

Comparison of anti-inflammatory efficacy of lercanidipine and Tanacetum parthenium with indomethacin in rats

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ABSTRACT

Background: Inflammation can be classified as either acute or chronic. NSAIDs are the most commonly prescribed drugs worldwide, and mostly have adverse effects. Lercanidipine a CCB of (DHPs) blocks the mediators of inflammation and has additional anti-inflammatory potential. Tanacetum parthenium (Feverfew) extracts have also shown its anti-inflammatory effects in experimental studies. It was decided to study anti-inflammatory effects of Lercanidipine and Tanacetum parthenium which was compared with Indomethacin. The present study was aimed to evaluate and compare the anti-inflammatory effect of lercanidipine and Tanacetum parthenium with Indomethacin in rats.

Methods: The study was conducted in the department of Pharmacology UPUMS, Saifai after getting approval from IAEC. A total of 24 animals divided into 4 groups of six (n=6) animals each group were used, and the anti-inflammatory effects of both drugs were evaluated by Carrageenan-induced Paw Edema Model by digital Plethysmometer in rats, drug administration was with the same frequency.

Results: The result of the present study had shown that lercanidipine produced anti-inflammatory effect compared to Indomethacin, while its efficacy in reducing paw edema was better at 1st hour, 48 and 72 hours while at 2nd hour and 3rd hour Indomethacin had better efficacy. Tanacetum parthenium also decreased paw edema at 2nd, 3rd, 48 and 72 hour while at 1st hour no effect was seen. However, at 72 hours, shown good efficacy compared to lercanidipine and Indomethacin.

Conclusions: Lercanidipine could be a promising anti-inflammatory drug in reducing the inflammation and edema. However, herbal drug (Tanacetum parthenium) has shown anti-inflammatory efficacy when compared with Indomethacin. Both drugs were found safe during our study.

Keywords: Carrageenan, Inflammation, Lercanidipine, Tanacetum parthenium, Plethysmometer

INTRODUCTION

Inflammation is a reaction of vascularised connective tissue to local injury. Inflammation is a fundamentally protective response, the ultimate goal of which is to get rid of both initial cause of cell injury and the consequences of such injury. Without inflammation infections would go unchecked, wounds would never heal and injured organs would become permanent festering sores.¹

Inflammation can also be evoked by a wide variety of noxious agents (e.g., infections, drugs, physical injuries). The ability to mount an inflammatory response is essential for survival in environmental pathogens and injury; in some situations and diseases, the inflammatory response may be exaggerated and sustained without apparent benefit and even with severe adverse consequences.²

Inflammation is normally a protective mechanism, but when inflammation persists for longer duration along with pain leads to pathology then it needs to be treated.

The development of NSAIDs, with reduced potential to cause gastric ulcers, was released and demonstrated that clinically useful NSAIDs inhibit the cyclooxygenase enzymes, which were also present in the gastric mucosa.³

The finding that cyclo-oxygenase present in inflammatory lesions (COX2) was distinct from that found in the stomach (COX1) led to the development of selective COX2 inhibitors, such as celecoxib. These drugs provide relief from many of the symptoms of arthritis and have a reduced potential to cause gastric ulceration.⁴

The drugs available for the treatment of inflammation are:

1. Non-steroidal anti-inflammatory drugs (Selective, Non selective, Preferential COX)
2. Drugs modifying anti-rheumatic drugs
3. Corticosteroids

Drugs opted for the studies were:

Lercanidipine hydrochloride

Lercanidipine is an L-type calcium channel blocker of the dihydropyridine class, that block the entry of calcium into the muscle cells of the heart and the blood vessels. Calcium ions increase the lipoxygenase products by activating 5-lipoxygenase enzyme and eicosanoids synthesis by activating cytosolic phospholipase-A₂. So inhibiting these calcium ions proves to be a potential target for anti-inflammatory drugs.⁵

