acid secretion.
H3	CNS, presynaptic nervous system acts as auto receptors in histaminergic neurons	Decreased neurotransmitter release. Histamine acetylcholine nor-epinephrine serotonin. H3 exists as post synaptic inhibitory heteroceptors.
H4	Found primarily in basophils and in the bone marrow. It is also found in thymus. Small intestine, spleen and colon.	Unknown physiological role.

Antihistamines, mostly the first generation agents are known to have side effects such as sedation but the second generation antihistamines are advantageous due to lack of this effect. Hence we are attempting to see the effect of mizolastine, a new H1 second generation antihistamine on the psychomotor function by performing psychometric tests in comparison with loratadine and placebo. Further we are also attempting to evaluate the anticholinergic action of mizolastine by salivary flow method in comparison with that of loratadine and placebo.

The objective of the study is to compare the pharmacological activity and safety of mizolastine 10 mg administered orally in comparison with placebo and loratadine 10 mg in healthy human volunteers with special reference to histamine prick test.

The following are the materials used in the study;

- Healthy male human volunteers
- Drugs: mizolastine, loratadine, placebo
- Formulations: tablets
- Route: oral
- Dose: mizolastine-10 mg single dose (treatment A) loratadine-10 mg single dose (treatment B) placebo-10 mg single dose (treatment C)
- Weighing machine and height scale
- Multi-channel monitor
- Other drugs: histamine solution 100 mg/ml, spirit, cotton swab, normal saline, disposable insulin syringes, lancet, transparent sheets, graph paper, red and blue fine tipped marker pens, measuring scale, chlorpheneramine injection, adrenaline injection, atropine injection, adenosine injection, amiodarone injection, asthaline solution, calcium injection, dobutamine injection, dopamine injection, decadron injection, ifcorlin injection, isoprenaline injection, potassium chloride injection, midazolam injection, nitroglycerine injection, promethazine injection, phenytoin injection, rantidine injection, sodium bicarbonate injection, xylocaine 2% injection, isoprinosine injection, diazepam injection, salbutamol inhaler.
- Apparatus: reaction time apparatus, flicker fusion threshold apparatus, set of playing cards, digit letter substitution sheets, six letter cancellation tests, visual analogue scale for measuring sedation and itch, stop watch, calculator, black ball point pen, sterilised cotton balls, polythene covers, electronic sensitive balance.

The design of this study was randomized double blind placebo controlled crossover study with washout period of seven days between the treatments.

The duration of this study was twenty four hours.

Patients and procedure

After serving dinner at 9 pm, the subjects were given an information leaflet, were asked to report any adverse events during the study period and were discharged after 24 hours of drug administration. They were asked to come to the study for the second and third runs after 7 days of washout between each period and the same procedures were repeated. The data recorded were entered in the case record form.

Inclusion criteria

A willing study participant to become eligible for this must fulfill all the following criteria.

- Provide informed consent
- Must be healthy adult human being within18-45years of age ,both inclusive
- Must have normal health as determined by medical history, physical examination and laboratory investigations performed 14 days prior to the commencement of the study.

Exclusion criteria

A willing study participant will be excluded from the study if any of the following are present:

- Wheal area for histamine prick test is <20 sqmm.
- Systolic blood pressure is <90mmHg or >140 mmHg
- Diastolic blood pressure is <60mmHg or > 90 mmHg
- Oral temperature is < 95^0F or > 98^0F
- Pulse rate is <50 or>100 beats/minute
- History of hypersensitivity/idiosyncratic reactions to investigational drug or any related drugs.
- Any evidence of impairment of renal, hepatic, lung, cardiac or gastro intestinal function.
- Regular smoker who has the habit of smoking nine cigarettes per day and has difficulty of abstaining smoking during the study period.
- Habit of alcoholism and difficulty in abstaining alcohol during the study period.
- Difficulty in abstaining from xanthene containing food or beverages during the study period.
- Intake of over the counter or prescribed medications and enzyme modifying medication or systemic medication for the past 30days.
- Confirmed positive in selected drug abuse.
- Participated in any other clinical investigation using experimental drug or donated blood in past 90 days before start of the study.

METHODS

The study protocol was detailed protocol and case record form and subject's informed consent form were reviewed and approved by the institutional ethics committee (IEC) of Nizam's Institute of Medical Sciences. The subjects who voluntarily came forward for participation in the study were explained in detail about the study protocol and conduct of the study by the investigator and were given volunteer information leaflet. They were asked to give their written informed consent within two days.

The subject recruitment was done after screening, the participants were thoroughly examined clinically and vital parameters like blood pressure, heart rate and respiratory rate were recorded to rule out clinical and systemic abnormalities.

In addition, training was given to obtain the simple reaction time (SRT),choice reaction time (CRT),choice discrimination time (CDT) on the reaction time apparatus and for digit letter substitution test (DLST), six letter cancellation test (SLCT) and card sorting test (CST), in three sessions.[4] Similarly critical flicker fusion threshold (CFFT) was obtained on the flicker fusion apparatus.

Histamine prick test was performed to see if they are hypersensitive or insensitive to the histamine prick test.[5] Only those having a wheal >/= 20 sqmm were recruited into the study

Measurement of histamine wheal and flare reaction

The test procedure was performed in the sitting position after 30 minutes of adaptation to the testing room,on the inner side of the forearm near the ante-cubital area i.e. 5 cm below the elbow. The area was gently cleaned with spirit cotton about 2 minutes before the testing. The subject was asked to express the sedation on visual analogue scale (VAS) (showing measurements from 0-100 mm) 2 minutes before the histamine prick test. A new disposable prick needle was introduced into the lancet. Three to four drops of histamine solution were placed on the selected area of the skin where the prick was to be made. The lancet was placed on the drops of histamine solution with minimal pressure so that the prick was delivered through the drop placed on the skin. Histamine solution was gently swabbed off with tissue paper after 5 minutes after the prick. The subject was asked to express the itching on VAS during the 15 minutes and sedation was also recorded. Wheal and flare are recorded after 15 minutes with different colored fine-tip marking pens.[6] The wheal and flare markings were traced on the tracing sheet.[7,8]

Calculation of wheal and flare areas[9]

- Fixed the marked tracing sheet on graph paper firmly.
- Counted the complete squares within the area marked.(A)=No. of sqof 1 sqcm x100
- Counted smaller squares within the area(B) No. of squares of 1/4 sqcmx25
- Each smallest square was counted individually(C) = No. of squaresx1
- Excluded the squares less than0.5 sqmm
- Summed all the values (A+B+C) which gives the total area in mm.

Measurement of salivary flow

The subject was asked to rinse the mouth with clean water for 2-3 times and was seated comfortably with eyes open and head tilted slightly forward. After a rest for 5minutes to minimize the orofacial movements, four unweighed cotton balls were placed, one in each buccal pouch on either side, below the tongue. They were left for 2 minutes to collect the residual saliva and discarded. A second set were similarly placed for 60 seconds, removed and placed in plastic cover and weighed. Again a third set were placed in the same position as before for the same period. The difference between the initial and final weight of cotton balls were recorded. An average of the 2 readings was taken to calculate the salivary flow in gram/minute.[10]

The study was conducted in three volunteers per batch with a washout period of one week between each run. On the evening of the previous day of the study .they were housed in the research ward overnight and nothing was allowed orally after 10pm.On the day of the study, they were evaluated in the pharmacodynamic laboratory. The base line recordings were taken between 6am-9am for psychometric tests like SRT, CRT, CDT, CFFT, DLST, SLCT and CST.[11,12] Histamine prick test for wheal and

flare reaction was done along with VAS for sedation and itch followed by salivary flow test. Vitals were recorded using multi-channel monitor.[6,10,13,14]

The three subjects were randomized to receive either of the treatment A, B, C (Latin square design). Further each of the subjects received each of these treatments A, B and C after two successive washout periods of 7 days each. Each of these subject received treatments 1hour apart from each other at 7 am, 8 am, 9 am respectively. Histamine wheal and flare reaction was done at 0 hour, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours along with itch, sedation recorded on VAS.[8,14] SRT, CRT, CDT, CFFT, DLST, SLCT, CST were measured at 0 hour, 1.5 hours, 4.5 hours, 8,5 hours. Salivary flow was measured at 0 hour 0.51.75 hour, 3.75 hours.[15] Vitals are measured at 0 hour, 10 minutes, 2 hours 10 minutes, 4 hour 10 minutes 8 hours 10 minutes, 24 hours 10 minutes. Breakfast and lunch were served at 4 hours and 6 hours after drug administration.

