

Evaluation of analgesic and anti-inflammatory activity of Levocetirizine in albino rats**Dipti R. Sonawane, Jugalkishor B. Jaju*, Ganesh R. Pawar, Punam A. Gosavi**

Department of Pharmacology,
Government Medical College,
Latur, Maharashtra, India

Received: 25 May 2019**Revised:** 10 June 2019**Accepted:** 02 July 2019***Correspondence to:**

Dr. Jugalkishor B. Jaju,
Email: jkb.jaju@gmail.com

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ABSTRACT

Background: Levocetirizine, the R-enantiomer of Cetirizine has pharmacokinetically and pharmacodynamically favourable characteristics, with rapid onset of action, high bioavailability, high affinity for and occupancy of the H1-receptor, limited distribution, minimal hepatic metabolism together with minimal side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years for analgesic, anti-inflammatory, and more recently in the case of aspirin, antithrombotic purposes. Because of the significant side effect profiles of steroidal and NSAID medications, there is a greater interest in newer compounds such as antihistaminic drugs. This article will consider the potential or otherwise of the reported analgesic and anti-inflammatory effects of levocetirizine to enhance its effectiveness in the treatment of allergic disease with pain.

Methods: Albino Wistar rats of either sex weighing 150-250 grams were used. For both Analgesic activity and Anti-inflammatory activity, 4 groups consisting of 6 animals per group were used. Group I: Control: 1% Gum acacia. 2ml/kg, Group II: Standard drug: Diclofenac sodium 4.5mg/kg; Group III: Test Drug 1: Levocetirizine 1mg/kg; Group IV: Test Drugs 2: Levocetirizine 1mg/kg+Diclofenac sodium 4.5mg/kg. Drugs were administered orally. For analgesic activity, Tail clip method and Hot plate method was used. For acute anti-inflammatory activity Carrageenan induced rat paw oedema method was used.

Results: Levocetirizine, is found to have significant analgesic activity in rats (1 mg/kg dose) alone and in combination with Diclofenac Sodium in Haffner's Tail Clip method and Eddy's Hot Plate Method. Levocetirizine also has got prominent anti-inflammatory activity in acute models evidenced by percentage inhibition of acute rat paw oedema.

Conclusions: Levocetirizine possess analgesic and acute anti-inflammatory activity alone and in combination with Diclofenac sodium.

Keywords: Analgesic activity, Anti-inflammatory Activity, Antihistaminic drugs, Diclofenac Sodium, Levocetirizine

INTRODUCTION

The IASP (The International Association for the Study of Pain) defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".¹ Pain is a consequence of tissue injury (trauma, inflammation) causing the release of chemical mediators like histamine, serotonin, bradykinin and prostaglandins which activate nociceptors,

defined as receptors that are capable of distinguishing between noxious and innocuous stimuli in the tissue.^{2,3} Since the last century it has been known that histamine, present in the majority of cells, is a pain mediator. It activates polymodal nociceptors and produces pain when injected in the human skin. Tissue damage releases histamine causing local pain, vasodilation and edema.⁴ Inflammation is defined as series of molecular and cellular responses acquired during evolution designed to eliminate foreign agents and promote repair of

damaged tissues. According to Celsus, the characteristics of inflammation are Rubor (redness), Tumor (swelling), Calor (heat), Dolor (pain) and Functio laesa (loss of function). Acute inflammation is a short-term response that usually results in healing leukocytes infiltrate the damaged region, removing the stimulus and repairing the tissue. Various mediators of inflammation are histamine, bradykinins, serotonin, leukotrienes and prostaglandins.⁵ These mediators even in small quantities can elicit pain response.

The current management of pain and inflammation involves use of non-steroidal anti-inflammatory agents. In spite of tremendous development in the field of synthetic drugs during recent era, long-term use of these drugs are associated with serious adverse effects like gastrointestinal damage, nephrotoxicity, hypertension and thrombosis.⁶ The other group of drugs for pain like opioids have well known side effects ranging from sedation to drug dependence. So, a search for a drug for analgesia with high therapeutic effect and fewer side effects will be a boon for the patients. Hence, the search for a new, safe analgesic and anti-inflammatory drug is still going on. Peripheral histamine is involved in the stimulation of nociceptive fibers, and its antagonists show anti-nociceptive effects whose study has been neglected.⁷ Histamine being a potential target plays a major role in inflammation by increasing vascular permeability, vasodilatation and chemotaxis.⁸ The release of histamine from mast cells during antigen antibody reactions is well known, as is its involvement in the inflammatory response to skin injury.⁹ However, the role of histamine in acute inflammation is associated with mast cell degranulation in non-rodent species including man where as its role in chronic inflammation is yet to be established.

