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# EVALUATION OF ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF CETIRIZINE AND LEVOCETIRIZINE: AN EXPERIMENTAL STUDY

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**Keywords:**

Formalin induced arthritis, Carrageenan, Paw oedema, Tail flick method

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**ABSTRACT: Aim of the study:** To evaluate analgesic and anti-inflammatory activities of cetirizine and levocetirizine in different experimental models in rats. **Materials and Methods:** Analgesic activity of cetirizine and levocetirizine was assessed in tail flick model in rats (n = 6), where it was compared with aspirin and tramadol. Reaction time in seconds was used as the unit for measurement of pain and an increase in reaction time was indicative of analgesia. Anti-inflammatory activity of cetirizine and levocetirizine was evaluated using carrageenan-induced rat paw oedema model for acute inflammation (n=6). Percentage inhibition of oedema was compared in different groups. Formalin-induced arthritis model in rats (n=6) was used to evaluate activity in chronic inflammation, where it was compared with aspirin. Linear cross-section (LCS) immediately below the ankle joint of right hind paw was measured daily with Vernier Calliper. The difference in LCS on day 1 and day 10 was calculated for all groups. **Results:** Both cetirizine and levocetirizine were found to have significant analgesic action which was comparable to aspirin in tail-flick model of analgesia in rats. The effect of tramadol was significantly more than the other drugs at all observation times. In the models of acute and chronic inflammation, both cetirizine and levocetirizine showed significant anti-inflammatory activity which was comparable to aspirin. **Conclusion:** Cetirizine and levocetirizine possess analgesic and anti-inflammatory activity, which is comparable to aspirin.

**INTRODUCTION:** Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. It is considered as an indicator of some underlying disease that brings the patient to the physician's recognition [1]. Inflammation is a physiologic response of the immune system of the body to tissue injury and infection. It can be acute, as in response to tissue injury or maybe chronic, leading to progressive tissue destruction, as seen in chronic infections, autoimmunity, and certain cancers [2].

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Although inflammation and pain can serve as defensive mechanisms of body-protecting an individual from further damage, pain is more of an emotional experience, and its perception differs from individual to individual [3].

Analgesic and anti-inflammatory agents provide only symptomatic relief without affecting the cause. Currently prescribed frontline therapy for the management of pain and inflammation involve steroidal and non-steroidal anti-inflammatory drugs. Their long-term use is frequently associated with adverse effects, which are often inseparable from desired effects. Hence, there is need to search for new and safe analgesic and anti-inflammatory agents with high efficacy [4].

Most of the histamine in the human body is stored in granules of mast cells and basophils. It has a pivotal role in acute inflammatory response by

producing increased vascular permeability, vaso-dilatation, and chemotaxis, whereas its role in the chronic inflammatory response is yet to be established [5]. Peripheral histamine is also involved in the stimulation of nociceptive fibers, and it has been demonstrated that its antagonists show anti-nociceptive effects [6].

Cetirizine and Levocetirizine are second-generation $H_1$ antihistaminic drugs having desirable pharma-cokinetic properties and high safety profile. They have well-established role in rhinitis, urticaria and conjunctivitis [7]. Analgesic and anti-inflammatory activity of these drugs have been evaluated in a few studies. Levocetirizine was reported to have significant analgesic activity in the hot plate method and prominent anti-inflammatory activity in a model of acute inflammation in rats [8]. Analgesic activity of cetirizine was reported in another study using different models in mice [9]. Anti-inflammatory activity of cetirizine has been reported in *in-vitro* models but we did not come across any study reporting anti-inflammatory activity of cetirizine in animal models [5]. Since there is limited published data about analgesic and anti-inflammatory activity of these two commonly prescribed antihistaminic drugs, these drugs need to be further explored for these activities. Hence, this study was planned with the objectives of evaluating the analgesic and anti-inflammatory activities of Cetirizine and levocetirizine in various experi-mental models.

## MATERIALS AND METHODS:

**Animals:** Albino Wistar rats of either sex weighing 150-250 grams were used. The study was conducted after approval from the Institutional Animal Ethics Committee, which is an approved body by CPCSEA (Committee for the purpose of Control and Supervision of Experiments on Animals) Reg. number: 2092-94.

