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"To Study The Dose Dependent Analgesic Effect Of Lornoxicam With Etoricoxib Using Digital Analgesiometer By Tail Flick Method In Rats"

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Abstract: *Pain is a subjective experience, it occurs only in consciousness, in the mind. Analgesics are the drugs which possess significant pain relieving properties by acting in the CNS or on peripheral pain receptors without significantly affecting consciousness. Among Opioid's and NSAIDs, NSAIDs became mostly used analgesic agents act by inhibition of COX enzyme, but also associated with side effects like stomach upset, nausea, vomiting and heartburn. In the Indian journal of physical medicine and research (IJPMR), NSAID drug Lornoxicam – is a nonselective COX inhibitor which is associated with less gastrointestinal complications but possess effective analgesic activity.* ***Materials and Methods:****In current study, Normal saline as control, Etoricoxib as standard and Lornoxicam as test drug are used. The analgesic activity of selected drugs is assessed by Tail flick method on albino rats with Digital analgesiometer.* ***Result:*** *At doses of 5mg/kg, 10mg/kg and 15mg/kg, Etoricoxib and Lornoxicam after 30mins of interval had shown a mean reaction time in seconds as 14 and 12.3, 16.7 and 16.3, 19.3 and 18.8 respectively.****Conclusion:****Compared to normal saline, standard drug and test drug are showing analgesic activity. Etoricoxib is having more analgesic property when compared to Lornoxicam at low doses but at high doses it is showing analgesic property nearly to Etoricoxib with insignificant variation in mean reaction time.*

Key Words: *Analgesic Effect, Lornoxicam, Etoricoxib, Digital Analgesiometer*.

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I. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is not a disease by itself. It is a warning signal of noxious stimulus [1]. It is the symptom of many conditions like trauma, inflammation, spasm of smooth and skeletal muscles, malignancy etc.[8]. Pain motivates us to withdraw from potentially damaging situations, to protect a damaged body part while it heals, and to avoid those situations in the future [2]. One of the greatest services a doctor can do to his patient is to acquire skill in the management of pain. Success in the treatment depends on correct diagnosis and attention towards the cause by employing specific measures against the cause. When the cause of pain cannot be removed, then drugs are generally used to relieve it [3].

NSAIDs are used to treat integument pain. NSAIDs act by inhibition of COX enzyme. NSAIDS are associated with side effects like stomach upset, nausea, vomiting, heartburn, headache, diarrohea, constipation, drowsiness, and unusual fatigue may occur. Some NSAIDs inhibit both isoforms of COX enzymes that is COX 1 and COX 2. Some NSAIDs inhibit only one isoform of COX enzymes so they are termed as selective COX inhibitors.

I read in the *Indian journal of physical medicine and research* (IJPMR) that a newer NSAID drug Lornoxicam – is a nonselective COX inhibitor which is associated with less gastrointestinal complications but possess effective analgesic activity [4]. This tempted me to compare the dose dependent analgesic effect of Lornoxicam with Etoricoxib (selective COX2 inhibitor).

Etoricoxib exhibits anti-inflammatory, analgesic and antipyretic activities. It is potent, orally active, highly selectivecyclooxygenase-2 (COX-2) inhibitor. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation and fever. Selective inhibition of COX-2 by Etoricoxib decreases these clinical signs and symptoms with decreased Gastro-intestinal toxicity and without effects on platelet function [5].It is indicated in conditions like acute pain and inflammation, chronic musculo-skeletal pain, osteoarthritis, rheumatoid arthritis, acute gouty arthritis, primary dysmenorrhea, ankylosing spondylitis [6] .
Lornoxicam, a congener of tenoxicam, it is a new NSAID belonging to the oxicam class. It has strong analgesic and anti-inflammatory activity compared to other NSAIDs. It acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoforms in the same concentration range i.e. COX-1/ COX-2 = 1. Thus, a perfectly balanced inhibition of COX- 1 and COX-2 is achieved [7].It has no first pass effect [8] Maximum pain relief occurs in 2 hours [4]. It is indicated in conditions likeAcute and Chronic Pain, Anti-Inflammation,Herpetic Stromal Keratitis etc.

II.Materials and Methods:

The animals used for the study are albino rats weighing 200-250mg provided from the central animal house of Dr. PSIMS & RF which is maintained under standard conditions.
Equipment: Digital analgesiometer, Insulin syringes, Measuring jar, Glass beaker, Animal weighing balance, Motor & pestle, Spirit, Cotton, Stop watch.

