A Comparative Evaluation of Anti-Inflammatory and Arthritic Effects of bradykinin inhibitor Zaltoprofen over Piroxicam in Murine models: A randomized experimental study.

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Abstract

Background and Aims: Inflammation is an essential biochemical protective response of vascularized tissues, broadly classified into acute and chronic inflammation. Zaltoprofen, a unique propionic acid group of NSAID, acts by blocking the augmenting effect of bradykinin. The present study was conducted to evaluate the acute and chronic anti-inflammatory (arthritic) potential of Zaltoprofen over piroxicam in murine models.

Methods:

A total of 24 healthy Wister rats (200–250 g) of either sex (24 in each model) were obtained from the central animal house, AIIMS, Bhopal and categorized into four different groups, six in each. Zaltoprofen was used as a test and Piroxicam as a Standard (Per Os) agent. The anti-inflammatory or arthritic potential was evaluated and compared by acute and chronic inflammation (carrageenan and formalin-induced) models.

Results:

In the acute inflammation model, Zaltoprofen when compared to Negative control (NaCl 10ml/kg) there was a significant inhibition in paw volume ($P < 0.001$) at different time scales with two different doses of Test compound (Zaltoprofen 10 & 20mg/kg). However, in the chronic inflammation model, Zaltoprofen 10 mg/kg & 20mg/kg doses of the Test compound had been shown a significant reduction in the chronic inflammation comparable to the negative control (NaCl 10ml/kg), though the efficacy was lesser than Positive control (Piroxicam 10mg/kg) ($P \leq 0.05$).

Conclusions:

Zaltoprofen possesses significant acute and chronic anti-inflammatory and arthritic effects by inhibiting various inflammatory mediators. Therefore, Zaltoprofen can be explored as a potential alternative agent for the treatment of acute inflammatory and chronic inflammatory or arthritis conditions in human beings.

Introduction

Inflammation is an essential biochemical protective response of vascularized tissues that delivers leukocytes and molecules of host defence from the circulation to the sites of infection and cell damage to eliminate the offending agents [1]. It serves to clear the host of both the initial cause of cell injuries like microorganisms and toxins and the consequences of such injury, which may be necrosis of cells and tissues. Various mediators of defence include phagocytic leukocytes, antibodies, and complement proteins. During the inflammation, circulating inflammatory cells and proteins reach the injured tissues and activate the recruited and resident cells, as well as the soluble molecules, which could help to get rid of the harmful or unwanted substances. Inflammation is essential for survival to overcome the infections and healing of wounds

Acute inflammation develops within some minutes of tissue injury or infection, having characteristics of fluid and plasma proteins exudation, leading to oedema, and the migration of leukocytes, primarily neutrophils, and is very short in duration. However, if the offending stimulus is removed, the reaction subsides, and residual injury is repaired. Rheumatoid arthritis (RA) is a type of chronic inflammation, which is longer in duration and is associated with more tissue destruction and scarring [1]. Both Steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs for the prevention and treatment of inflammation. However, on long term use, NSAIDs are associated with gastrointestinal, hepatic, renal and cardiac side effects, etc. [2]. Hence, it is very essential to find drugs with lower side effects for the treatment of inflammatory diseases.

