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# Comparison of Analgesic Activity of Venlafaxine with Etoricoxib, Using Digital Analgesiometer.

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**ABSTRACT**

Non-steroidal antiinflammatory drugs (NSAIDs) make up one of the largest groups of pharmaceutical agents used worldwide. In the past, NSAIDs are used by 20% or more of the population. The gastro-sparing agents known as "coxibs" became widely prescribed drugs (nearly 80 million people around the globe take these drugs) for pain and skeletal-muscular inflammatory disorders. . Literature showing that, newer antidepressants are having good analgesic activity. But there is no experimental evidence. This tempted me to select Venlafaxine (a newer antidepressant) for evaluation of analgesic activity. For evaluation of analgesic activity of Venlafaxine, I selected Etoricoxib as a standard drug. For analysis of analgesic activity Hot-plate method & Tail flick method was used.Analysis was done at 0,5,15 & 30 minutes. In comparison between standard and test drug, it was found mean reaction time was increased gradually after 5 minutes, 15 minutes and 30 minutes of drug administration. Better results observed with the Etoricoxib than with Venlafaxaine.

**Keywords:-**NSAIDs, coxibs, Hot-plate/Tail flick.

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## INTRODUCTION

Non-steroidal antiinflammatory drugs (NSAIDs) make up one of the largest groups of pharmaceutical agents used worldwide. In the past, NSAIDs are used by 20% or more of the population [1]. NSAIDs are also one of the most common causes of adverse drug reactions (ADRs) reported to drug regulatory agencies as well as in many clinical and epidemiological studies. The most common ADRs are those pertaining to gastrointestinal (GI) system, notably dyspepsia and bleeding. Clinical [2] and experimental [3] data as well as reviews [4] suggest that use of selective COX-2 inhibitors is associated with increase in systolic blood pressure and cardiovascular morbidity and mortality due to myocardial infarction. The risk of GI complications varies widely among individual NSAIDs and so does the cost. Since there are no important differences among these drugs with regard to efficacy, the choice of first line treatment should be based on their relative toxicity.

Cyclooxygenase enzymes (COXs) catalyze the metabolism of arachidonic acid into prostaglandins. This is a rate-limiting step in the formation of prostaglandins (PGs). Sir John Vane (1971) for the first time reported that aspirin and other aspirin like drugs show their biological effects by inhibiting the COX enzymes thereby the prostaglandin synthesis [5]. Subsequently, wide exploration of arachidonic acid - prostaglandin pathways led to the discovery of two isoforms of the COX enzyme, namely, COX-1 and COX-2. This was a landmark discovery in the pharmacotherapy of pain and inflammation as it helped to delineate the side effects of NSAIDs from their therapeutic usefulness [6]. Also, this led to the designation of COX enzymes as constitutive (housekeeping, COX-1) and inducible (inflammation, COX-2) isoenzymes [7]. Further, a new generation of COX-2 inhibitors were developed for selective action. The gastro-sparing agents known as "coxibs" became widely prescribed drugs (nearly 80 million people around the globe take these drugs) for pain and skeletal-muscular inflammatory disorders. Rofecoxib and celecoxib were the first coxibs approved by the USFDA as a new generation of NSAIDs with reduced gastrointestinal side effects of NSAIDs. These agents acted by sparing the COX-1 enzyme in the gastric epithelium. The second generation COX-2 inhibitors, valdecoxib, etoricoxib and lumiracoxib, supposed to be highly selective inhibitors of the enzyme followed soon. A number of clinical trials have demonstrated the supremacy of coxibs over the classical NSAIDs in gastrointestinal tolerability [8,9]. The COX-2 inhibitors became blockbusters and were soon nicknamed "The new super aspirins" because they appeared to deliver a double whammy, knocking out both inflammation and pain without gut-wrenching side effects. Due to gastro-sparing properties, these drugs have been aggressively marketed throughout the world. Celecoxib is approved for rheumatoid arthritis, osteoarthritis and the reduction of the number and size of precancerous polyps in patients with Familial adenomatous polyposis (FAP). Rofecoxib is approved for osteoarthritis and acute pain of primary dysmenorrhea. In recent years as we understood more about their clinical utility, their COX-2 selectivity has been a cause for concern for their cardiovascular safety [10,11]. Since they do not inhibit the COX-1 enzyme, which plays a key role in thrombosis and vasoconstriction they do not possess the antithrombotic property of aspirin [12]. The recent withdrawal of rofecoxib by the innovator has questioned the safety vs. clinical efficacy of this class of NSAIDs. This article briefly reviews

the developments in COX-theory and the clinical efficacy and safety of coxibs to highlight their cardiovascular concerns.