Levocetirizine is a second generation antihistaminic drug, popularly used for allergic reactions, rhinitis, urticaria and conjunctivitis. It has got selective H₁ antihistaminic activity. It has desirable pharmacokinetic properties with high safety profile.² It is a selective racemic H₁ receptor inverse agonist, metabolite of hydroxyzine. The analgesic and anti-inflammatory action of Levocetirizine has not been fully evaluated due to lack of studies.

Thus, Levocetirizine being a commonly used antihistaminic drug, deserves further evaluation from the standpoint of its analgesic and anti-inflammatory effect in therapy. So, in this study an earnest attempt is made to explore its Analgesic and Anti-inflammatory activity of levocetirizine in various animal models of pain and inflammation.

METHODS

Animals

Albino Wistar rats of either sex weighing 150-250 grams were used. 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).

The rats were grouped in separate polypropylene cages on husk bedding with six animals in each group. Animals were fed with standard pellet diet and water ad libitum. The 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 in a colony room at ambient temperature of 25±2°C with help of air coolers and enough humidity on a 12 hour light-dark cycle. They had free access to food and water. Study was conducted during the daytime (between 10.00 to 18.00 hrs).

Drugs and chemicals

Drugs (Levocetirizine and Diclofenac Sodium) were obtained from Sigma Aldrich, Aurangabad, India in pure powder form. Chemicals (carrageenan and diethyl ether) were obtained from Ozone Laboratory Chemicals, Mumbai, India and Qualigens Scientific sales and services, Latur, India. Chemicals were of analytical grade. All the drugs were dissolved in 1% Gum Acacia. Fresh solutions were prepared half an hour before experiment. All the drugs were administered per oral.

Instruments

- Haffner's Tail Clip: Dolphin, Mumbai.
- Eddy's Hot Plate Analgesiometer: Dolphin, Mumbai.
- Digital Plethysmometer : Dolphin, Mumbai.

Study design

Grouping of animals

For each experiment 4 groups consisting of 6 animals per group were used. They were adapted for 10 days for the study condition.

For Analgesic activity and Anti-inflammatory activity

- Group I: Control: 1% Gum acacia. 2ml/kg^{8,10}
- Group II: Standard drug: Diclofenac sodium 4.5mg/kg⁸
- Group III: Test Drug: Levocetirizine 1mg/kg¹¹
- Group IV: Test Drugs Levocetirizine 1mg/kg + Diclofenac sodium 4.5mg/kg.

The doses of the drugs under study were calculated by extrapolating human into animal dose.⁸

The animals were subjected to the following experiments:

Analgesic activity

In this study, two analgesic models, Eddy's hot plate and Tail clip method were used to evaluate the analgesic activity of Cetirizine hydrochloride per se and in combination.

Tail clip method^{2,12}

This method was used to induce mechanical pain stimuli. All the rats were screened by applying a metal artery clip to the base of the tail with its jaw sheathed with thin cotton covering with cut off time of 10 seconds (Figure 1). After screening animals were divided in to four groups 6 animals each.



Figure 1: Tail clip method, response of a rat (Biting).

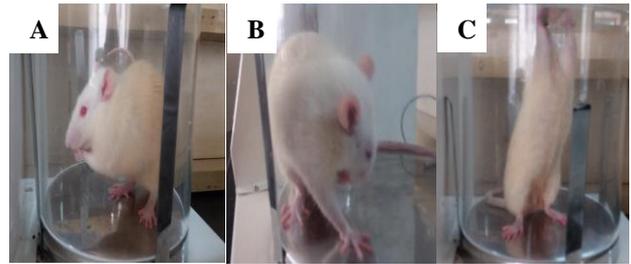
Food was withdrawn 12 hours prior to drug administration till completion of experiment. The drug were administered orally. During the experiment, an artery clip was applied to the root of the tail (approximately 1 cm from the body) to induce pain at 0, 15, 30, 60 and 90 minutes after drug administration. At each application of clip reaction of animal in the form of biting the clip, portion of tail near the clip was observed and reaction time was noted using a stopwatch.