Currently CCBs enjoy the status of first line anti-hypertensive drugs used singly or in combination, their antihypertensive efficacy is comparable to that of β -blockers. The choice of CCBs in combination therapy is influenced by coexisting disease such as angina, asthma, diabetes and peripheral vascular disease (PVD). These drugs possess some distinct advantages relative to other vasodilator.⁶

Tanacetum parthenium

Feverfew appears to be an inhibitor of prostaglandin synthesis. Its active constituent sesquiterpene lactones, inhibit production of inflammatory prostaglandins in rat and human leukocytes. Inhibition was irreversible. Feverfew extracts were found to inhibit mitogen-induced tritiated thymidine uptake by human peripheral blood mononuclear cells, interleukin-2-induced tritiated thymidine uptake by lymphoblasts, and prostaglandin release by interleukin-1-stimulated synovial cells. Parthenolide blocks tritiated thymidine uptake by mitogen-induced human peripheral blood mononuclear cells.⁷

The leaves of this plant are eaten or used as infusions in conditions like arthritis, migraine and asthma. It has also been claimed to be useful for treating conditions like tinnitus/vertigo, fever, menstrual disorders, difficulty in labour, stomach-ache, toothache and insect bites.^{8,9}

Indomethacin

Indomethacin, a methylated indole is indicated for the treatment of moderate to severe rheumatoid arthritis, osteoarthritis, and acute gouty arthritis; ankylosing spondylitis.¹⁰

Objectives of the study was:

- To evaluate anti-inflammatory effect of Lercanidipine and *Tanacetum parthenium* using Carrageenan induced paw edema model
- To compare anti-inflammatory effects of Lercanidipine and *Tanacetum parthenium* with Indomethacin using Carrageenan induced paw edema
- To find out adverse effects if any, during the study.

METHODS

The present study was conducted on adult rats (150-250g) of either sex in the Department of Pharmacology in UPUMS, Saifai. Healthy Wistar albino rats aged around 3-4 months weighing 150-250gm was obtained from the animal house, UPUMS Saifai, Etawah (U.P), after getting approval by Institutional Animal Ethical Committee (IAEC). Animals were acclimatized to the laboratory conditions for 7 days prior to the study and maintained on normal diet and ad libitum water.

Method of collection of data (including sampling procedure)

A total of 24 animals will be divided into 4 groups of six (n=6) animals each group, was subjected to the following tests.

Study design

The anti-inflammatory effects of Lercanidipine and *Tanacetum parthenium* were evaluated by Carrageenan-induced Paw Edema Model by digital Plethysmometer after giving the drugs in rats. Routes of drug administration were i.p. - For Lercanidipine and *Tanacetum Parthenium*

Inclusion criteria

- Wistar rat of either sex weighing 150-250gm.
- Aged 3-4 months.
- Healthy with normal behaviour activity.

Exclusion criteria

- Wistar rat <150g or >250g and aged <3 months or >4 months.

- Pregnant female rat or those who have delivered.
 - Animals previously used in other experiments
1. Group -I (Control) received normal saline in dose of 0.1ml/kg b.w. i.p once a day for carrageenan-induced paw edema model.
 2. Group -II (Indomethacin) received Indomethacin in dose of 10mg/kg b.w. i.p. once a day for carrageenan-induced paw edema model.
 3. Group- III (Lercanidipine) group received Lercanidipine in dose of 900µg/kg b.w. i.p. once a day for carrageenan-induced paw edema model.
 4. Group -IV (Tanacetum parthenium) group received *Tanacetum parthenium* 20mg/kg b.w. i.p. once a day for carrageenan-induced paw edema model.

Digital plethysmometer

Principal of operation

The measuring cell consists of two vertical interconnected Perspex tube, the larger of which is used to measure displacement. The water level in the smaller tube, which contains the transducer, follows that of the large one and is proportional to the volume dipped in the large tube. A sophisticated electronic circuit, monitored by the compensation electrodes, correct the level electrodes "reading" thus generating a signal proportional to the level only and hence to the dipped volume

Test used for assessing anti- inflammatory effects.