Dinner was served at 9 pm. Subjects were asked about any adverse events during the study period and were discharged after 24 hours after drug administration. They were asked to come to the study for second and third runs after 7 days of washout between each period and the same procedures were repeated. The data recorded were entered in the case record form.

Measurement of simple reaction time, choice reaction time, choice discrimination time[16,17]

The above tests were performed on reaction time apparatus manually. The apparatus consisted of subjective part, objective part, and digital part. The subjective part had two buttons on either side i.e. on left side and right side, in between the buttons there were two lights which were red and green. The objective part had controlling panel with red-green buttons. On pressing these buttons, the respective lights on the subjective part glowed till the button was pressed. The digital part in between these two parts consisted of the timer which showed the time taken for responding to the stimulus.[16,20] Reaction time parameters are subjective and are variable.

In SRT, the subject was seated in a chair in front of subjective part and was asked to press the key button with his index finger .The investigator sat on the side of the objective part. He set the time to 0 reading and alerted the subject by giving a beep signal to get ready for responding to the sensory stimulus. He was instructed to lift the finger as soon as he saw any of the lights. The time taken for response to the stimulus was noted on the digital part. Likewise six readings were taken and the average readings were calculated in milliseconds. The SRT tests the motor function

The CRT was measured by asking the subject to choose the color as the stimulus. He was asked to lift the finger whenever the chosen color lighted.

The time taken to respond to the stimulus was noted on the digital part. The test was repeated for six times. If he responded to the stimulus wrongly (he had lifted his finger to the unchosen light) the reading was not taken into consideration. The average time for response to the chosen lights was only calculated in milliseconds. CRT assesses the sensorimotor performance and the attention also.

The CDT was measured by asking the subject to lift the finger on the side on which the light glowed and the time was noted. The reading was not taken into consideration if he lifted the finger on the other side. The test was repeated for six times and the average of correct readings was noted in milliseconds as the CDT.

Measurement of critical flicker fusion threshold

CFFT is a well-established neurophysiological technique.[15] It was used as a means of measuring the ability to distinguish discrete sensory data and was taken as an index of overall central nervous system activity.

The critical flicker fusion apparatus consists of flickering light source against dark back- ground. A dial is provided to adjust the flicker per second number. The subject was asked to see the flickering object through the aperture after cutting off the surrounding light in the room. The dial was rotated slowly to increase the flickering per Hz and the subject was asked to raise his hand when the flicker light became steady.

This is known as flicker to fusion. The reading was noted in cycles per second. And the dial was turned in the opposite direction and the subject was asked to lift his hand when the flickering started again. This is known as fusion to flicker. The test was repeated three times and the average of flicker to fusion and fusion to flicker in cycles per second was calculated.

The test is dependent on experimental variables such as ambient illumination, size of image, luminance of stimulus, viewing distance and pupil size. The easiest way to control this is to fix the conditions under which the measurements are to take place and to hold them constant.

Performance of card sorting test: This is an excellent performance task since it includes sensory and motor and central components.[18] Subjects were asked to sort out 52 cards depending upon their design. The time taken to sort was noted in seconds as well as the number of correctly sorted and wrongly sorted cards. The readings were taken three times and the average was calculated in seconds and the average of the number of cards sorted was also calculated

Performance of digit-letter substitution test

The subject was given a sheet containing targeted letters. The working sheet consists of 144 target digits placed in 9 rows and 16 columns. Care was taken that the same digit does not appear consequently in any row or column. This is one of the most widely used test measuring attention response speed, central integration, visuomotor coordination. It is also a useful indicator of drug induced changes in sensory processing performance.[19]

Performance of six letter cancellation test

This test is used to assess the attention.[16,18,20] This test uses a response sheet containing six letter targets that are distributed among pseudo random letters. The six key letter targets are printed on top of the sheet. Subjects were asked to work through the sheet and cross the target letters that they found in 90 seconds. The number of correct cancellations for the target letters was noted. This test was repeated 3 times and the average of the number of correct cancellations for the target letters was calculated.

RESULTS

A total of healthy male volunteers with a mean age of 30.1±5.3years, mean height of 153.7±4.4 cm and a mean weight of 62.4±8.1 kg entered into the study .At screening, each subject demonstrated a histamine induced wheal and flare cutaneous response. On entry, none of the volunteers had any sign of illness, as indicated by medical history and examination. They had normal electrocardiograms and clinically acceptable serum and urine biochemistry, hematology, serology. None of the subjects were taking any prescribed or investigational drug during the study and 4 weeks preceding enrolment. All the subjects had given written informed consent before entering into the study which was approved by the institutional ethics committee.

Fifteen minutes after the intradermal prick with the lancet placed on the histamine solution drops placed on the skin, histamine produced a wheal and flare response in all the subjects. The histamine produced wheal and flare areas were recorded before and after 1,2,4,8, and 24 hours of administration of mizolastine 10 mg tablet, loratadine 10mg and placebo tablet. The effect of the three treatments on histamine induced wheal and flare response is shown in Tables 1A, 1B, 1C and 2A, 2B, 2C, (Figure 1, 2). The mean % change from base line on histamine induced flare was noted.

At baseline, wheal and flare responses were not found to be significantly different between the three treatment groups. Administration of mizolastine and loratadine significantly inhibited the wheal and flare response at all the time points ($p<0.001$). Mean inhibition on histamine induced wheal and flare response with mizolastine was highly significant as compared to placebo from 1 hour onwards and persisted even up to 24 hours ($p<0.001$). On the maximum inhibition of 98.1±1.8%was seen at 4 hours for the wheal respse and was 85.1±24.8 percent at 8 hours for the flare response. The mean inhibition on histamine induced response with loratadine as compared to placebo was significant from 2 hours up to 24 hours ($p<0.05$) for wheal area and 1 hour onwards up to 24 hours ($P<0.01$) for flare area. The maximum inhibition of 56.2±31.6 percent and 60.1±14.2 percent was however seen at 8hours for both wheal and flare respectively. Though the mean inhibition on histamine induced wheal area with mizolastine as compared to loratadine was significant from 1 hour onwards ($p<0.05$). It became highly significant from 2 hours onwards and this persisted even up to 24 hours ($p<0.001$). However the mean inhibition on histamine induced flare area was highly significant from 2 hours onwards up to 24 hours ($p<0.001$).

At baseline the histamine induced itch was not found to be significantly different in any of the treatment groups. The effect of each of the three formulations on histamine induced itch is shown in Table 3. The mean %change from base line on histamine induced itch is shown in Figure 3. The itch response was significantly inhibited at all the time points ($p<0.05$) and at 2, 4, 8, and 24 hours with Mmizolastine and loratadine. Mean inhibition on histamine induced itch with Mizolastine was also significant as compared to placebo from 4 hours onwards and persisted up to 24 hours ($p<0.05$). The maximum inhibition of 58.6±54.2 percent was seen at 8 hours for the itch response. However the mean inhibition on histamine induced response with loratadine as compared to placebo was not significant at any of the time points. The maximum inhibition of 55.1±59.7 percent was however seen at 24 hours at the itch response. There was no significant difference at any time points in the mean inhibition on the histamine induced itch response with mizolastine as compared to loratadine.

There was no significant change in mean effect on sedation with mizolastine, loratadine and placebo which was assessed on a visual analogue scale of 0-100 mm (Figure 4). Compared to placebo there was an interindividual variation in sedation seen with mizolastine and loratadine. Few subjects reported higher values of sedation on visual analogue scale at some time of the study.

There was no noticeable alteration on simple reaction time in each of the three treatment groups. The mean percentage increase in the simple reaction time was only 17.7±28.5 percent with mizolastine at hour, 1.0±11.0% with loratadine at 8 hours and 1.2±14.0% with placebo at 1 hour table (Figure 5).