*Hot plate method*¹³⁻¹⁶

In this method painful stimuli in the form of heat was given using Eddy's Hot Plate Analgesiometer, consisting of an electrically heated surface. The temperature was controlled between 55° to 56°C. Swiss albino rats weighing between 150-250 grams were screened with a cut off time fixed at 30 seconds to prevent injury to tissues of paws¹⁷. After screening animals were grouped into 4 groups. Food was withdrawn 12 hours prior to drug administration till completion of experiment. The drugs were given orally. After 30 minutes of drug administration, the animals were placed on the hot plate. The response in the form of jumping, withdrawal of the paws or the licking of the paws (Figure 2) was observed and response latency recorded by a stop-watch before, and after 0, 30, 60, 90 and 120 mins of drug administration for all groups.

Average reaction times were then calculated, and the percentage protection variation was calculated using the following ratio:

$$\text{Percentage protection} = \frac{\text{Drug latency} - \text{Baseline latency}}{\text{Drug latency}} \times 100$$



(A): Paw elevation, (B): licking of paws, (C): Jumping Figure 2: Hot plate method.

Anti-inflammatory activity

Acute Anti-inflammatory method

Carrageenan induced-rat paw oedema^{6,8}

The method used herein is comprised of the study of inflammatory reaction induced by Phlogistic agent, Carrageenan injected into the sub plantar surface of the either right/left hind paw of each rat according to the method of Winter et. al, with some modifications.^{18,19} The instrument used in this study for recording the paw oedema was Digital Plethysmometer (Figure 3).

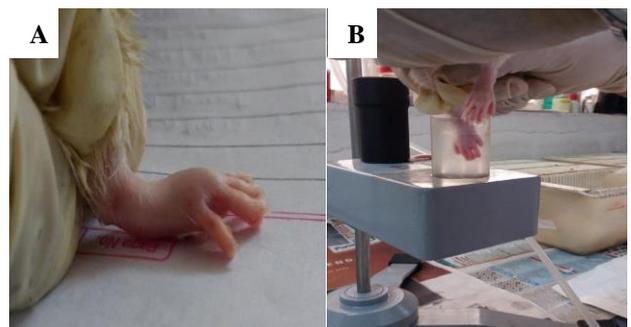


Figure 3: Carrageenan induced rat paw oedema method. (A): Carrageenan induced paw oedema, (B): Water displacement during right paw insertion.

Swiss albino rats weighing between 150-250 grams were used for evaluation of anti-inflammatory activity; 4 groups consisting of 6 animals were formed to carry out the experiment. Food was withdrawn 12 hours prior to drug administration till completion of experiment. Left paw was marked with ink at the level of lateral malleolus; basal paw volume was measured plethysmographically by volume displacement method using Digital Plethysmometer by immersing the paw till the level of lateral malleolus.²⁰ All the drugs were administered orally. 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 plethysmometrically just before 1% carrageenan injection, that is, at "0" h and then at 1st, 2nd, 3rd and 4th hr after carrageenan injection.²¹ Same

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

$$\text{Percent inhibition} = \frac{V_c - V_t}{V_c} \times 100$$

Where, V_c = Volume of paw oedema in control animals,
 V_t = Volume of paw oedema in drug treated animals.

Statistical analysis

Data was analysed by using Graph pad Prism software version 5. Comparison between different groups was done by one way ANOVA followed by Tukey’s test. The ‘p’ value less than 0.05 (p value <0.05) was considered as statistically significant.

RESULTS

For analgesic activity

In both these methods mean increase in latency time, is considered as a measure of analgesia and the ability to increase in latency as compared to control suggests analgesic activity.