Carrageenan-induced Paw Edema Model

Paw edema was induced in the hind right paw of rats by injecting 0.1ml of freshly prepared 1% solution of carrageenan. The left paw served as control Paw volume up to the ankle joint was measured in drug treated and untreated groups before and 3h after carrageenan injection using digital plethysmometer to record the paw volume at 15, 30, 60, 90, 120, 150, 180 and 210 min after carrageenan challenge. Percent change in paw volume was calculated and expressed as the amount of inflammation.¹¹

The data was compared by using statistical tests such as student's t test and ANOVA test followed by *post hoc* test. Results was expressed as mean±SD. p value was calculated, referring to the appropriate drug. Value of p<0.05 was considered as statistically significant.

Statistical analysis

1. Student's -t test was used to evaluate significance of the drugs, within the individual groups.
2. Different groups were compared by using ANOVA test.¹²

All the drugs and reagents were procured from Sigma Aldrich Pharmaceuticals Pvt. Ltd. for studying anti-inflammatory effect.

RESULTS

At 1st hour lercanidipine and Indomethacin had shown anti-inflammatory effects as evidenced by decrease paw edema with maximum efficacy of lercanidipine compared to Indomethacin (Table 2). *Tanacetum parthenium* has not shown any anti-inflammatory effect.

However between lercanidipine and tanacetum parthenium, lercanidipine was superior as compared to *Tanacetum parthenium* and has decreased paw edema significantly.

At 2nd hour all the three drugs (Lercanidipine, *Tanacetum parthenium* and Indomethacin) had shown anti-inflammatory effect with maximum efficacy of Indomethacin compared to other two test drugs which was statistically significant (Table 3).

However, between lercanidipine and tanacetum parthenium, lercanidipine has decreased paw edema which was statistically significant.

At 3rd hour all the three drugs (Lercanidipine, *Tanacetum parthenium* and Indomethacin) had shown anti-inflammatory effect with maximum efficacy of Indomethacin compared to other two test drugs which was statistically significant (Table 4). However, between lercanidipine and tanacetum parthenium, lercanidipine has decreased paw edema which was statistically significant.

Table 1: Mean paw volume changes in different groups from day 1 at (1st, 2nd, 3rd hr) to 72 hours in Carragenan Induced Paw Edema Model.

	0 hrs	1 st hr	2 nd hr	3 rd hr	48 hr	72hr
	Rt	Rt	Rt	Rt	Rt	Rt
Control	1.29±0.07	1.34±0.16	1.44±0.14	1.49±0.05	1.42±0.10	1.4±0.09
Standard (Indomethacin)	1.20±0.07	1.32±0.01	1.24±0.03	1.22±0.03	1.22±0.06	1.14±0.08
Test I (Lercanidipine)	1.2±0.05	1.27±0.01	1.28±0.03	1.26±0.03	1.21±0.04	1.03±0.06
Test II (Tanacetum Parthenium)	1.28±0.1	1.43±0.01	1.38±0.11	1.39±0.04	1.31±0.04	.95±0.05
P value	0.325	<0.01	<0.01	0.01	0.0026	0.20

Table 2: Mean paw volume after administration of lercanidipine, tanacetum parthenium and indomethacin at 1st hour.

S. No		Mean	SD	P value
1	Control	1.34	0.16	p value <0.01
	Indomethacin	1.32	0.01	
2	Control	1.34	0.16	p value <0.01
	Lercanidipine	1.27	0.01	
3	Control	1.34	0.16	p value <0.01
	Tanacetum Parthenium	1.43	0.01	
4	Standard	1.32	0.01	p value 0.91
	Lercanidipine	1.27	0.01	
5	Standard	1.32	0.01	p value 0.91
	Tanacetum Parthenium	1.43	0.01	
6	Lercanidipine	1.27	0.01	p value 0.91
	Tanacetum Parthenium	1.43	0.01	

Table 3: Mean paw volume after administration of lercanidipine, tanacetum parthenium and indomethacin at 2nd hour.