Zaltoprofen is a unique NSAID from the propionic acid group with a tri-cyclic formula. Its chemical name is 2-(6-oxo-5H-benzo[b][1]benzothiepin-3-yl) propanoic acid [3]. It has a potent analgesic and antipyretic activity [4–6]. It acts by blocking the, augmenting effect of bradykinin a potent endogenous algescic or sensitizing substance, acts through Bradykinin-1 (inducible) and Bradykinin-2 (constitutive) receptors. Zaltoprofen acts by inhibiting Gq protein-coupled B2 receptor-mediated action on α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) currents, through the inhibition of protein kinase-C activation in the primary sensory neurons [7]. Additionally, several different signal transduction pathways, including phospholipase C (PLC), phospholipase A₂, lipooxygenase (LOX), cyclooxygenase (COX) enzymes in dorsal root ganglion (DRG) cells [7]. Zaltoprofen also exhibits an anti-inflammatory effect by inhibiting the cyclooxygenase-2 (COX2) enzyme selectively and inhibits prostaglandin-E2 production at inflammatory sites [6–8]. Findings of an *in vivo* study by Tang et al. has shown that Zaltoprofen inhibits bradykinin-induced 12-lipoxygenase (LOX) activation in vitro and the slow bradykinin-induced onset of substance P release from dorsal root ganglion (DRG) neurons [9]. A study by Matsumoto et al. concluded that Zaltoprofen has inhibitory action specifically on bradykinin-induced nociception in nociceptor endings through B2-type bradykinin receptors [10]. An experimental study finding by Kameyama et al., has shown that zaltoprofen inhibits bradykinin-induced nociceptive responses more significantly, with a better safety margin, having less potential to induce gastric ulcers than indomethacin [6]. Santenna C et al. concluded that zaltoprofen analgesic efficacy was non-inferior to a standard NSAID piroxicam in experimental murine models of acute pain [5]. A multicentric, double-blind, double-dummy, randomized, parallel-group comparative study by Pareek et al. concluded that clinically zaltoprofen is non-inferior to Diclofenac [11]. Akihico T et al., had shown that zaltoprofen might be a potential agent to act against malignant phenotypes in chondrosarcomas via activation of PPAR γ and inhibition of MMP 2 activity [12]. A randomized placebo-controlled, double-blind, phase II trial by Akihico T et al., had found that Zaltoprofen can be a potential newer therapeutic agent, to stabilize disease progression for patients with diffuse tenosynovial giant cell tumour (D-TGCT) or unresectable L-TGCT [13]. A study by Okamoto et al., had reported that Zaltoprofen improves the loss of body weight in both the Con A-induced mouse and carbon tetrachloride-induced rat sickness behaviour models, like other commonly used NSAIDs Aspirin and Indomethacin [14] [Figure 1].

Zaltoprofen has shown its anti-inflammatory action at ED₅₀, 1–5 mg/kg, per oral [4]. Hence we have planned to study the dose range above 5 mg/kg body weight. In addition, till now there were no studies on the anti-inflammatory activity comparative efficacy of zaltoprofen over the very commonly prescribing anti-inflammatory agent piroxicam. Therefore, considering this background, we have evaluated and compared the anti-inflammatory and arthritic activity of Zaltoprofen efficacy over piroxicam in the Murine models of acute and chronic inflammation or arthritis.

Methodology

Experimental Animals:

Total 48 healthy male Wister albino rats (200–250 g) were used for the experimentations which were obtained from the Central Animal House of the institution, All India Institute of Medical Sciences (AIIMS) Bhopal, India. All the animals were adapted to the new environment minimum of two weeks before initiating the experiments using six animals in each group. The animal house temperature was maintained at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with 12 hours of light and 12 hours day cycle and they were allowed to have free access to standard pellet diet and water. The present experimental study was carried out as per the Committee for the purpose of control and supervision of experiments on animals (CPCSEA) guidelines after the approval by the Institutional Animal Ethics Committee (IAEC), AIIMS Bhopal, India (AIIMS/BHOPAL/IAEC/2017/03 Date: 10th August 2017).

Chemicals and drugs:

Chemicals Carrageenan and Formalin were obtained from Himedia Laboratories Pvt. Ltd (Mumbai, India). The Test compound Zaltoprofen was obtained from the JB Chemicals and Pharmaceuticals Ltd (Mumbai, India) and the standard agent Piroxicam from the **Medipol Pharmaceutical India Pvt. Ltd.** (New Delhi, India).

Experimental Dosing:

All the 24 experimental rats were randomly divided into four different groups (n=6 in each group) in each model [Figure 2].

Group I (Negative Control) were treated orally with normal saline (NS) 10 ml/kg body weight.

Group II (Positive Control) were treated orally with piroxicam 10 mg/kg body weight (PRC10).

Group III (Test-I) were treated orally with Zaltoprofen 10 mg/kg body weight (ZLT10).

Group IV (Test-II) were treated orally with Zaltoprofen 20 mg/kg body weight (ZLT20).