There was no significant change in choice reaction time with each of the three treatments. However mean percentage rise in choice reaction time seen with mizolastine was 3.3±16.4 percent and with loratadine 1.4±22.2% at 1 hour only (Figure 6).

Table 2: (A) Effect of mizolastine, loratadine, placebo on histamine induced wheal area.

	Mizolastine						Loratadine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	127	40	25	0	0	31	109	55	50	44	36	50	180	160	154	164	152	169
	78	40	10	1	2	18	101	75	50	24	15	65	123	108	100	89	88	84
	125	98	10	2	4	98	100	70	45	52	31	68	111	100	94	88	87	99
	86	32	21	7	3	52	116	105	60	30	20	60	128	48	78	98	126	84
	99	90	15	1	4	18	63	50	36	23	19	65	43	65	38	55	83	90
	68	40	22	2	1	15	62	50	49	39	75	12	78	45	40	35	40	45
	85	40	3	0	0	7	61	57	49	39	24	25	84	57	45	64	92	84
	126	75	6	0	1	15	85	51	62	48	25	48	98	84	74	76	84	97
	70	40	2	1	1	25	116	105	60	30	20	60	91	60	78	98	71	61
	72	67	45	2	1	26	78	78	70	69	28	82	87	70	82	67	65	59
	56	29	10	1	2	26	81	66	83	75	70	75	70	72	41	63	80	112
	85	42	20	2	1	12	60	58	20	29	18	44	66	43	35	31	17	19
	46	55	17	1	1	38	65	50	38	24	21	34	71	58	86	58	58	84
	96	33	2	1	1	15	80	52	60	65	92	74	80	52	60	65	92	74
	63	16	4	1	4	26	67	65	46	29	31	43	82	54	58	59	64	67
	64	35	3	1	2	22	58	47	31	48	25	24	61	70	33	38	55	44
	78	19	4	2	3	35	90	64	49	33	30	45	61	59	32	39	59	50
	69	33	19	1	4	49	64	53	42	36	30	45	89	69	58	64	72	79
Mean	82.9	45.8	13.2	1.4	1.9	29.3	82	63.8	50.3	4170.6	33.4	51.5	89.1	72.8	67.0	68.1	76.9	77.9
STD	±23.8	±22.7	±11.1	±1.5	±1.4	±21.0	±19.8	±17.1	±15.7	±15.6	±22.2	±19.6	±31.3	±28.4	±32.0	±30.3	±30.0	±32.4
Lower 95% CI	71.7	34.5	7.7	0.7	13	18.9	72.2	55.3	42.5	33.8	22.4	41.8	73.5	58.7	51.1	55.1	62.0	61.8
Upper 95% CI	94.8	57.1	18.8	2.2	2.6	39.8	91.8	72.3	58.1	49.4	44..5	61.2	104.6	87.0	83.0	93.2	91.9	91.9

All values are given as mean(sq mm)Mean inhibition on histamine induced wheal response with Mizolastine was highly significant as compared to placebo from 1 hour onwards and persisted even up to 24 hours (p<0.

Table 2: (B) Effect of loratadine and placebo on histamine induced wheal area.

	Loratadine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	109	55	50	44	36	50	180	160	154	164	152	169
	101	75	50	24	15	65	123	108	100	89	88	84
	100	70	45	52	31	68	111	100	94	88	87	99
	116	105	60	30	20	60	128	48	78	98	126	84
	63	50	36	23	19	65	43	65	38	55	83	90
	62	50	49	39	75	12	78	45	40	35	40	45
	61	57	49	39	24	25	84	57	45	64	92	84
	85	51	62	48	25	48	98	84	74	76	84	97
	116	105	60	30	20	60	91	60	78	98	71	61
	78	78	70	69	28	82	87	70	82	67	65	59
	81	66	83	75	70	75	70	72	41	63	80	112
	60	58	20	29	18	44	66	43	35	31	17	19
	65	50	38	24	21	34	71	58	86	58	58	84
	80	52	60	65	92	74	80	52	60	65	92	74
	67	65	46	29	31	43	82	54	58	59	64	67
	58	47	31	48	25	24	61	70	33	38	55	44
	90	64	49	33	30	45	61	59	32	39	59	50
	64	53	42	36	30	45	89	69	58	64	72	79
Mean	82.9	63.8*	50.3*$	41.6*$$-	33.4*$$$	51.5*$$$	89.1	72.8	67.0	68.1	76.9	77.9
STD	±19.8	±17.1	±15.7	±15.6	±22.2	±19.6	±31.3	±28.4	±32.0	±30.3	±30.0	±32.4
Lower 95% CI	72.2	55.)3	42.5	33.8	22.4	41.8	73.5	58.7	51.1	55.1	62.0	61.8
Upper 95% CI	91.8	72.3	58.1	49.4	44..5	61.2	104.6	87.0	83.0	93.2	91.9	91.9

All values are given as mean(sqmm); *-p<0.001 compared to base line) $=p<0.05 compared to placebo; $$=p<0.01(compared to placebo.)$$$=p<0.001 compared to placebo); Mean inhibition on histamine induced response with Loratadine as compared to placebo was significant from 2 hours up to 24 hours(p<0.05)

Similarly no significant change was seen in choice discrimination time with each of these three treatments. Slight non-significant change was seen with mizolastine at 8 hours 0.3±15.6% and with loratadine at 1 hour 4.6±17.5% and 2.7±16.3% at 8 hours also (Figure 7).

The effect of mizolastine, loratadine and placebo on critical flicker to fusion and critical fusion to flicker

frequency are shown in Table 4 A, 4 B respectively. The critical flicker to fusion threshold after a single dose of the above said formulations did not alter significantly (Table 4 C). The percentage change from flicker to fusion threshold was 5.0±5.2, 3.8±13.0 and 3.8±15.7at 1 hour, 5.1±9.1, 5.2±17.8 and 11.7±11.5 at 4 hours and 11.6±11.8, 7.1±13.9 at hours with mizolastine, loratadine and placebo respectively (Figure 8).

Table 2: (C) Effect of mizolastine and loratadine on histamine induced wheal area.

	Mizolastine						Loratadine					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	127	40	25	0	0	31	109	55	50	44	36	50
	78	40	10	1	2	18	101	75	50	24	15	65
	125	98	10	2	4	98	100	70	45	52	31	68
	86	32	21	7	3	52	116	105	60	30	20	60
	99	90	15	1	4	18	63	50	36	23	19	65
	68	40	22	2	1	15	62	50	49	39	75	12
	85	40	3	0	0	7	61	57	49	39	24	25
	126	75	6	0	1	15	85	51	62	48	25	48
	7	40	2	1	1	25	116	105	60	30	20	60
	72	67	45	2	1	26	78	78	70	69	28	82
	56	29	10	1	2	26	81	66	83	75	70	75
	85	42	20	2	1	12	60	58	20	29	18	44
	46	55	17	1	1	38	65	50	38	24	21	34
	96	33	2	1	1	15	80	52	60	65	92	74
	63	16	4	1	4	26	67	65	46	29	31	43
	64	35	3	1	2	22	58	47	31	48	25	24
	78	19	4	2	3	35	90	64	49	33	30	45
	69	33	19	1	4	49	64	53	42	36	30	45
Mean	82.9	45.8®	13.2®®	1.4®®	1.9®®	29.3®®	82	63.8	50.3	4170.6	33.4	51.5
STD	±23.8	±22.7	±11.1	±1.5	±1.4	±21.0	±19.8	±17.1	±15.7	±15.6	±22.2	±19.6
Lower 95% CI	71.7	34.5	7.7	0.7	13	18.9	72.2	55.3	42.5	33.8	22.4	41.8
Upper 95% CI	94.8	57.1	18.8	2.2	2.6	39.8	91.8	72.3	58.1	49.4	44..5	61.2

All values are given as mean (sqmm); ®=P<0.05(COMPARED TO LORATADINE®®=p<0.001 Compared to loratadine maximum inhibition of 98.1±1.8%was seen at 4 hours for the wheal response Mean inhibition on histamine induced wheal area with Mizolastine as compared to Loratadine was significant from 1 hour onwards (p<0,05).