Drugs: Etoricoxib,Lornoxicam**,** Double distilled water, Normal saline

Dose: Normal saline- 0.2 ml intraperitoneally.
Etoricoxib- According to body weight intraperitoneally
Lornoxicam- According to body weight intraperitoneally

This figure showing the analgesic reaction of Rat with Analgesiometer

I**nstrument Description:** Digital Analgesiometer is the instrument meant for studying the analgesic effect of pain by observing the flicking of tail due to heat. It is provided with an arrangement for holding the tail of the rat, a wire is connected between two terminals through which heat is generated. The instrument is also provided with a metallic rat carrier for proper holding of rat. This also facilitates easy positioning of the tail of rat in the groove provided for holding the tail above the heater wire.

The Tail Flick Method (Rat): The tail flick procedure was originally described by D'amor& smith (1941) for testing analgesics in both rats and mice. Male albino rats are selected for the experiments and weighed with the help of weighing machine. The animals were divided into 3 groups. Each group contains 6 animals. First group is control, second group is standard (Etoricoxib) and third group is test drug (Lornoxicam). For identification

each group was marked with different colors. Control group of animals are marked with black ink, standard group with blue ink and test group with red ink.
Prior to the experiment all animals normal reaction time for heat was tested for at least 5 times and reaction was tabulated. The timer in the analgesiometer will automatically record the tail flick latency. The instrument was operated at 2.5 amps current throughout the experiment.
Insert the rat in the metallic rat holder and take out the tail of the rat from the slit provided in the rat holder. Position the tail of the rat in the groove provided. Insert the mains plug in to the mains socket for powering the analgesiometer. Rotate the set current knob anti-clock wise fully.
Current meter will start indicating current in the meter now set the desired level by observing the color of the wire connected between the two terminals below the tail of the rat. It shall be near to red hot. Observe the flicking of the tail of the rat and note the time taken for flicking of the tail after heat is applied.
A cut off period of 20 seconds is observed to prevent damage to tail. Any animal failing to withdraw its tail within cut off period is rejected from the study. Take at least 3-5 reading for each rat at a gap of 5 min to the normal behavior of the animal. Now, Control group is treated with 0.2 ml normal saline, standard group with Etoricoxib 5 mg/kg 10mg/kg and 15mg/kg, and test group with test drug Lornoxicam 0.133 mg/kg. 0.266 mg/kg. 0.399 mg/kg are treated. Tail flick latency was recorded for 3 groups of animals with time intervals of 5, 15 and 30 mins after administration of drugs.

III.Result& Discussion:

The dose dependent analgesic activity of Lornoxicam was evaluated by digital analgesiometer.Etoricoxib is a selective Cyclooxygenase-2 inhibitor was selected as standard drug whereas Lornoxicam a non-selective Cyclooxygenase inhibitor was selected as test drug.

Total rats are divided into3 groups, 6 rats in each group. First group of rats were considered as controls and treated with 0.2 ml normal saline. Second group were considered as standard and treated with Etoricoxib at doses of 5mg/kg, 10mg/kg,and 15 mg/kg, third group were considered as test drug and treated with Lornoxicamat doses of 0.133mg/kg, 0.266mg/kg, and0.399 mg/kg body weight.

"Unpaired T test" was used to find out the statistical difference in between the control, standard and test group of animals.

Results shown:

1) In control group with 0.2 ml of normal saline there was no significant change in mean reaction time at 0 minutes, 5 minutes, 15 minutes and 30 minutes.
2) At low doses: Etoricoxib 5mg/kg, Lornoxicam 0.133mg/kg (Table-1)

Table-1: Comparison of mean responses at low doses of control with standard and test drug

S. No.	Drugs	Dose	0min	5 min	15 min	30 min
1.	NormalSaline	0.2 ml	9.8	9.66	10.16	11.33
2.	Etoricoxib	5 mg/kg BW	10.5	11.0	12.3	14.0
3.	Lornoxicam	0.133 mg/kg BW	9.7	9.67	11	12.83

- Before administration of standard drug Etoricoxib in standard group mean reaction time was 10.5 with SE of 0.496, After administration of standard drug Etoricoxib in group at time intervals of 5, 15, 30 minutes, the mean reaction time shown were 11.0, 12.3& 14.0 with SE of 0.496, 0.422& 0.308 respectively. Where as in test group before administration of Lornoxicam the mean reaction time was 9.1 with SE of 0.616. After administration Lornoxicam drug in same group at time intervals of 5, 15, 30 minutes mean reaction time shown were 9.67, 11.0 & 12.3 with SE of 0.422, 0.334 & 0.422 respectively

3). At medium doses: Etoricoxib 10mg, Lornoxicam 0.266mg/kg (Table-2)

Table-2: Comparison of mean responses at medium doses of control with standard and test drug

S. No.	Drugs	Dose	0 min	5 min	15 min	30 min
1	Normal Saline	0.2 ml	9.8	9.6	10.6	11.3
2	Etoricoxib	10 mg/kg BW	10.4	11.4	13.6	16.8
3	Lornoxicam	0.266 mg/kg BW	10.6	11.3	13.5	16.3