The rats were grouped in separate polypropylene cages on husk bedding with six animals in each group. Animals were fed with a standard pellet diet and water *ad libitum*. Animals were allowed to adjust to the laboratory conditions such as light, temperature and noise before being subjected to the experiment (acclimatization). They were kept under standard conditions at ambient temperature of 25±2°C with the help of air coolers and enough humidity on a 12 h light-dark cycle. They had free access to food and water. They were adapted for 10 days for the study conditions. Study was conducted during the daytime (between 10.00 to 18.00 hours).

**Drugs and Chemicals:** Drugs - Levocetirizine, Cetirizine, Aspirin and chemicals like sodium carboxymethylcellulose (CMC) were obtained from Medley Pharmaceuticals Ltd., Mumbai, India, in pure powder form. Carrageenan and Tramadol were obtained from commercial sources. Chemicals were of analytical grade. All the drugs were dissolved in 0.9% normal saline, while aspirin was suspended with CMC in normal saline. Fresh solutions were prepared half an hour before the experiment.

**Study Design:**

**Analgesic Activity:** For Analgesic activity, animals were grouped as follows: Group I: Control: Normal saline 2 ml/kg (p.o.), Group II: Standard drug: Tramadol 10 mg/kg (i.p.), Group III: Standard drug: Aspirin 300 mg/kg (p.o.), Group IV: Test Drug: Levocetirizine 1mg/kg (p.o.), Group V: Test Drug: Cetirizine 1mg/kg (p.o.)

In this study, Tail flick model was used to evaluate the analgesic activity of Cetirizine and Levocetirizine.

**Tail Flick Method:** [10] Analgesic activity was evaluated using a modified method of D Amour and Smith called a tail-flick method using an analgesiometer. Reaction time in seconds was used as the unit for measurement of pain and an increase in reaction time was indicative of analgesia. The time between placing the tail of the rat on the radiant heat source and sharp withdrawal of the tail was recorded as ‘reaction time’ or ‘latency period’. A cut-off time of ten seconds was imposed in all sets of experiments taken as maximum latency so as to rule out thermal injury while noting down the reaction time.

Animals that showed a mean reaction time outside the range of five-six seconds were discarded. In all the groups, the tail-flick test was performed prior to drug administration and at 30, 60, 90, and 120 min after drug administration, and the reaction time at each time interval (test latency) was calculated.

Average reaction times were then calculated, and the percentage analgesia was calculated using the following formula:

Percentage analgesia = (TL-BL / ML-BL) × 100

Where M.L. = Maximum latency, T.L. = Test latency, B.L. = Basal latency or control latency

**Anti-inflammatory Activity:** For anti-inflammatory activity animals were grouped as follows:

Group I: Control: Normal saline 2 ml/kg (p.o.), Group II: Standard drug: Aspirin 300 mg/kg (p.o.), Group III: Test Drug Levocetirizine 1mg/kg (p.o.), Group IV: Test Drug Cetirizine 1mg/kg (p.o.)

**Acute Inflammation:**

**Carrageenan Induced-Rat Paw Oedema:** [11] Acute inflammatory reactions were induced by Phlogistic agent, Carrageenan injected into the sub plantar surface of the right hind paw of each rat. The instrument used in this study for recording the paw oedema was Mercury Plethysmometer (modified by Hardayal Singh and Ghosh) [12].

Right paw of the animal was marked with ink at the level of lateral malleolus; basal paw volume was measured by volume displacement method using mercury Plethysmometer by immersing the paw till the level of lateral malleolus [13]. After one hour of drug administration 0.1 ml of 1% Carrageenan (1% in 0.9% Normal Saline solution) was injected into sub plantar region of the hind paw of the rat.

The paw volume was measured by Plethysmometer just before 1% carrageenan injection, that is, at '0' hour and then at 30, 60 and 120 minutes after carrageenan injection [14].

Same procedure was adopted for rats of all the groups. The percentage inhibition of oedema in animals of all groups was calculated by using the formula:

Percentage inhibition = (Vc-Vt) / Vc × 100

Where, Vc = Paw volume in control group; Vt = Paw volume in test group

**Chronic Inflammation:**

**Formalin Induced Arthritis in Rats:** [15] Chronic inflammation was induced by subcutaneous injection of 0.1 ml of 2% formalin under the plantar aponeurosis of right hind paw of rats on first and third day of the experiment.