Table 3: (A) Effect of mizolastine, loratidine and placebo on histamine induced flare area.

	Mizolastine						Loratidine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	515	302	259	52	20	180	1006	602	514	348	264	480	987	885	655	210	275	410
	825	501	156	60	100	105	654	650	450	252	302	648	795	603	598	326	530	790
	987	885	655	110	175	410	1001	874	374	399	692	798	945	980	760	405	250	670
	925	675	320	110	60	320	1320	760	750	500	220	870	875	950	850	725	1120	750
	1705	524	268	100	90	249	780	635	600	330	310	480	794	770	508	664	530	775
	900	398	230	106	65	198	701	673	412	316	215	100	985	610	404	575	830	930
	853	635	207	0	0	173	640	387	387	301	205	200	1035	757	727	775	905	960
	930	480	100	90	40	150	1225	1108	910	605	424	470	910	887	1050	1120	740	510
	145	330	110	132	87	100	960	810	690	520	600	700	680	995	880	800	1080	1300
	960	760	435	72	25	125	995	800	764	645	300	700	551	445	410	276	152	145
	702	645	256	37	49	200	980	680	800	560	630	660	935	964	415	600	900	995
	940	490	280	90	28	114	780	668	534	412	316	514	985	390	382	195	120	127
	1250	1120	515	77	220	795	830	580	590	460	190	700	870	730	925	870	845	680
	425	185	37	18	27	90	768	469	358	350	298	464	865	675	565	550	855	455
	630	190	145	40	50	445	715	560	540	370	225	480	995	910	170	80	80	370
	865	675	565	550	855	455	738	617	408	316	303	407	745	1265	1195	1045	1460	950
	785	305	102	35	31	455	967	742	610	356	398	404	730	1065	1014	1036	1074	1036
	895	670	534	36	42	103	814	608	405	290	401	394	910	843	795	786	789	814
Mean	846.5	542.8	287.4	95.3	109.1	259.3	881.9	671.9	560.9	407.2	349.6	526.1	866.2	818.0	683.5	613.2	696.4	703.7
STD	±326	±244	±182	±119	±194	±188	±189	±160	±166	±115	±151	±198	±128.4	±220	±275	±313	±395	±316
Lower 95%CI	684.2	421.6	197.1	36.0	12.6	165.9	787.9	599.5	478.3	349.9	274.7	427.8	815.5	752.5	704.6	650.0	597.0	653.0
Upper 95% CI	1009.0	664.0	377.8	154.5	205.7	352.6	975.9	758.6	643.5	464.5	424.5	624.3	940.8	933.2	898.5	868.7	905.5	909.7

All values are given as mean (sq mm); Mizolastine showed maximum inhibition of 85.1±24.8percent at 8 hours for the flare response.

Table 3: (B) Effect of mizolastine and placebo on histamine induced flare area.

	Mizolastine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	515	302	259	52	20	180	987	885	655	210	275	410
	825	501	156	60	100	105	795	603	598	326	530	790
	987	885	655	110	175	410	945	980	760	405	250	670
	925	675	320	110	60	320	875	950	850	725	1120	750
	1705	524	268	100	90	249	794	770	508	664	530	775
	900	398	230	106	65	198	985	610	404	575	830	930
	853	635	207	0	0	173	1035	757	727	775	905	960
	930	480	100	90	40	150	910	887	1050	1120	740	510
	145	330	110	132a	87	100	680	995	880	800	1080	1300
	960	760	435	72	25	125	551	445	410	276	152	145
	702	645	256	37	49	200	935	964	415	600	900	995
	940	490	280	90	28	114	985	390	382	195	120	127
	1250	1120	515	77	220	795	870	730	925	870	845	680
	425	185	37	18	27	90	865	675	565	550	855	455
	630	190	145	40	50	445	995	910	170	80	80	370
	865	675	565	550	855	455	745	1265	1195	1045	1460	950
	785	305	102	35	31	455	730	1065	1014	1036	1074	1036
	895	670	534	36	42	103	910	843	795	786	789	814
MEAN	846.5	542.88*$	287.4*$	95.3*$	109.1*$	259.3*$	866.2	818.0	683.5	613.2	696.4	703.7
STD	±326	±244	±182	±119	±194	±188	±128.4	±220	±275	±313	±395	±316
Lower 95% CI	684.2	421.6	197.1	36.0	12.6	165.9	815.5	752.5	704.6	650.0	597.0	653.0
Upper 95% CI	1009.0	664.0	377.8	154.5	205.7	352.6	940.8	933.2	898.5	868.7	905.5	909.7

All values are given as mean(sqmm)*=P<0.001(COMPARED TO BASELINE)$=P<0.001COMPARED TO PLACEBO); Mean inhibition on histamine induced flare area was highly significant from 2 hours onwards upto 24 hours (p<0.001.).

Table 3: (C) Effect loratidine and placebo on histamine induced flare area.

	Loratidine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	1006	602	514	348	264	480	987	885	655	210	275	410
	654	650	450	252	302	648	795	603	598	326	530	790
	1001	874	374	399	692	798	945	980	760	405	250	670
	1320	760	750	500	220	870	875	950	850	725	1120	750
	780	635	600	330	310	480	794	770	508	664	530	775
	701	673	412	316	215	100	985	610	404	575	830	930
	640	387	387	301	205	200	1035	757	727	775	905	960
	1225	1108	910	605	424	470	910	887	1050	1120	740	510
	960	810	690	520	600	700	680	995	880	800	1080	1300
	995	800	764	645	300	700	551	445	410	276	152	145
	980	680	800	560	630	660	935	964	415	600	900	995
	780	668	534	412	316	514	985	390	382	195	120	127
	830	580	590	460	190	700	870	730	925	870	845	680
	768	469	358	350	298	464	865	675	565	550	855	455
	715	560	540	370	225	480	995	910	170	80	80	370
	738	617	408	316	303	407	745	1265	1195	1045	1460	950
	967	742	610	356	398	404	730	1065	1014	1036	1074	1036
	814	608	405	290	401	394	910	843	795	786	789	814
MEAN	881.9	671.9	560.9	407.2	349.6	526.1	866.2	818.0	683.5	613.2	696.4	703.7
STD	±189	±160	±166	±115	±151	±198	±128.4	±220	±275	±313	±395	±316
Lower 95% CI	787.9	599.5	478.3	349.9	274.7	427.8	815.5	752.5	704.6	650.0	597.0	653.0
Upper 95% CI	975.9	758.6	643.5	464.5	424.5	624.3	940.8	933.2	898.5	868.7	905.5	909.7

All values are given as mean (sqmm) *-p<0.001 compared to base line) $=p<0.01 compared to placebo; $$=p<0.001(compared to placebo.) The mean inhibition on histamine induced response with Loratadine as compared to placebo was significant from 1 hour onwards up to 24 hours (P<0.01) for flare area.

Performance of digit letter substitution test after administration of each of the three treatments also did not show any significant effect (Table 5). An apparent reduction in substitution was seen with loratadine at 1

hour (3.0±20.6%) and 4 hours (3.8±20.5) and with placebo at all-time points 2.3±11.1%) at 1 hour (5.7±15.6% at 4 hours and 4.4±17.7% at 8 hours (Figure 9).

Similarly reduction which was seen in the performance of six letter cancellation test after administration of each of the three treatments was also insignificant (Table 6). This was minimal with mizolastine at 8 hours (1.0±29.1%) loratadine at 4 hours (5.4±22.5 and with placebo at all the time points-(2.4±18.6%) at 1 hour, 1.8±21.6%) at 4 hours and (0.7±19.1%) at 8 hours (Figure 10).

Table 4: Effect of mizolastine, loratidine and placebo on histamine induced Itch.