Tail clip method

In Tail clip method we observed that at 60 mins interval Levocetirizine (1.74±0.03 secs) mean reaction time was significantly increased (p<0.001) as compared to control (0.67±0.04), also Levocetirizine in combination with Diclofenac Sodium (1.78±0.05 secs) showed significant increase in mean reaction time (p<0.001) as compared to control (0.67± 0.04) (Table 1). These results have shown that there is significant increase in latency time of Levocetirizine, Diclofenac Sodium and both in combination as compared to control. Highest latency time has been found to be present at 60 mins interval in figure 4.

Hot plate method

In Eddy’s Hot Plate Method latency time was noted at 0, 30, 60, 90 and 120 mins after the administration of drugs. Levocetirizine (7.04±0.45) has shown significant results (P<0.05) with 44.46% protection alone and in combination with Diclofenac sodium (8.28±1.53) it has got 52.77% protection as compared to control at 90 mins. Whereas Diclofenac Sodium (9.54±0.12) showed significant increase in latency time with (P <0.01) 59.01% protection (Table 2).

Table 1: Effect of different drugs on nociception in Tail clip method.

Groups	Dose of Drugs	Reaction Time (in seconds)				
		0 min	15 mins	30 mins	60 mins	90 mins
I Control Gum Acacia	1% (2 ml/kg)	0.73±0.07	0.62±0.05	0.63±0.05	0.67±0.04	0.73±0.05
II Diclofenac Sodium	4.5 mg/kg	1.47±0.11*	1.22±0.05*	2.11±0.07*	2.26±0.10***	0.69±0.03
III Levocetirizine	1 mg/kg	1.43±0.11	1.13±0.04#	0.84±0.05#	1.74±0.03***#	1.16±0.03
VI Levocetirizine + Diclofenac sodium	1 mg/kg + 4.5 mg/kg	1.25±0.02	1.14±0.03#	1.67±0.03#	1.78±0.05***#	0.58±0.04

[Values are expressed in Mean ± S.E.M. (Standard error of mean), n=6 in each group, df=5,30. * p value < 0.05 as compared to control. ** p value < 0.01 as compared to control. *** p value < 0.001 as compared to control. # p>0.05 as compared with Diclofenac sodium] ***P<0.001 a significant analgesic activity in the hot plate as evidenced by increase in latency time in seconds (Table 1) as compared with control at the end of 60 mins, Mean increase in latency time, is considered as a measure of analgesia and the ability to increase in latency as compared to control suggests analgesic activity.

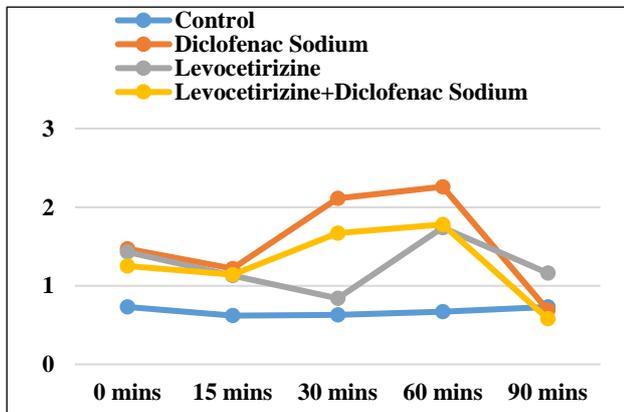


Figure 4: Effect of different drugs on nociception in Tail clip method.

Levocetirizine in combination with Diclofenac sodium have shown more analgesic activity as compared to levocetirizine alone at 90 mins in Figure 5.

Carrageenan induced rat paw oedema

At the end of 3 hours we observed that Levocetirizine (0.265±0.014) per se and in combination (0.185±0.001) was able to inhibit the increase in paw volume (ml) significantly (p<0.001) as compared to control (0.341±0.008).

The percentage inhibition of Carrageenan induced rat paw Oedema by Diclofenac Sodium was 43.69% while that of Levocetirizine alone was 22.22% whereas percentage inhibition in combination with Diclofenac Sodium was 45.74% (Table 3).

Levocetirizine in combination with Diclofenac sodium have shown maximum paw oedema inhibition as compared to alone in figure 3.