	Mean	SD	P value
Control	1.44	0.14	<0.01
Indomethacin	1.24	0.03	
Control	1.44	0.14	<0.01
lercanidipine	1.28	0.03	
Control	1.44	0.14	0.40
Tanacetum Parthenium	1.38	0.11	
Indomethacin	1.24	0.03	0.91
lercanidipine	1.28	0.03	
Indomethacin	1.24	0.03	0.004
Tanacetum Parthenium	1.38	0.11	
lercanidipine	1.28	0.03	0.004
Tanacetum Parthenium	1.38	0.11	

Table 4: Mean paw volume after administration of lercanidipine, tanacetum parthenium and indomethacin at 3rd hour.

	Mean	SD	P value
Control	1.49	0.05	0.09
Indomethacin	1.22	0.03	
Control	1.49	0.05	0.09
lercanidipine	1.26	0.03	
Control	1.49	0.05	0.43
Tanacetum Parthenium	1.39	0.04	
Indomethacin	1.22	0.03	0.91
lercanidipine	1.26	0.03	
Indomethacin	1.22	0.03	0.49
Tanacetum Parthenium	1.39	0.04	
lercanidipine	1.26	0.03	0.49

At 48 hour maximum anti-inflammatory effect was shown by lercanidipine followed by *Tanacetum parthenium* and Indomethacin which was statistically significant (Table 5). However, between lercanidipine and tanacetum parthenium, lercanidipine was superior as compared to tanacetum parthenium, and has decreased paw edema significantly.

Table 5: Mean paw volume after administration of lercanidipine, tanacetum parthenium and indomethacin at 48 hour.

	Mean	SD	P value
Control	1.42	0.1	0.09
Indomethacin	1.22	0.06	
Control	1.42	0.1	<0.01
lercanidipine	1.21	0.01	
Control	1.42	0.1	0.001
Tanacetum Parthenium	1.31	0.04	
Indomethacin	1.22	0.06	<0.01
lercanidipine	1.21	0.01	
Indomethacin	1.22	0.06	0.17
Tanacetum Parthenium	1.31	0.04	
lercanidipine	1.21	0.01	0.001
Tanacetum Parthenium	1.31	0.04	

Table 6: Mean paw volume after administration of lercanidipine, tanacetum parthenium and indomethacin at 72 hour.

	Mean	SD	P value
Control	1.4	0.09	0.64
Indomethacin	1.14	0.08	
Control	1.4	0.09	0.17
lercanidipine	1.03	0.06	
Control	1.4	0.09	0.05
Tanacetum Parthenium	0.95	0.05	
Indomethacin	1.14	0.08	0.32
lercanidipine	1.03	0.06	
Indomethacin	1.14	0.08	0.11
Tanacetum Parthenium	0.95	0.05	
lercanidipine	1.03	0.06	0.51
Tanacetum Parthenium	0.95	0.05	

At 72^{hr} surprisingly maximum efficacy was shown by *Tanacetum parthenium* followed by lercanidipine and Indomethacin (Table 6). However, lercanidipine and *Tanacetum parthenium* have shown similar effect which was not significant.

The findings of the present study are summarised in the following statements:

At 1st hour lercanidipine and Indomethacin had shown anti-inflammatory effects as evidenced by decrease paw edema with maximum efficacy of lercanidipine compared to Indomethacin. *Tanacetum parthenium* has not shown any anti-inflammatory effect. However between

lercanidipine and tanacetum parthenium, lercanidipine was superior as compared to tanacetum parthenium and has decreased paw edema significantly.

At 2nd all the three drugs (Lercanidipine, Tanacetum parthenium and Indomethacin) had shown anti-inflammatory effect with maximum efficacy of Indomethacin compared to other two test drugs which was statistically significant. However, between lercanidipine and tanacetum parthenium, lercanidipine has decreased paw edema which was statistically significant.

At 3rd hour all the three drugs (Lercanidipine, Tanacetum parthenium and Indomethacin) had shown anti-inflammatory effect with maximum efficacy of Indomethacin compared to other two test drugs which was statistically significant. However, between lercanidipine and tanacetum parthenium, lercanidipine has decreased paw edema which was statistically significant.