	Mizolastine						Loratidine						Placebo					
	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr	0hr	1hr	2hr	4hr	8hr	24hr
	3	4	4	4	4	4	24	8	10	20	18	5	8	20	14	16	18	10
	26	27	4	8	5	6	26	21	17	21	28	31	26	28	26	17	24	13
	10	15	5	50	2	0	7	4	3	3	2	2	10	8	8	9	9	7
	5	3	4	0	0	0	20	25	15	18	4	15	5	5	4	5	6	5
	2	4	3	3	3	2	2	2	2	2	2	2	6	4	3	2	1	2
	5	2	7	2	4	4	5	25	2	7	2	1	14	28	20	22	18	26
	2	0	0	0	0	0	9	4	4	2	1	1	3	3	3	5	7	7
	7	0	0	0	0	0	1	0	0	0	0	0	7	6	5	3	2	2
	5	4	3	1	1	0	5	1	5	2	2	1	5	0	3	2	1	4
	1	1	0	0	0	0	2	5	12	2	1	3	2	1	5	3	2	4
	1	1	1	1	0	0	1	0	2	0	0	0	2	3	6	3	4	1
	3	2	1	0	0	2	2	3	0	2	0	0	3	5	8	6	4	6
	22	10	32	10	10	15	42	17	10	5	4	3	22	18	20	24	26	24
	13	7	5	6	4	3	22	1	2	15	2	2	13	6	8	6	4	4
	20	10	10	6	4	19	15	5	15	0	5	0	20	25	29	26	28	24
	3	1	2	5	5	5	2	2	5	5	6	4	5	4	4	3	6	3
	15	5	10	0	5	5	5	1	2	1	0	0	15	11	4	3	4	12
	19	10	15	2	5	7	15	7	10	3	6	7	19	18	9	5	4	10
MEAN	9.0	5.9	5.9	2.9	2.9	4	11.4	7.3	6.4	6	4.6	4.3	10.3	10.7	9.9	8.9	9.3	9.1
STD	±8.1	±6.7	±7.7	±3.1	±2.7	±5.3	±11.5	±8.5	±5.6	±7.2	±7.2	±7.6	±7.5	±9.5	±8.3	±8.2	±9.1	±7.9
Lower 95% CI	5.0	2.5	2.1	1.4	1.5	1.4	5.7	3.0	3.7	2.4	1.0	0.5	6.5	6.0	5.8	4.8	4.8	5.2
Upper 95% CI	13.0	9.2	9.7	4.5	4.3	6.6	17.1	11.6	9.2	9.6	8.2	8.1	14.0	15.4	14.1	13.0	13.9	13.1

Mean inhibition on histamine induced itch with Mizolastine was significant as compared to placebo from 4 hours onwards and persisted up to 24 hours($p<0.05$).The maximum inhibition of 58.6±54.2percent was seen at 8 hours for the itch response

Table 4: (A) Effect of mizolastine, loratidine and placebo on critical flicker to fusion frequency.

	Flicker to fusion											
	Mizolastine				Loratidine				Placebo			
	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
	23.3	23.2	22.5	22.8	23.6	23.4	23.2	23.3	23.4	23.2	23.0	23.1
	23.3	23.3	22.8	23.2	23.8	23.5	23.5	23.3	23.6	23.6	23.1	23.5
	23.4	23.3	22.7	23.6	24.4	23.5	23.7	23.6	23.9	23.0	23.2	23.1
	23.4	23.3	23.4	22.8	23.5	23.6	23.8	23.7	23.5	23.5	23.7	23.8
	23.5	23.5	23.6	23.4	23.4	23.5	23.7	22.8	23.5	23.6	23.6	23.5
	23.3	23.3	23.6	22.3	24.1	23.4	23.7	23.8	23.7	23.7	24	22.9
MEAN	23.4	23.3	23.1	23	23.8	23.5	23.6	23.4	23.6	23.4	23.4	23.4
STD	±o.1	±0.1	±0.5	±0.5	±0.4	±0.1	±0.2	±0.4	±0.2	±0.3	±0.4	±0.4
Lower 95% CI	23.3	23.2	22.6	22.5	23.4	23.4	23.4	23	23.4	23.1	23.0	22.9
Upper 95% CI	23.5	23.4	23.6	23.5	24.2	23.6	23.8	23.8	23.8	23.7	23.8	23.6

All values are given as mean(Hz/Sec); No change significantly in critical flicker to fusionfrequency with Mizolastine,Loratidine and Placebo.

The effect after administration of mizolastine, loratadine and placebo on card sorting test also did not show any significant effect (Table 7, Figure 11). The percentage change from card sorting test was 1.1±30.8, 12.8±28.3 and 0.7±17.5 at 1hour, 4.518.0, 14.7±38.2 and 0.5±15.9 at 4 hours, 1.9±23.7, 12.4±38.4 and -0.8±16.2 at 8 Hours with mizolastine loratadine and placebo respectively.

Table 4: (B) Effect of mizolastine, loratidine and placebo on critical fusion to flicker frequency.

	Fusion to flicker											
	Mizolastine				Loratidine				Placebo			
	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
	33	33.1	33.6	34.5	35.1	33.9	33.9	33.9	34.1	34.2	34.5	35.6
	33	33.7	33.5	35.8	34.5	34.9	34.2	34.2	33.8	34.2	33.5	33.5
	32.9	33.8	33.5	33.6	33.5	33.6	34.3	34.3	33.2	34.1	33.9	33.9
	33.4	34.3	33.4	33.5	31.6	33.5	34.7	34.7	32.5	34.4	35	35
	33.6	33.3	33.3	33.2	33.5	34.1	34.0	34.0	33.6	33.4	33.4	33.5
	33.6	33.9	33.4	33.6	36.2	33.9	34.0	34.0	34.9	32.5	32.6	32.8
MEAN	33.3	33.7	33.5	34.0	34.1	34.0	34.2	34.2	33.7	33.8	33.8	33.7
STD	±0.3	±0.4	±0.1	±1.0	±1.6	±0.5	±0.3	±0.3	±0.8	±0.7	±0.7	±0.8
Lower 95% CI	32.9	33.2	33.3	33.0	32.4	33.5	33.9	33.9	32.8	33.0	32.9	32.9
Upper 95% CI	33.6	34.1	33.6	35.1	35.8	34.5	34.5	34.5	34.5	34.6	34.7.	35.2

All values are given as mean (Hz/Sec); The percentage change from flicker to fusion threshold was 5.0±5.2, 3.8±13.0 and 3.8±15.7 at 1 hour , 5.1±9.1, 5.2±17.8 and 11.7± 11.5 at 4 hours and 11.6±11.8, 7.1±13.9 at hours with Mizolastine, Loratadine and placebo respectively.

Table 4: (C) Effect of mizolastine, loratidine and placebo on critical flicker fusion threshold.

	Mizolastine				Loratidine				Placebo			
	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
	9.7	9.9	11.1	11.7	11.5	10.5	10.7	10.6	10.7	11.0	11.5	12.5
	9.7	10.4	10.7	12.6	10.7	11.5	10.7	10.9	10.2	10.6	10.4	10.0
	9.5	10.5	10.9	10	9.1	10.1	10.6	10.7	9.3	11.1	10.7	10.8
	9.0	11.0	10.0	10.7	8.1	9.9	10.9	11	9.0	10.9	11.3	11.2
	10.1	9.8	9.7	9.8	10.1	10.6	10.3	11.2	10.1	9.8	9.8	10.0
	10.3	10.6	9.8	11.3	12.1	10.5	10.3	10.2	11.2	8.8	8.6	9.9
MEAN	9.9	10.4	10.4	11	10.3	10.5	10.6	10.8	10.1	10.4	10.4	10.7
STD	±0.3	±0.5	±0.6	±1.1	±1.5	±0.5	±0.2	±0.4	±0.8	±0.9	±1.1	±1.0
Lower 95% CI	9.6	9.9	9.7	9.9	8.7	10	10.3	10.4	9.2	9.4	9.3	9.6
Upper 95% CI	10.2	10.8	11.0	12.1	11.8	11	10.8	11.1	10.9	11.3	11.5	11.7

All values are given as mean (Hz/Sec); The critical flicker to fusion threshold after a single dose of the above said formulations did not alter significantly.