DISCUSSION

This study was designed to explore the effects of Levocetirizine on known experimental models of pain and inflammation in rats. For evaluating analgesic activity of Levocetirizine, we used two methods i.e. Haffner’s Tail clip method and Eddy’s Hot plate method.

In this study, Levocetirizine at a dose of 1 mg/kg showed statistically significant analgesic activity as compared to control in rats and maximum possible analgesia was observed at one hour after drug administration in Tail Clip

Method. Levocetirizine in combination with Diclofenac Sodium has more analgesic activity than Levocetirizine alone but less analgesic activity than Diclofenac sodium.

In hot plate method too, authors observed that Levocetirizine alone and in combination with Diclofenac sodium has got significant analgesic activity as compared to control. There was a significant increase in reaction time from 30 minutes onwards till 120 minutes in all the three groups as compared to control group.

In this method also, it has been observed that Levocetirizine in combination with Diclofenac Sodium has more analgesic activity than Levocetirizine alone but less analgesic activity than Diclofenac sodium.

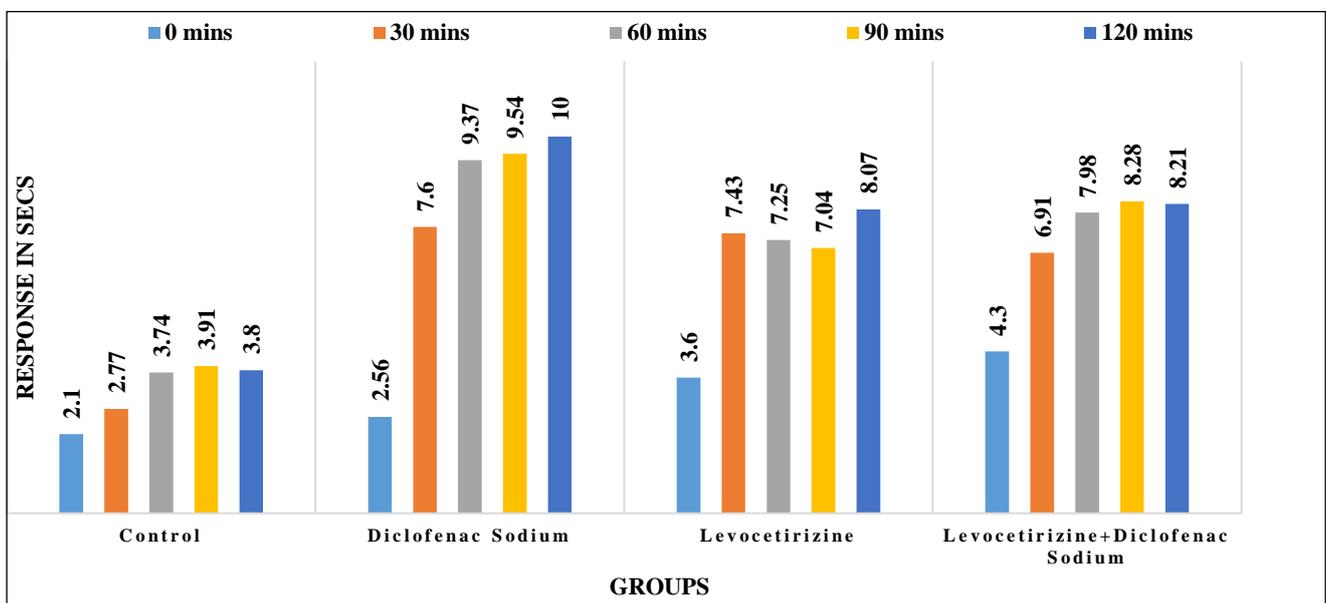


Figure 5: Mean analgesic activity of different drugs by hot plate method.

Table 2: Effect of different drugs on nociception in hot plate method.