Experimental induction of acute and chronic inflammation:

Carrageenan-Induced Acute Inflammation:

Carrageenan induced paw oedema is the unique model of acute inflammation having large reproducibility. Inflammation was induced in rats according to previous standard research protocols [15]. Six animals of either sex in each group were used in the total four groups. Rats were administered orally 0.9% NaCl (10ml/kg), zaltoprofen (10 mg/kg and 20 mg/kg), and piroxicam (10 mg/kg) dissolved in 0.9% normal saline, 1 h before carrageenan administration. After that 0.1 ml of 1% carrageenan dissolved in normal saline was injected subcutaneously into the right hind paw for the induction of acute inflammation. The average volume of the left hind paw of each mouse was measured before injecting carrageenan, and at 30 minutes, 1 hour, 2 hours, and 3 hours after injection of carrageenan, using a digital plethysmometer (ORCHID Scientific & Innovative India, Pvt. Ltd. India) [15]. By using the following formula we have calculated the percentage of inhibition in comparison with the control group.

% Inhibition = [(Volume of oedema (control) – Volume of oedema (test)) / Volume of oedema (control) × 100.

Formalin-induced arthritis:

In the formalin-induced chronic inflammation model, paw oedema was induced by subaponeurotic administration of 0.1 ml of 2% formaldehyde 30 minutes after the oral administration of standard /test/vehicle compounds on day 1 and day 3 respectively. Experimental animals were administered daily, with test drug Zaltoprofen (10mg/kg and 20 mg/kg) and standard piroxicam (10 mg/kg) orally for 10 days. The daily changes in paw oedema or linear cross-section (LCS) of each rat, below the ankle joint, was measured daily with a digital vernier calliper (1). The difference in the paw volume on day 1 and day 10 was considered as inflammatory oedema. Volume changes in Test I, Test II and standard groups were compared with that of control and percentage inhibition was calculated.

The percentage inhibition of the inflammation was determined by the formula;

$$\text{\% Inhibition} = 1 - (dt/dc) \times 100.$$

Statistical procedure: Data were analyzed using SPSS version 22.0. Results were expressed as mean $\pm$ SD ($n = 6$). The percentage inhibition of the inflammation was calculated for each model. Comparison between all the four different groups was done by using one-way ANOVA followed by Bonferroni's test to compare the difference between groups at different time intervals. P-value less than 0.005 was considered statistically significant when compared with control (*p < 0.005).

Results

Acute anti-inflammatory activity:

The mean of the basal paw oedema volume was comparable in all the groups (**Table.1**). After 60 and 120 minutes, the mean decrease in paw volume in all three groups (ZLT10mg/kg, ZLT 20 mg/kg & PRC10mg/kg) was statistically significant when compared to the negative control group ($P < 0.001$). For the negative control group, the injection of carrageenan caused localized oedema, after 30 min. The swelling increased progressively from 30 min onwards. A maximum volume of the paw was observed in animals of negative control at 120 min (2.31 ± 0.348) (0.289 ± 0.008 ml) after injecting carrageenan. Test-I (zaltoprofen 10mg/kg) and Test-II (zaltoprofen 20 mg/kg) caused significant decrease in the paw volume ($***P = < 0.001$) compared to control (1.43 ± 0.068 and 1.36 ± 0.128) with 38.24% and 40% inhibition of inflammation respectively [**Table I and Figure 3**]. The standard drug (piroxicam 20mg/kg) significantly reduced ($***P < 0.001$) the paw volume (1.28 ± 0.088) with 44.52% inhibition of inflammation. Percentage inhibition of acute inflammation was greater in the standard drug piroxicam group (Positive Control) compared to Test groups I&II (ZLT10mg/kg and ZLT20mg/kg), at all-time intervals. Similarly, the percentage inhibition in the Test-II (ZLT20mg/kg) group was greater than that of Test-I (zaltoprofen 10mg/kg) at all-time intervals [**Table II and Figure 4**].

Chronic anti-inflammatory (Arthritic) activity:

Administration of formalin caused an increase in paw thickness in all groups. In the case of negative control, the highest increase in paw thickness was observed on day 3 and slowly reduced, but not restored to its original paw thickness which was on day 1. Table.III and IV depict the mean $\pm$ SD difference in paw volume (LCS) calculated from day 1 to day 10, for each group. Lower the difference in the increase in paw volume (LCS), higher is the anti-inflammatory action. The mean difference in LCS in all the three drug-treated groups was significantly less when compared to Negative Control ($P < 0.001$), though the mean difference in LCS was higher in Test I and II (zaltoprofen 10 and 20 mg/kg) than that in the piroxicam group (Positive Control). The lowest difference in LCS was found in the Positive Control (piroxicam 10mg/kg) group. Formalin-induced paw oedema was reduced significantly ($p < 0.001$) with the administration of Test I and Test II (zaltoprofen 10 mg and 20mg), which was found to be a time-dependent and highest reduction in paw thickness or arthritis was observed on day 7 and (zaltoprofen 10mg/kg) Day 5 (Zaltoprofen 20mg/kg) respectively [**Figure 5**]. Percentage inhibition of chronic inflammation was higher in the piroxicam group (35.60%) when compared to Test-I (zaltoprofen 10mg/kg) (18.90%) and Test-II (zaltoprofen 20mg/kg) (27.76%) at all-time intervals. Similarly, the percentage inhibition in Test-II (zaltoprofen 20mg/kg) group was higher than that of Test-I (zaltoprofen 10mg/kg) at all-time intervals [**Table IV**].

Discussion

The present experimental study has compared acute and chronic anti-inflammatory or arthritic potential of Zaltoprofen, using well-established experimental murine models. The Test drug Zaltoprofen was investigated and compared over piroxicam by using two different doses of Test compound (ZLT 10 and 20 mg/kg vs. PRC10mg/kg) in carrageenan-induced acute inflammation and formalin-induced chronic inflammation or arthritis models, and the results were depicted (Tables 1-3; Figures 1-3).

Carrageenan induced acute inflammation is a standard experimental model for acute inflammation. A major advantage of carrageenan is, single oral doses of drugs at non-toxic levels are effective; and it is similar to the early exudative stage of inflammation in humans and the model is linked with the activation of various inflammatory autacoids like histamine, serotonin, bradykinin, prostaglandins and leukotrienes. After injecting the carrageenan into the hind paw it induces progressive oedema that reaches its maximum within 3 hours [15]. Both the test doses of zaltoprofen showed significant anti-inflammatory activity in comparison to the negative control (NaCl 10ml/kg). However, when compared to a positive control (Piroxicam 10mg/kg) anti-inflammatory activity of test doses (TEST I & II) of zaltoprofen were less than standard piroxicam. Inhibition of carrageenan-induced oedema by zaltoprofen can be attributed to its ability to inhibit the various mediators of inflammation like kinins and prostaglandins.

Formalin-induced chronic inflammation is a model for arthritis and is considered the most suitable experimental animal model which closely resembles arthritis in human beings. It is associated with the proliferative phase of chronic inflammation in human beings and is biphasic, an early neurogenic phase is mediated by substance-P and bradykinin followed by a later tissue mediated response where, histamine, 5-hydroxytryptamine (5-HT), prostaglandins (PGs) and bradykinin are known to be involved [16]. Zaltoprofen has shown a significant inhibition in paw volume in the formalin-induced chronic inflammation or arthritis model. Test-I (Zaltoprofen 10 mg/kg) inhibited 19% of paw oedema, Test-II (zaltoprofen 20mg/kg) inhibited 28% of paw oedema, and standard drug piroxicam decreased 36% paw oedema respectively. Both the test doses showed significant anti-arthritic activity, though it was less than positive control piroxicam 10 mg/kg. Therefore, as this model is more suitable and very commonly used to evaluate anti-inflammatory agents with probable anti-proliferative activity, the inhibitory effect of zaltoprofen on formalin-induced chronic inflammation, indicates its significant anti-proliferative and arthritic activity [17].

Conclusion

In conclusion, zaltoprofen in a dose-dependent manner is an effective agent in attenuating carrageenan and formalin-induced acute and chronic inflammation and arthritis cascade in experimental murine models of inflammation or arthritis. Therefore, it can be explored and used as a potential therapeutic agent for acute and chronic inflammatory clinical conditions in humans, particularly those associated with arthritis.

Declarations

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Conflicts of interest: Nil

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Tables

Animal Group	Before Drug	0 Hours	1 hour	2 hour	3 hour
Control (NS 10ml/kg, PO)	1.11±0.114	1.61±0.074	1.71±0.067	1.94±0.101	2.31±0.348
ZLT10(10 mg/kg, PO)	1.08±0.147	1.58±0.057	1.59±0.048	1.48±0.062	1.43±0.068***
ZLT20(20 mg/kg, PO)	1.10±0.116	1.60±0.193	1.55±0.189*	1.45±0.132***	1.36±0.129***
PRC10(10 mg/kg, PO)	1.00±0.031	1.58±0.092	1.48±0.083**	1.40±0.067***	1.28±0.088***

Table I : Effect of Different Drugs Dosages On Paw Volume In Carrageenan-Induced Paw Oedema in Rats. Values are expressed as mean ± Standard Deviation (n = 6 in each group).