The drug to be tested was given daily for 10 days. Linear cross-section (LCS) immediately below the ankle joint of right hind paw was measured daily with Vernier Calliper. The difference in LCS on day1 and day 10 was calculated for all groups. Percentage anti-inflammatory effect of drug was calculated by:

Percentage anti-inflammatory effect = Mean difference in LCS Control group - Mean difference in LCS Test group × 100 / Mean difference in LCS Control group

**Statistical Analysis:** Data was analysed by using Graph pad Prism software version 8.0.2. Comparison between different groups was done by one way ANOVA followed by Tukey's test. P value less than 0.05 (p value <0.05) was considered as statistically significant.

**RESULTS: Table 1** shows that during all observation times, mean reaction time of cetirizine and levocetirizine was comparable. At 30 minutes, mean reaction time of cetirizine and levocetirizine was significantly less than that of aspirin (P<0.01) and tramadol (P<0.001). At 60, 90 and 120 minutes, mean reaction time of cetirizine and levocetirizine was comparable to aspirin while it was significantly less than that of tramadol (P<0.01).

**TABLE 1: MEAN REACTION TIME OF DRUGS IN TAIL FLICK MODEL OF ANALGESIA IN RATS (N=6)**

| Drugs and doses (mg/Kg) | Mean Reaction time (seconds) | | | | |
|---|---|---|---|---|---|
| | At 0 min | At 30 min | At 60 min | At 90 min | At 120 min |
| Normal saline (2 ml/Kg p.o.) | 3.45 ± 0.25 | 3.52 ± 0.12 | 3.53 ± 0.13 | 3.45 ± 0.11 | 3.45 ± 0.1 |
| Aspirin (300 mg/Kg p.o.) | 3.62 ± 0.32 | 7.97 ± 0.11 | 7.28 ± 0.07** | 6.77 ± 0.06** | 6.67 ± 0.04** |
| Tramadol (10 mg/Kg i.p.) | 3.78 ± 0.5 | 8.38 ± 0.60 | 8.97 ± 0.06 | 8.78 ± 0.06 | 8.40 ± 0.09 |
| Cetirizine (1 mg/Kg p.o.) | 3.55 ± 0.51 | 6.95 ± 0.28**@ | 7.20 ± 0.28** | 7.85 ± 0.2* | 7.30 ± 0.18* |
| Levocetirizine (1 mg/Kg p.o.) | 3.33 ± 0.26 | 6.65 ± 0.18**@ | 7.63 ± 0.22* | 7.05 ± 0.36** | 6.92 ± 0.31** |

Data analysed using one way analysis of variance (ANOVA) followed by Tukey's test. Values are expressed as mean ± S.E.M (n = 6 in each group). Where p.o. = per os (by mouth); i.p. = intraperitoneal. *P< 0.01 and **P< 0.001 when compared to tramadol in column 2, 3, 4 and 5; @P<0.01 when compared to aspirin in column 2.

**Table 2** shows that in tail-flick method, cetirizine and levocetirizine produced maximum percentage analgesia at 90 min (66.35%) and 60 min (64.53%) respectively. While the percentage analgesia of

aspirin was maximum at 30 min (68.14%). Amongst all the drug-treated groups, tramadol produced highest percentage analgesia at all the time intervals.

**TABLE 2: PERCENTAGE ANALGESIA OF DRUGS IN TAIL FLICK MODEL OF ANALGESIA IN RATS (N=6)**

| Drugs and doses (mg/Kg) | Percentage analgesia | | | |
|---|---|---|---|---|
| | At 30 min | At 60 min | At 90 min | At 120 min |
| (Normal saline 2 ml/Kg p.o.) | ---- | ---- | ---- | ---- |
| Aspirin (300 mg/Kg p.o.) | 68.14 | 57.27 | 49 .22 | 47.63 |
| Tramadol (10 mg/Kg i.p.) | 73.94 | 83.14 | 80.23 | 74.27 |
| Cetrizine (1 mg/Kg p.o.) | 52.16 | 56.18 | 66.35 | 56.86 |
| Levocetrizine (1 mg/Kg p.o.) | 49.80 | 64.53 | 55.61 | 40.17 |

Values are expressed in percentage (n= 6 in each group). Where p.o. = per os (by mouth); i.p. = intraperitoneal.

**Table 3** shows that at all the observation times, paw volume in all the drug treated groups was significantly less than that in the control group (P<0.001). No significant difference was observed between the paw volumes of cetirizine, levocetirizine and aspirin groups. While at the interval of 120 min, paw volume of levocetirizine was significantly less than that of aspirin group (P<0.05).