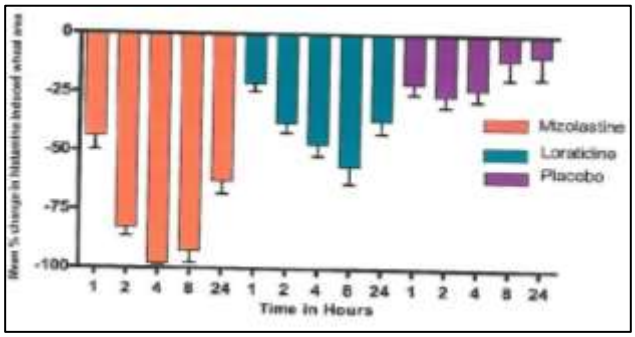

Figure 1: Mean % change of mizolastine, loratadine and placebo on histamine induced wheal.

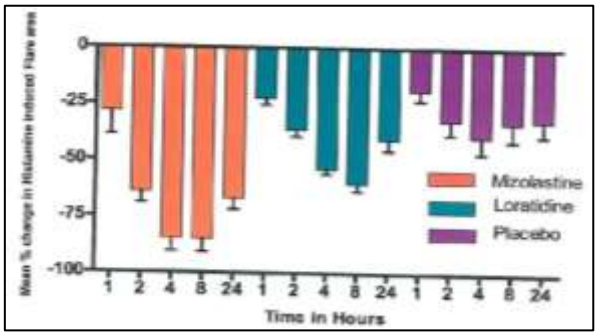

Figure 2: Mean % change of mizolastine, loratadine and placebo on histamine induced flare.

Mean inhibition on histamine induced wheal response with mizolastine was highly significant as compared to placebo from 1 hour onwards and persisted even up to 24 hours ($p<0.001$).

The mean inhibition on histamine induced flare area was highly significant from 2 hours onwards up to 24 hours ($p<0.001$).

Table 5: Effect of mizolastine, loratidine and placebo on digit letter substitution test.

	Mizolastine				Loratidine				Placebo			
	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
	42.0	37.3	42.0	41.7	38.0	45.0	40.0	35.3	38.3	46.0	44.6	46.5
	46.0	42.3	39.0	36.0	70.3	69.6	45.3	73.0	53.3	54.6	52.6	54.3
	43.3	36.6	34.6	55.6	41.0	55.0	65.0	44.0	37.0	39.3	48.3	46.0
	71.0	58.7	54.3	45.3	65.0	41.0	58.0	59.3	51.0	43.0	41.6	43.3
	56.6	46.3	44.3	58.3	46.0	43.0	48.3	43.0	36.6	39.3	43.0	46.0
	54.6	59.0	51.0	47.6	39.0	44.0	47.7	42.0	60.6	52.0	64.6	42.0
	61.0	52.3	49.0	46.3	53.0	44.3	57.3	48.0	55.3	53.3	54.0	52.6
	37.6	44.0	36.6	36.6	49.0	50.6	50.3	38.0	38.6	50.0	56.3	54.0
	59.6	65.0	62.6	59.3	57.6	59.8	59.0	62.0	55.3	54.0	58.6	56.6
	57.3	53.6	54.6	55.6	45.0	50.3	60.6	59.0	47.0	42.3	43.3	46.6
	59.0	55.0	55.0	56.0	65.3	61.6	61.0	63.3	77.6	77.6	68.0	57.6
	53.3	61.0	56.6	56.0	44.6	63.0	40.0	38.3	57.3	60.0	57.3	58.6
	60.6	55.3	58.6	57.3	44.3	61.6	51.0	57.0	44.6	48.3	47.0	49.3
	54.6	51.0	53.3	51.6	57.6	57.0	58.0	66.6	45.0	44.6	50.0	47.6
	55.6	57.3	57.3	52.6	48.6	47.0	48.0	40.6	52.6	53.8	54.6	58.3
	71.0	68.0	72.0	71.6	66.0	52.0	54.0	56.6	67.0	74.0	76.0	76.3
	51.3	49.0	49.0	47.0	60.0	55.0	62.0	55.0	58.6	59.6	53.0	56.8
	45.3	44.0	45.3	46.0	65.6	60.0	61.6	64.0	58.3	55.0	57.0	58.3
MEAN	54.4	52.0	50.8	51.1	53.1	53.3	52.7	52.5	51.9	52.6	53.9	52.8
STD	±9.1	±9.0	±9.5	±8.8	±10.5	±8.2	±7.7	11.5	±11.0	±10.5	±9.1	±8.1
Lower 95% CI	49.9	47.5	46.1	46.7	47.9	49.2	49.5	47.8	46.8	47.4	49.3	48.8
Upper 95% CI	59.0	56.4	55.6	55.5	58.3	57.4	57.5	58.2	57.4	57.8	58.4	56.9

Mean values (digit substituted in 90 seconds) p = (not significant); Did not show any significant effect

Table 6: Effect of mizolastine, loratadine, placebo onsixletter cancellation test.

Mizolastine				Loratidine				Placebo			
0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
28.0	22.3	17.6	18.67	15.3	13	18.7	19.3	19.6	16.6	18.0	18.6
20.0	17.6	32.0	15.67	38.3	31.0	38.7	16.3	29.6	29.0	35.6	17.3
22.0	13.3	16.3	20.6	21.3	25.3	27.3	33.3	18.3	20.3	20.0	20.0
44.0	42.0	13.3	19.6	45.6	32.6	40.0	35.0	19.0	16.3	16.6	15.6
22.6	17.6	32.3	38.0	21.6	22.6	20.0	25.0	15.0	19.3	21.3	16.3
32.3	25.0	29.3	39.3	16.6	14.6	18.6	29.6	25.3	19.0	22.6	22.6
40.0	30.6	34.3	41.6	35.3	35.3	1 8.3	35.0	31.3	39.3	44.0	39.6
31.6	23.6	33.0	39.6	26.6	31.6	25.6	31.0	36.0	40.3	44.0	43.6
38.6	36.6	38.0	39.0	39.0	45.0	46.6	32.3	39.0	39.3	42.3	35.3
33.0	33.3	36.0	39.6	36.6	31.0	28.6	34.7	38.0	40.3	40.6	46.3
43.3	37.3	32.3	30.3	41.3	40.3	36.0	33.6	35.3	40.0	33.0	34.0
38.0	34.0	37.6	45.6	41.0	34.6	33.3	40.0	56.0	57.3	39.0	42.0
46.0	20.3	33.6	31.0	21.0	36.6	32.6	22.0	33.6	22.3	30.6	32.0
52.0	45.3	36.6	49.3	34.0	41.0	35.3	39.6	29.3	32.3	26.3	36.0
56.3	48.0	35.0	59.0	21.0	19.0	18.3	16.3	22.0	31.0	26.0	28.3
32.6	55.0	56.0	43.0	31.6	23.0	48.0	39.6	53.0	49.0	53.3	54.0
32.3	39.3	56.0	31.3	35.3	23.0	29.6	21.6	39.0	36.0	23.0	33.3
27.6	25.0	27.3	29.9	31.0	29.0	33.6	33.6	36.0	34.6	34.0	38.3
35.6	31.5	33.1	35.1	30.8	29.8	31.6	28.8	32.0	32.4	31.7	31.8
±10.1	11.7±	±11.1	±11.5	±9.4	±8.8	±9.1	±8.2	±11.2	±11.7	±10.6	±11.4
30.5	25.6	29.3	26.1	25.4	27.1	24.7	26.4	26.6	26.4	26.4	26.2
40.6	37.3	38.7	40.8	35.6	34.2	36.2	32.9	37.6	38.2	37.0	37.6

Mean values (digit substituted in 90 seconds) p = (not significant); Six letter cancellation test after administration of each of the three mizolastine, loratadine, placebo treatments was also insignificant.

None of the treatments used in the present evaluation showed any noticeable change in salivary flow. The effect of the treatments on salivary flow was insignificant (Table 8). An apparently insignificant decrease of

1.0±22.95% (Figure 12) in salivary flow was seen with Loratadine at 1 hour only. However, salivary flow remained unaffected at all the other time points with mizolastine, loratadine, and placebo.