At 48 hour maximum anti-inflammatory effect was shown by lercanidipine followed by Tanacetum parthenium and Indomethacin which was statistically significant. However between lercanidipine and tanacetum parthenium, lercanidipine was superior as compared to tanacetum parthenium, and has decreased paw edema significantly.

At 72hr surprisingly maximum efficacy was shown by Tanacetum parthenium followed by lercanidipine and Indomethacin. However, lercanidipine and tanacetum parthenium have shown similar effect which was not significant.

DISCUSSION

Inflammation is characterized by increased blood flow and vascular permeability along with accumulation of fluid, leukocytes and inflammatory mediators. It is also characterized by the development of specific humoral and cellular immune responses to pathogens which are present at the site of tissue injury.

Inflammation is a common symptom of many diseases including autoimmune diseases like rheumatoid arthritis, SLE, gout, bronchial asthma, osteoarthritis, tenosynovitis, fracture, uveitis, erythema nodosum which are a challenge in medicine to control such type of manifestations, presently lots of NSAIDs available but none of them is ideal in controlling these symptoms and sometimes lifelong treatment is required. Medical fraternity needs an ideal drug for treatment which can be safe and cheaper and controls symptoms of patient.

As per literature search is concerned we found that lercanidipine which act through different mechanism (L-type channel) and a strong anti-inflammatory drug.

Khaksari M et al, performed a study on calcium channel blockers (verapamil and nifedipine) to evaluate their mechanism of action on inflammation in rat paw edema

model.¹³ This study indicated that these CCBs block L-type calcium channel and exert a potent anti-inflammatory action in rat paw. The study was conducted using carrageenan-induced rat paw edema model, two different doses of nifedipine and verapamil (25µg/kg and 400µg/kg i.p.) were used. Edema was assessed by calculating the paw volume changes.

Authors use *Tanacetum parthenium* because it is a herbal drug which is quite safe compared to available NSAIDs. So present study designed for its anti-inflammatory evaluation and we used Carrageenan edema model. Authors have not come across in literature regarding their study till now and safety is an important issue for any drug to be used.

Present study was designed to evaluate the anti-inflammatory effect of lercanidipine a CCB of DHP class. The present study also evaluated the anti-inflammatory effect of *Tanacetum parthenium* which also had been studied by many scientists. Other main objective of present study was to evaluate anti-inflammatory effect of concomitant use of lercanidipine and *Tanacetum parthenium* in rats. As per literature search till date, effects of concomitant use of lercanidipine and *Tanacetum parthenium* were never been studied.

Previous studies were different compared to present study because of limitations of number of groups used in their study and we have taken more groups of animals. They have used large doses and we have used different doses of the drugs administered in the study.

CONCLUSION

The result of the present study had shown that lercanidipine produced anti-inflammatory effect in carrageenan induced paw edema model and its effect was comparable to standard drug Indomethacin while its efficacy in reducing paw edema was better at 1st hour, 48 and 72 hours while at 2nd hour and 3rd hour Indomethacin has better efficacy. These findings were statistically significant.

Tanacetum parthenium had shown mild anti-inflammatory effect compared to Indomethacin and lercanidipine as it has decreased paw edema at 2nd, 3rd, 48 and 72 hour while at 1st hour *Tanacetum parthenium* has not shown any effect and has shown good efficacy at 72 hours, compared to lercanidipine and Indomethacin, this probably may be due to different mechanism of action and its onset may be slow while duration of action may be longer.

This study showed that in carrageenan edema model lercanidipine had shown good anti-inflammatory efficacy which is comparable to Indomethacin, while *Tanacetum parthenium* had shown mild anti-inflammatory compared to Indomethacin and lercanidipine probably due to delayed onset of action.

No adverse effects were observed during the entire course of study. Further studies including clinical use of these drugs are needed to substantiate the above mentioned findings of the present study.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Animal Ethical Committee UPUMS, Saifai Etawah, India

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