**TABLE 3: MEAN PAW VOLUME IN CARRAGEENAN INDUCED PAW OEDEMA IN RATS (N=6)**

| Drugs and doses (mg/Kg) | Mean Paw volume (ml) | | | |
|---|---|---|---|---|
| | At 0 min | At 30 min | At 60 min | At 120 min |
| (Normal saline 2ml/Kg p.o.) | 0.37 ± 0.03 | 0.98 ± 0.06 | 1.32 ± 0.06 | 1.65 ± 0.06 |
| Aspirin (300mg/Kg p.o.) | 0.32 ± 0.03 | 0.53 ± 0.05@ | 0.43 ± 0.03@ | 0.37 ± 0.03@ |
| Cetrizine (1 mg/Kg p.o.) | 0.38 ± 0.048 | 0.65 ± 0.02@ | 0.52 ± 0.03@ | 0.45 ± 0.03@ |
| Levocetrizine (1 mg/Kg p.o.) | 0.35 ± 0.06 | 0.60 ± 0.05@ | 0.57 ± 0.05@ | 0.5 ± 0.04@* |

Data analysed using one way analysis of variance (ANOVA) followed by Tukey's test. Values are expressed as mean ± S.E.M. (n = 6 in each group) Where p.o. = per os (by mouth); @P<0.001 when compared to control in column 2, 3 and 4, *P<0.05 when compared to aspirin in column 4.

**Table 4** shows that the percentage inhibition of carrageenan induced paw oedema was maximum at 120 min in all three study groups. The Aspirin group showed maximum percentage inhibition followed by levocetirizine and cetirizine group at 30, 60, and 120 min.

**TABLE 4: PERCENTAGE INHIBITION OF CARRAGEENAN INDUCED PAW OEDEMA IN RATS (N=6)**

| Drugs and doses (mg/Kg) | Percentage inhibition | | |
|---|---|---|---|
| | At 30 min | At 60 min | At 120 min |
| Aspirin (300mg/Kg p.o.) | 46.19 | 67.14 | 77.28 |
| Cetrizine (1 mg/Kg p.o.) | 33.28 | 60.22 | 72.59 |
| Levocetrizine (1 mg/Kg p.o.) | 38.11 | 57.07 | 69.3 |

Values are expressed in percentage (n= 6 in each group). Where p.o. = per os (by mouth).

**Table 5** shows the mean difference between LCS (Linear cross section) on tenth day and first day. Lower the difference in LCS, higher is the anti-inflammatory action. Mean difference in LCS in all the three drug-treated groups was statistically significantly less when compared to control (*P*< 0.001). There was no statistically significant difference in LCS in the three drug-treated groups indicating that anti-inflammatory activity of cetirizine and levocetirizine in chronic inflammation was comparable to that of aspirin.

**TABLE 5: EFFECT OF DIFFERENT DRUGS ON LINEAR CROSS-SECTION BELOW THE ANKLE JOINT IN FORMALIN INDUCED ARTHRITIS IN RATS (N=6)**

| Drugs and doses (mg/Kg) | Mean initial LCS | Mean Day 10 LCS | Mean difference in LCS | Percentage anti-inflammatory effect |
|---|---|---|---|---|
| (Normal saline 2ml/Kg p.o.) | 4.72 ± 0.20 | 7.55 ± 0.27 | 2.83 ± 0.22 | ---- |
| Aspirin (300 mg/Kg p.o.) | 4.4 ± 0.26 | 4.75 ± 0.17 | 0.35 ± 0.18* | 87.75 |
| Cetrizine (1 mg/Kg p.o.) | 4.32 ± 0.21 | 5.25 ± 0.14 | 0.93 ± 0.22* | 67.14 |
| Levocetrizine (1 mg/Kg p.o.) | 3.95 ± 0.24 | 4.75 ± 0.15 | 0.80 ± 0.24* | 71.85 |

Where, LCS = Linear Cross Section. Data analysed using one way analysis of variance (ANOVA) followed by Tukey's test. Values are expressed as mean ± S.E.M. (n = 6 in each group). *P<0.001 when compared to control.

**DISCUSSION:** $H_1$ receptor blockers have an established and valued place in the treatment of itching of allergic and non-allergic origin [16]. This study was designed to explore the effects of cetirizine and levocetirizine, second-generation $H_1$ receptor blockers, in experimental models of pain and inflammation in rats. The doses of these drugs were used in accordance with the earlier studies [9, 17, 18].