- Before administration of Etoricoxib in a group showed mean reaction time was 10.4 with SE of 0.496, After administration of drug Etoricoxib in same group at time intervals of 5, 15, 30 minutes the mean reaction time were 11.4, 13.6 & 16.7 with SE of 0.426, 0.334 & 0.426 respectively. Before administration of Lornoxicam in test group the mean reaction time was 10.6 with SE of 0.912. After administration of

Lornoxicam in same group at time intervals of 5, 15, 30 minutes the mean reaction time were 11.3, 13.5 & 16.3 with SE of 0.885, 0.766 & 0.544 respectively.
4).At high doses: Etoricoxib 15mg/kg &Lornoxicam 0.399mg/kg (Table-3)

Table-3: Comparison of mean responses at high doses of control with standard and test drug

S.No.	Drugs	Dose	0 min	5 min	15 min	30 min
1	Normal Saline	0.2 ml	9.8	9.66	10.16	11.33
2	Etoricoxib	15 mg/kg BW	10.3	11.3	14.5	19.3
3	Lornoxicam	0.399 mg/kg BW	10.2	11.2	14.3	18.8

- Before administration of Etoricoxib in a group, showed mean reaction time was 10.3 with SE of 0.564, After administration of drug Etoricoxib in same group at time intervals of 5, 15, 30 minutes the mean reaction time were 11.3, 14.5 & 19.3 with SE of 0.751, 0.602 & 0.334 respectively. Before administration of Lornoxicam in test group showed mean reaction time was 10.2, with SE of 0.559. After administration of Lornoxicam in same group at time intervals of 5, 15, 30 minutes showed mean reaction time was 11.4, 14.3 & 18.8 with SE of 0.308, 0.846 & 0.717 respectively.

5). In comparison between standard and test drug, at different doses (low, medium and high) it was found that mean reaction time was increased gradually after 5 minutes, 15 minutes and 30 minutes of drug administration. Better results observed with standard drug than with Lornoxicam. (Table 14, 15 and 16)

Table-5(a):Comparison of mean responses ofstandard with test drug.

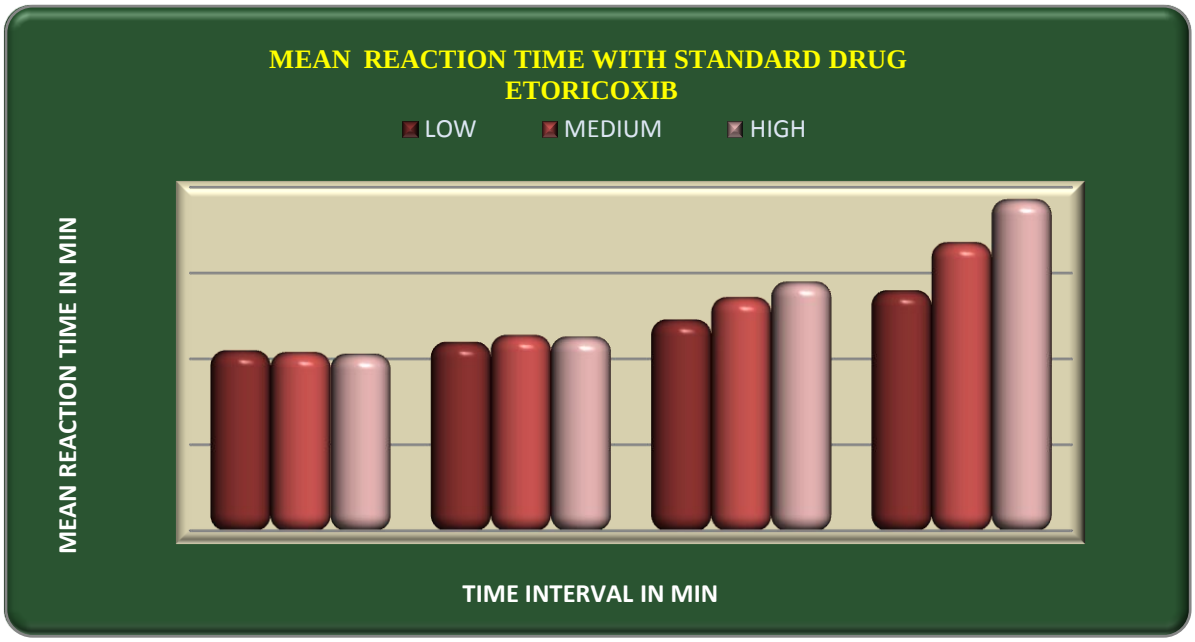
S.NO	Drugs	Dose	0 min	5 min	15 min	30 min
1.	Etoricoxib	5 mg/kg BW	11.3	10.6	12.3	14.8
		10 mg/kg BW	10.9	11.5	14.3	17.5
		15 mg/kg BW	10.5	10.8	15.2	19.3
2.	Lornoxicam	0.133 mg/kg BW	9.7	12.7	13.7	15.3
		0.266 mg/kg BW	10.6	12.5	14.5	16.8
		0.399 mg/kg BW	10.3	12.2	14.3	18.3