Table 7: Effect of mizolastine, loratadine, and placeboon card sorting test.

	Mizolastine				Loratadine				Placebo			
	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr	0hr	1hr	4hr	8hr
	48.3	44.6	53.3	54.3	56.6	57.6	66.0	66.0	31.0	33.3	32.3	30.6
	78.3	69.0	76.6	76.6	24.0	33.3	45.0	46.0	42.3	43.0	53.3	46.0
	68.3	66.3	70..0	66.0	24.2	43.0	47.0	49.3	53.0	49.3	58.6	58.6
	45.3	35.6	45.6	33.7	32.5	41.3	48.3	46.6	71.6	70.0	66.0	65.6
	33.7	33.3	34.0	35.0	54.0	49.3	40.7	47.6	57.2	61.0	63.3	46.6
	53.3	46. 6	48.3	43.3	50.0	66.0	54.2	68.3	40.6	39.0	34.3	31.0
	56.3	56.6	57.0	49.0	60.0	52.0	61.6	53.3	54.3	51.6	52.6	54.0
	58.6	62.3	71.6	60.0	68.2	60.0	60.0	67.3	60.6	59.3	65.3	65.6
	31.3	65.6	48.6	55.6	53.3	56.0	54.3	49.0	45.3	51.0	52.6	54.6
	57.0	57.3	56.0	55.4	45.0	39.0	37.0	39.6	57.0	53.6	55.6	61.3
	50.3	60.6	57.6	57.6	36.0	65.0	65.6	53.3	63.0	45.3	35.6	49.0
	45.0	47.3	52.6	56.6	56.0	55.0	65.6	51.0	57.0	56.6	57.0	56.0
	72.3	46.3	58.0	44.6	49.0	50.0	53.6	51.0	67.7	76.6	78.6	69.0
	48.6	59.0	43.0	59.6	55.0	55.0	56.3	39.3	65.6	43.0	56.3	59.3
	47.6	32.0	47.0	41.3	71.0	80.0	61.3	76.3	50.6	54.2	41.6	45.6
	50.3	67.0	59.0	61.3	70.0	70.3	58.5	52.6	55.3	56.0	55.0	44.3
	66.3	52.0	69.0	47.6	60.6	62.6	43.0	43.6	44.3	67.0	42.6	61.3
	69.3	53.3	54.6	77.6	52.6	51.6	55.6	56.0	52.3	52.0	56.3	57.6
MEAN	54.5	53.0	55.7	54.2	51.0	54.1	54.1	53.1	53.8	53.5	53.2	53.0
STD	±12.7	±11.7	±10.9	±12.3	±14.1	±11.6	±8.9	±10.2	±10.3	±10.9	±12.1	±11.0
Lower 95% CI	48.1	47.2	50.2	48.1	44.0	49.0	49.7	48.0	48.7	48.1	47.2	47.5
Upper 95% CI	60.8	58.8	61.1	60.3	58.0	60.6	58.5	58.2	59.0	58.9	59.2	58.5

All values are given as mean (time in seconds to sort 52 cards) p-not significant; Mizolastine Loratadine and placebo on card sorting test did not show any significant effect.

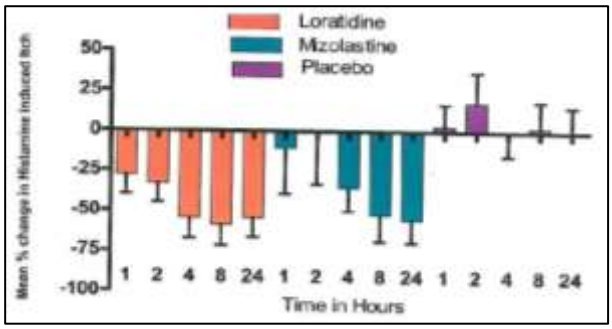

Figure 3: Mean % change of mizolastine, loratadine and placebo on histamine induced itch.

Itch response was significantly inhibited at all the time points ($p<0.05$) and at 2, 4, 8, and 24 hours with mizolastine and loratadine.

The systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature were recorded at base line and one hour, 2 hours, 4 hours, 8 hours and 24 hours after administration of mizoastine, loratadine, and placebo. None of the test drugs studied produced any alteration in vital parameters in healthy subjects.

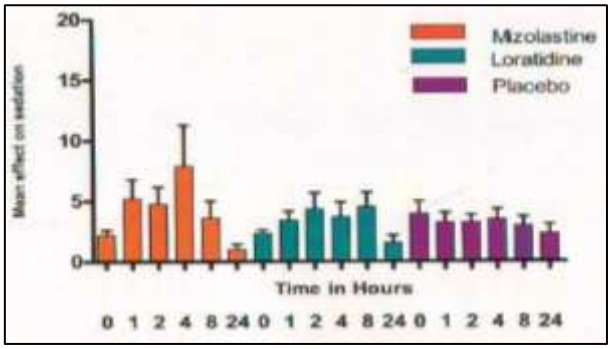

Figure 4: Mean % change of mizolastine, loratadine and placebo on histamine induced sedation.

There was no significant change in mean effect on sedation.

Table 8: Effect of mizolastine loratadine and placebo on salivary flow.

	Mizolastine				Loratadine				Placebo			
	0hr	1hr	2hr	4hr	0hr	1hr	2hr	4hr	0hr	1hr	2hr	4hr
	0.71	0.40	0.66	0.65	0.68	0.44	1.06	0.69	1.09	1.11	0.89	1.07
	1.31	1.04	0.76	0.92	0.45	0.43	0.58	0.66	1.22	1.33	0.73	1.46
	1.56	1.00	0.78	2.16	0.55	0.50	0.68	0.99	0.27	0.43	0.31	0.34
	0.40	1.02	1.05	1.87	0.59	0.55	1.04	0.55	0.86	1.04	0.89	0.92
	0.50	1.43	1.07	0.55	1.36	1.33	1.03	0.41	1.09	0.82	0.99	0.76
	0.78	0.48	0.66	0.69	1.41	1.22	1.34	2.21	0.43	0.66	0.74	0.56
	1.86	1.97	1.37	2.86	0.87	1.32	1.10	1.36	0.87	1.0	1.56	1.53
	0.79	0.99	0.93	1.04	0.84	0.83	0.69	1.11	0.78	0.93	0.59	1.04
	1.06	1.50	1.09	1.03	3.31	2.31	2.46	2.69	4.72	2.90	2.47	4.73
	1.45	0.82	0.81	0.65	0.75	0.69	0.55	1.20	0.88	1.19	1.01	1.10
	0.64	0.78	0.76	1.04	0.68	0.73	0.99	0.99	0.37	0.57	0.61	0.70
	1.53	1.25	1.12	2.39	3.09	2.36	1.59	2.16	0.74	1.29	1.18	1.26
	0.89	1.00	1.96	0.62	0.88	0.91	1.05	1.10	1.32	1.54	1.65	1.83
	0.80	0.45	0.85	0.32	3.10	3.65	1.96	4.23	1.55	1.42	1.77	2.77
	2.14	1.60	1.67	1.23	1.63	1.00	1.02	1.09	1.56	1.56	1.69	0.77
	1.56	1.00	0.78	2.16	1.05	0.96	1.35	1.45	1.69	2.40	1.59	1.87
	0.50	1.43	1.07	0.55	0.85	1.05	1.35	1.05	1.58	1.89	2.00	1.98
	1.05	0.54	0.84	0.98	1.06	1.35	1.05	0.85	1.98	1.89	1.67	1.64
Mean	1.1	1.0	1.0	1.2	1.3	1.2	1.2	1.4	1.3	1.3	1.2	1.5
STD	±0.5	±0.4	±0.4	±0.8	±0.9	±0.8	±0.5	±0.9	±1.0	±0.6	±0.6	±1.0
Lower 95% CI	0.8	0.8	0.8	0.8	0.8	0.8	0.9	0.9	0.8	1.0	0.9	1.0
Upper 95% CI	1.3	1.3	1.2	1.6	1.7	1.6	1.4	1.8	1.8	1.6	1.5	2.0

The effect of the treatments on salivary flow was insignificant.