***P < 0.001, **P < 0.01, *P < 0.05 when compared to control.

Abbreviations: NS: Normal saline; ZLT10: Zaltoprofen 10 mg/kg, ZLT20: Zaltoprofen 20 mg/kg, PRC10: Piroxicam 10 mg/kg, PO: Per Os.

Animal Group	Before Drug	0 Hours	%inhibition at 1 hour	%inhibition at 2 hour.	%inhibition at 3 hour.
Control (NS 10 ml/kg PO)	0.00	0.00	0.00	0.00	0.00
ZLT(10 mg/kg PO)	2.69	2.07	7.12	24.10	38.24
ZLT(20 mg/kg PO)	1.35	0.83	9.26	25.21	41.05
PRC(10 mg/kg PO)	10.03	1.86	13.55	27.96	44.52

Table II: Effect of Different Drug Dosages on Percentage Inhibition Of Carrageenan Induced Acute Inflammation (n=6 in each group).

Abbreviations: NS: Normal Saline; **ZLT10:** Zaltoprofen 10 mg/kg, **ZLT20:** Zaltoprofen 20 mg/kg, **PRC10:** Piroxicam 10 mg/kg, **PO:** Per Os.

Animal Group	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Control (NS 10 ml/kg PO)	3.45±0.207	6.78±0.331	7.58±0.440	7.12±0.488	6.18±0.360	5.70±0.276	5.43±0.276	5.15±0.616	4.93±0.484	4.73
ZLT(10 mg/kg PO)	3.38±0.223	6.37±0.378	6.15±0.513	5.93±0.308**	5.62±0.214	5.35±0.459	5.20±0.452	4.92±0.519	4.75±0.362	4.60
ZLT(20 mg/kg PO)	3.30±0.167	4.90±0.576	5.87±0.501	5.42±0.512**	5.15±0.327	4.90±0.424	4.77±0.423	4.62±0.387	4.52±0.387**	4.40
PRC(10 mg/kg PO)	3.05±0.259	4.55±0.622	4.90±0.420	4.58±0.331	4.42±0.382	4.35±0.383**	4.32±0.172	4.15±0.164	4.02±0.402	3.87

Table 3 : Effect of Different Drug Dosages On Formalin Induced Chronic Inflammation in Rats. Values are expressed as Mean ± Standard Deviation (n = 6 in each group).

***P < 0.001, **P < 0.01, *P < 0.05 when compared to control.

Abbreviations: NS: Normal saline; **ZLT10:** Zaltoprofen 10 mg/kg, **ZLT20:** Zaltoprofen 20 mg/kg, **PRC10:** Piroxicam 10 mg/kg, **PO:** Per Os.

Animal Group	Mean difference in LCS (mm)	Percentage Inhibition
Control (NS 10ml/kg)	1.23±0.027	-
ZLT10 (10 mg/kg PO)	1.17±0.063***	18.90
ZLT20 (20 mg/kg PO)	1.05±0.350***	27.76
PRC10 (10 mg/kg PO)	0.48±0.049***	35.60

Table 4: Effect of Different Drugs Doses On The Linear Cross-Section (LCS) Below The Ankle Joint In The Formalin-Induced Chronic Inflammation Or Arthritis In Rats. Values are expressed as Mean ± Standard Deviation (n = 6 in each group). *P < 0.001 when compared to control.**

Abbreviations: NS: Normal saline 10 ml/kg; **ZLT10:** Zaltoprofen 10 mg/kg, **ZLT20:** Zaltoprofen 20 mg/kg, **PRC10:** Piroxicam 10 mg/kg, **PO:** Per Os.

Figures

Figure 1
Mechanism of Action of Zaltoprofen.

Figure 2
Graphical abstract of Study methodology.

Figure 3

Effect of different drugs on Carrageenan induced paw oedema at different time intervals in Rats.

Figure 4

Effect of different drug dosages on percentage inhibition (mean) of Carrageenan-induced acute inflammation in Rats.

Figure 5

Effect of different drugs on Formalin-induced chronic inflammation or arthritis in Rats.