Groups	Reaction Time					% protection
	0 mins	30 min	60 mins	90 mins	120 mins	
I Control: Gum Acacia, (1%, 2ml/kg)	2.10±0.19	2.77±0.32	3.74±0.36	3.91±0.14	3.80±0.12	-
II Diclofenac Sodium, (4.5 mg/kg)	2.56±0.10	7.60±0.51**	9.37±0.20***	9.54±0.12***	10.00±1.2***	59.01%
III Levocetirizine, (1mg/kg)	3.6±0.36	7.43±1.64**	7.25±0.46*#	7.04±0.45*#	8.07±0.68*#	44.46%
VI Levocetirizine (1mg/kg)+Diclofenac sodium (4.5mg/kg)	4.3±0.27	6.91±0.65*	7.98±1.15***#	8.28±1.53***#	8.21±1.2*#	52.77%

Values are expressed in Mean±S.E.M. (Standard error of mean), n=6 in each group, df=5.30. * p value <0.05 as compared to control. ** p value <0.01 as compared to control. *** p value <0.001 as compared to control. # p>0.05 as compared with Diclofenac sodium, ***P<0.001 a significant analgesic activity in the hot plate as evidenced by increase in latency time in seconds (Table 2) as compared with control at the end of 90 mins, Mean increase in latency time, is considered as a measure of analgesia and the ability to increase in latency as compared to control suggests analgesic activity.

Table 3: Effect of different drugs on carrageenan induced rat paw oedema.

Groups	Mean paw volume (ml)			% inhibition calculation at the end of 3 hours
	At 0 hours	At the End of 3 hours	Mean difference at the end of 3 hours	
I Control: Gum Acacia (1%, 2ml/kg)	1.097±0.006	1.438±0.089	0.341±0.008	-
II Diclofenac Sodium (4.5 mg/kg)	0.681±0.027	0.873±0.038	0.192±0.001***	43.69%
III Levocetirizine (1mg/kg)	0.785±0.017	1.050±0.048	0.265±0.014***	22.22%
VI Levocetirizine (1mg/kg) ± Diclofenac sodium (4.5mg/kg)	0.785±0.037	0.970±0.025	0.185±0.001***#	45.74%

Values are expressed in Mean±S.E.M. (Standard error of mean), n=6 in each group, df=5,30. *** p value <0.001 as compared to control. # p>0.05 as compared with Diclofenac sodium, mean paw volume increase, is considered as a measure of inflammation and the ability to control this increase as compared to control suggests anti-inflammatory activity.

Findings from these analgesic study demonstrated that the Levocetirizine prolonged the reaction time in the tail clip and hot plate method. This might indicate sensitivity of the spinally mediated reflex response in the tail clip method and supraspinal anti-nociceptive response. Analgesic drugs which are centrally acting elevate pain threshold of animals towards heat and pressure. Therefore, the analgesic effect of the Levocetirizine on this pain-state model indicates that it might be centrally acting.

The role of histamine in pain is different in the central and peripheral nervous systems. Central histamine has both pro and anti-nociceptive actions. H₂ receptors seem to be anti-nociceptive, while H₁ receptors are pro-nociceptive. Histamine is also released from local cells and directly excites nociceptors.⁷ Also, it is possible to increase sensitivity to noxious stimuli by activating histamine H₁-receptors; mainly H₁ receptor. It thus seems likely that the histaminergic system, like many other neuronal systems, plays an important role in the modulation of central perception of nociceptive stimuli.²²

Hot plate method produces two measurable behavioral components in response to thermal pain, with regard to their reaction times. Responses such as paw licking and jumping in rats are considered to be supraspinally integrated. The hot plate method is useful in the elucidating centrally mediated anti nociceptive responses, which focuses mainly on changes above the spinal cord level. Thus, Levocetirizine may possess anti nociceptive property in this analgesic experimental model as nerve growth factor (NGF) is a major mediator of inflammatory and neuropathic pain it decreases nerve growth factor peptides and since histaminic receptors have been shown to be involved in mediating nociception. Levocetirizine is supposed to possess analgesic activity by preventing pain transmission but not as much as Diclofenac sodium.

The effective and widely used model for inflammation is carrageenan-induced paw oedema, carrageenan is polysaccharides of sulfated galactose units and is derived from Irish Sea moss *Chondrus crispus*, which initially releases histamine and serotonin followed by prostaglandins, protease, and lysosomes.²⁰ Therefore for evaluating anti-inflammatory activity of Levocetirizine we used Carrageenan induced rat paw oedema method.