Table 5(b):

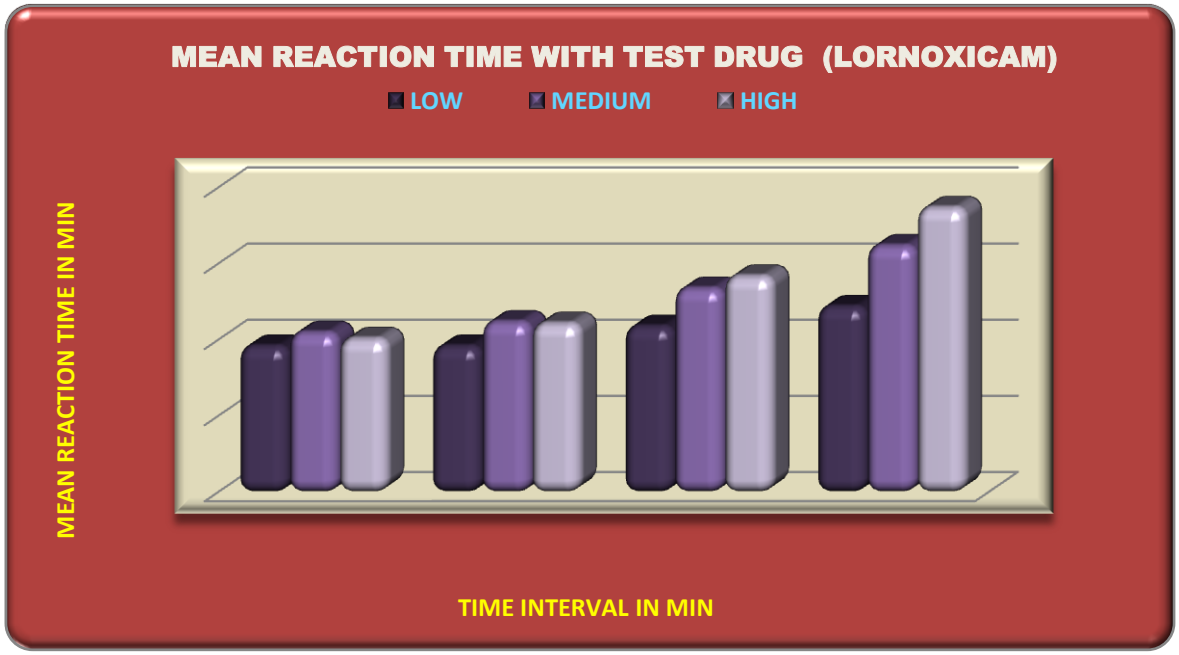
Analysis	Etoricoxib (5 mg/kg) Vs Lornoxicam (0.133 mg/kg)				Etoricoxib (5 mg/kg) Vs Lornoxicam (0.266 mg/kg)				Etoricoxib (5 mg/kg) Vs Lornoxicam (0.399 mg/kg)			
	0 min	5 min	15 min	30 min	0 min	5 min	15 min	30 min	0 min	5 min	15 min	30 min
T- Value	0.053	0.01	0.075	0.001	0.158	0.50	0.50	0.206	0.374	0.147	0.367	0.262
P- value	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant	Not Signi ficant

6) At medium doses test drug also possess better analgesic activity than at its low doses, but at higher doses test drug shows still better analgesic activity as like as standard drug.

GRAPH-1: Comparison of Mean Reaction Time Of Standard Drug At 0, 5, 15 & 30min.



GRAPH-2: Comparison of Mean Reaction Time of Test Drug at 0, 5, 15 & 30min.



IV. Conclusion

This study was carried out to evaluate the dose dependent analgesic activity of Lornoxicamof on rats by using digital analgesiometer. Male albino rats (200gms) were selected for the study divided into control, standard, and test groups, six rats in each group.

First group of rats were considered as controls and treated with 0.2 ml normal saline. Second group were considered as standard and treated withEtoricoxib, and third group were considered as test drug and treated with Lornoxicam.Analgesic property was assessed by using three different doses of each drug on digital analgesiometer. Tail flick of time was considered as reaction time.

At different times with normal saline there was no change in mean reaction time. That means normal saline does not show any analgesic property. Compared to normal saline, standard drugs and test drug shows analgesic activity. But Etoricoxib is having more analgesic property when compared to Lornoxicam.In

conclusion,Lornoxicam a novel Non-steroidal anti-inflammatory drug having dose dependent analgesic property at medium and high doses.

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