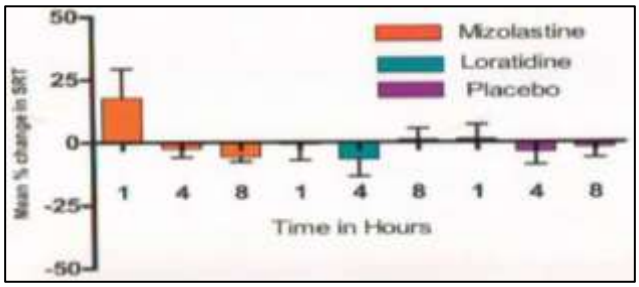

Figure 5: Mean % change of mizolastine, loratadine and placebo on simple reaction time.

There was no noticeable alteration on simple reaction time in each of the three treatment groups.

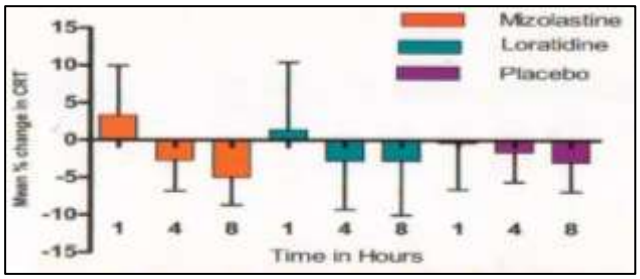

Figure 6: Mean % change of mizolastine, loratadine and placebo on choice reaction time.

There was no significant change in choice reaction time with each of the three treatments

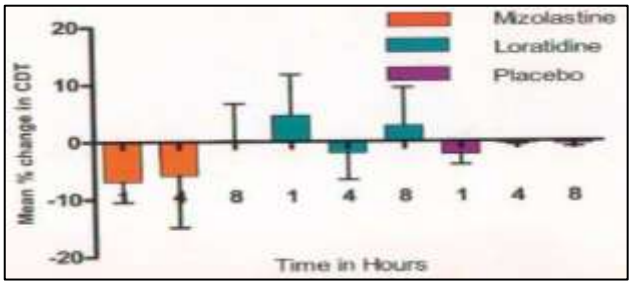

Figure 7: Mean % change of mizolastine, loratadine and placebo on choice discrimination time.

Slight non-significant change was seen with mizolastine at 8 hours 0.3±15.6% and with loratadine at 1 hour.

Tolerability

All the three formulations were well tolerated by all the volunteers. The only adverse effect reported was mild and transient headache experienced by one subject in the mizolastine group. None of the volunteers experienced serious adverse effects necessitating discontinuation of treatment.

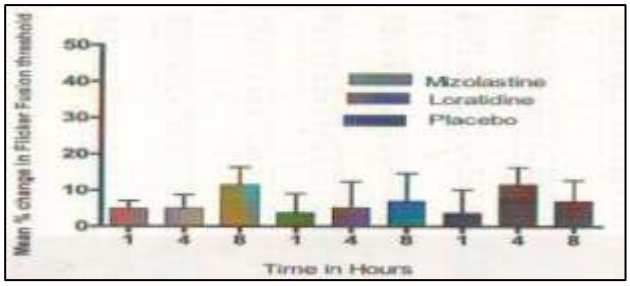

Figure 8: Mean % change of mizolastine, loratadine and placebo on critical flicker fusion threshold.

The critical flicker to fusion threshold after a single dose of the above said formulations did not alter significantly.

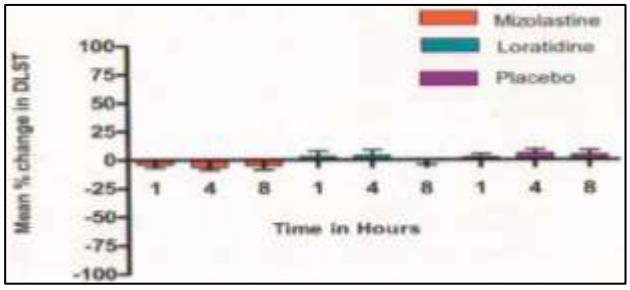

Figure 9: Mean % change of mizolastine, loratadine and placebo on digit letter substitution test.

Did not show any significant effect.

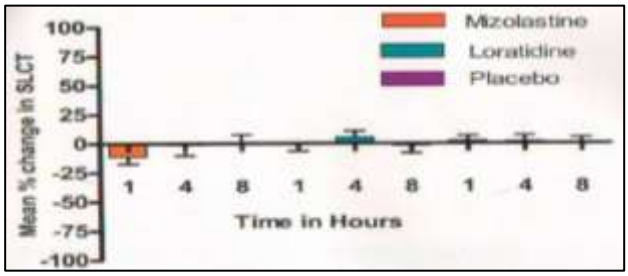

Figure 10: Mean % change of mizolastine, loratadine and placebo on six letter cancellation test.

It was minimal with mizolastine at 8 hours (1.0±29.1%) loratadine at 4 hours (5.4±22.5) and with placebo at all the time points.

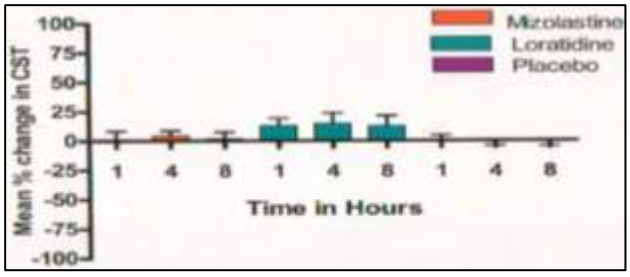

Figure 11: Mean % change of mizolastine, loratadine and placebo on card sorting test.

Did not show any significant effect

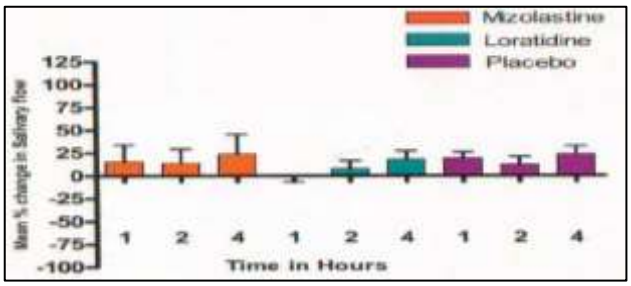

Figure 12: Mean % change of mizolastine, loratadine and placebo on salivary flow.

An apparently insignificant decrease of 1.0±22.95% in salivary flow was seen with loratadine at 1 hour only.

DISCUSSION

The purpose of this study was to investigate the possible differences between the three treatments (mizolastine, loratadine and placebo) in their potential for clinical effectiveness by measuring their potency as peripheral inhibitors of histamine induced wheal and flare and at the same time assessing their possible CNS effects also.[18] The separation of peripheral and central effects of antihistamines is of great importance in clinical situation where patients with allergies take their medication while continuing to undertake some of the risk prone activities of everyday living, including car driving, operating machinery and even domestic and recreational behaviour and where impaired judgment and /or skill could lead to accident or injury.[6,10,14]

Our study has demonstrated that mizolastine 10 mg and loratadine10mg caused a marked inhibition of histamine induced wheal and flare response in healthy volunteers as compared to placebo, that histamine induced skin prick test response is seen from first assessment at 1 hour after dosage to the last assessment of 24 hours after dosage. In addition, the degree of inhibition seen with mizolastine was comparatively more significant. Placebo does not show any relevant inhibition of histamine induced wheal and flare in these individuals.

Our study also did not show any significant reduction on histamine induced itch response with loratidine as compared to placebo, unlike mizolastine. There was no significant change in SRT, CRT, CDT, CST, CFFT, DST, SLCT, salivary flow or vital parameters.

In the present study we have studied the effect of two antihistamines namely mizolastine and loratadine for their peripheral antihistamine effects and effects on psychomotor performance. Mizolastine has good antihistaminic activity than loratadine. Similarly the itch response was also significantly prevented by these antihistamines as compared to placebo. Neither drug

causes any psychomotor impairment or has anticholinergic action.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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