Results has shown that Levocetirizine has significant anti-inflammatory activity. Also, Levocetirizine in combination with Diclofenac Sodium has more anti-inflammatory activity than Levocetirizine alone but less anti-inflammatory activity than Diclofenac sodium. By observing the decrease in paw oedema by Levocetirizine alone and in combination comparing with Diclofenac sodium was not significantly different.

Acute inflammation is characterized by vasodilatation, exudation of plasma, release of various inflammatory mediators, cytokines, growth factors and emigration of leukocytes. Anti-inflammatory drugs inhibit different stages of inflammation.¹⁹ Carrageenan induced rat paw oedema has been a popular inflammatory model to investigate anti-inflammatory effect of compounds. It has a biphasic effect.²³ The first phase is due to release of histamine and serotonin (5 HT) (02 hr.), plateau phase is maintained by a kinin like substance (3 hr) and second accelerating phase of swelling is attributed to PG release (>4 hr). Authors results revealed that administration of Levocetirizine and Diclofenac Sodium inhibit the oedema starting from the first hour and all phases of inflammation, which is probably inhibition of different aspects and chemical mediators of inflammation like Histamine.

The anti-inflammatory activities of second- and third-generation H₁-receptor antagonists have been evaluated in-vitro too. These studies have shown that many second-generation H₁-receptor antagonists (considered potentially or minimally sedating) and third-generation H₁-receptor antagonists (considered non-sedating) inhibit release or generation of multiple inflammatory mediators, including IL-4, IL-6, IL-8, and IL-13; PGD₂; LTC₄; tryptase; histamine; and the TNF- α induced chemokine RANTES.⁸

Although the majority of research into H₁-antihistamines has been focused on the histamine dependent early phase symptoms of the allergic response, it is now becoming clear that these drugs have anti-inflammatory effects. This follows the observation by Bakker and colleagues that histamine can activate NF- κ B, a transcription factor involved in the synthesis of many pro-inflammatory cytokines and adhesion molecules involved in the initiation and

maintenance of allergic inflammation.²⁴ It is a H1 receptor antagonist mechanism of its anti-inflammatory action could be possibly due to inhibition of histamine.

Histamine also enhances nerve growth factor secretion in pain and inflammation. Studies have shown that nerve growth factor (NGF) is a major mediator of inflammatory and neuropathic pain.²² It is also released from local cells and directly excites nociceptors. It also plays role in physiological and pathological pain perception.²²

Anti-histaminic plays a role to decrease pain and inflammation as histamine is an inflammatory mediator in acute inflammation associated with pain. Very few studies evaluated analgesic and anti-inflammatory activities of anti-histaminic. These studies have shown that anti-histaminic inhibit multiple inflammatory mediators like histamine, interleukins, prostaglandins.⁸

So in this study Levocetirizine in its therapeutically permissible dose showed promising results in acute models of experimental inflammation.

CONCLUSION

Levocetirizine, a selective H1 antihistaminic drug is found to have significant analgesic activity in rats (1mg/kg dose) alone and in combination with Diclofenac Sodium in Haffner's Tail Clip method and Eddy's Hot Plate Method. This effect might be due to blockade of H1 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.

The Anti-inflammatory property of Levocetirizine is due to its ability to prevent production of pro-inflammatory mediators like histamine, interleukins, leukotrienes, Bradykinin, ICAM expression, prostaglandins activation etc. This study proves that the use of Levocetirizine either as monotherapy or along with the conventional medications may have an added benefit of anti-inflammatory activity in various inflammatory disorders with/without allergic overlay.

Further studies need to be done in various other Analgesic and inflammatory models along with the human studies to strengthen the results and prove their efficacy of long term administration of Levocetirizine as potential Analgesic and anti-inflammatory agent in routine clinical practice in treatment of pain and inflammation.

So, it is hoped that this study will stimulate further efforts towards the development of new medications for the treatment of inflammatory and painful diseases.

ACKNOWLEDGEMENTS

The authors are thankful to The Dean, Dr. Rajaram powar, Government Medical College, Latur for continuing support.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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Cite this article as: Sonawane DR, Jaju JB, Pawar GR, Gosavi PA. Evaluation of analgesic and anti-inflammatory activity of Levocetirizine in albino Rats. *Int J Basic Clin Pharmacol* 2019;8:1805-12.