The exact mechanism of pain perception has not been elucidated till now, and there is a role of variety of chemical substances in pain transmission. Histamine is one of those chemical substances which modulates the central perception of nociceptive stimuli. Centrally, it has both pro-nociceptive and anti-nociceptive actions mediated through $H_2$ and $H_1$ receptors respectively [19]. A study conducted by Mobarakeh *et al*., demonstrated reduced response to noxious stimuli in H1 receptor knockout mice [20].

Histamine also plays a key role in the complex pathophysiological mechanism known as neuro-genic inflammation. This theoretically supports that $H_1$ receptor blocking agents like cetirizine and levocetirizine have potential for clinical develop-ment as treatments for pain and other symptoms associated with neurogenic inflammation.

In this study, the pain threshold increased significantly during the period of observation in all the four drug-treated groups, with maximum effect observed in the tramadol group. Though aspirin has a central component of action, it predominantly produces analgesia through a peripheral action. Tail flick method of analgesia is effective in estimating the efficacy and potency of centrally acting analgesics [15, 21]. Hence, the maximum analgesic action of aspirin cannot be evident in this method which may be the reason that analgesic activity of cetirizine and levocetirizine was comparable to aspirin. An earlier study has reported significant analgesic activity of cetirizine in tail-flick model of analgesia in Swiss albino mice [9].

This analgesic effect of cetirizine and levocetirizine might be due to blockade of $H_1$ histaminergic receptor, which mediates pain directly or indirectly by decreasing nerve growth factor peptide level, as histamine has an influence on the secretion of nerve growth factor peptide, which is responsible for hyperalgesia [22].

In the model of acute inflammation, both cetirizine and levocetirizine showed significant anti-inflammatory activity which was comparable to aspirin. Similar findings have been reported in a previous study in which levocetirizine showed significant reduction in carrageenan-induced rat paw oedema and the activity was comparable to diclofenac [8]. Carrageenan-induced paw oedema is the standard experimental model of acute inflammation.

Carrageenan is the phlogistic agent of choice for testing anti-inflammatory drugs as it is not known to be antigenic and is devoid of apparent systemic effects. This model exhibits a high degree of reproducibility and has significant predictive value for clinically useful anti-inflammatory drugs [23].

Carrageenan-induced oedema is a biphasic response. The first phase is mediated through the release of histamine, serotonin and kinins, whereas the second phase is due to the release of prostaglandin and slow reacting substances [24]. Inhibition of carrageenan induced oedema by cetirizine and levocetirizine can therefore be attributed to their ability to inhibit release of various mediators of inflammation.

Both cetirizine and levocetirizine showed significant anti-inflammatory activity, which was comparable to aspirin in formalin-induced arthritis model of chronic inflammation. The anti-inflammatory property of levocetirizine and cetirizine is due to their ability to prevent production of pro-inflam-matory mediators like histamine, interleukins, leukotrienes, bradykinin, prostaglandins activation *etc*. [5] A review of *in-vitro* experimental studies suggested that levocetirizine has anti-inflammatory properties not simply related to the antihistamine activity but also to the regulation of eosinophils which are independent of $H_1$ receptor blockade [5]. Both cetirizine and levocetirizine inhibit eotaxin-induced eosinophil trans-endothelial migration through both dermal and lung microvascular endothelial cells suggesting that, they have potential anti-inflammatory effects [25].

In this study, we used aspirin as a standard drug and observed that the activity of antihistamines was comparable to that of aspirin. These results are in

accordance with already published reports in literature which indicate that antihistamines do have an important role to play as analgesics and anti-inflammatory agents.

However, considering their current role in allergic conditions like rhinitis, urticarial, and the safety concerns involved with their use, as well as the availability of many other drugs having superior analgesic and anti-inflammatory activities, the routine use of antihistamines for these effects cannot be justified. However, these drugs can certainly emerge as useful alternatives in the treatment of diseases characterized by chronic inflammation particularly when there are coexisting allergic manifestations. Further, it appears that they may be particularly effective in the event of inflammatory nociception.

**CONCLUSION:** Levocetirizine and cetirizine, have significant analgesic activity in rats in the tail flick method. They also have significant anti-inflammatory activity in both acute and chronic inflammation in carrageenan-induced paw oedema and formalin-induced arthritis in rats, which is comparable to aspirin.

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**CONFLICTS OF INTEREST:** Nil

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