A doctor has been provided with numerous old drugs like opium, morphine and synthetic drugs like pethidine, methadone, pentazocine, codeine and aspirin. But non opioids like non steroidal anti inflammatory drugs are associated with so many adverse drug reactions like gastric ulceration, hypersensitivity with idiosyncratic, allergy, respiratory depression, blurring of vision, tolerance and dependence. So that, necessity arises for evaluation of newer agents having analgesic property. Literature showing that, newer antidepressants are having good analgesic activity. But there is no experimental evidence. This tempted me to select Venlafaxine (a newer antidepressant) for evaluation of analgesic activity. For evaluation of analgesic activity of Venlafaxine, I selected Etoricoxib as a standard drug.

## MATERIALS AND METHODS

This study was approved by Institutional Animal Ethics committee (IAEC).

### The Tail Flick Method (Rats)

- 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. Animals are weighed with the help of weighing machine. The animals weighing 250 gms on average are selected for the experiment. The animals were divided into 3 groups. First group is control, second group is standard and third group is test. 6 animals were selected in each group.
- For identification each group was marked with different colours. Darken a portion of the tail, using ink, at approximately 3 cm from the tip of the tail. Control group of animals are marked with black ink, standard group of animals are marked with blue ink and test group of animals are marked with red ink.
- Prior to the experiment all animals normal reaction time for the heat on analgesiometer was tested for at least 5 times and reaction was tabulated.
- Next, control group of animals was treated with 0.2 ml normal saline, standard group of animals was treated with Etoricoxib 10 mg/kg and test group of animals was treated with Venlafaxine 10 mg/kg.
- The timer in the analgesiometer will automatically record the tail flick latency. The instrument was operated at 2.5 amps current throughout the experiment
- The tail flick latency was recorded for 3 groups of animals after 5 minutes, 15 minutes, and 30 minutes after administration of drugs. Imposing a cutoff time at each test time period. The results were tabulated.

### Dose

Normal saline- 0.2 ml intraperitoneally
Etoricoxib- 10 mg/kg body weight intraperitoneally

Venlafaxine- 10 mg/kg body weight intraperitoneally
Time: 5, 15 and 30 minutes.

**Hot Plate Method (Rats)**

- The hot plate technique originally devised by Woolfe and Macdonald (1944) uses rodents such as mice and rats. Common used hot plates are based on the apparatus described by Eddy. And Leimbach (1953)
- Male albino rats are selected for the experiments. Animals are weighed with the help of weighing machine. The animals weighing 250 gms on average are selected for the experiment. The animals were divided into 3 groups. First group is control, second group is standard and third group is test. 6 animals were selected in each group.
- For identification each group was marked with different colours. Darken a portion of the tail, using ink, at approximately 3 cm from the tip of the tail. Control group of animals are marked with black ink, standard group of animals are marked with blue ink and test group of animals are marked with red ink.
- Control group of animals was treated with 0.2 ml normal saline, standard group of animals was treated with Etoricoxib 10 mg/kg and test group of animals was treated with Venlafaxine 10 mg/kg.
- 30 min after injections place the animals gently on the hot plate which has already been set at the desired temperature (55oc) and immediately start the stop watch to record the response of licking and jumping latency in seconds note that licking (front / hind paws) response usually will be followed by jumping response remove the animal from the hot plate soon after they have exhibited jumping.

**Dose:-**

Normal saline- 0.2 ml intraperitoneally
Etoricoxib- 10 mg/kg body weight intraperitoneally
Venlafaxine- 10 mg/kg body weight intraperitoneally
Time: 5, 15 and 30 minutes.

## RESULTS

The analgesic activity of venlafaxine was evaluated by digital analgesiometer.

Etoricoxib was selected as standard drug where as venlafaxine was selected as test drug.

Etoricoxib is a selective COX-2 inhibitor (cyclooxygenase-2), where as venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI), inhibits reuptake of NA & 5-HT in the descending pathways of pain.

Total rats are divided into 3 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 standard and treated with etoricoxib 10mg/kg, third group were test and treated with venlafaxine10mg/kg.

Tail flick time was considered as reaction time. Normal reaction time was noted for 5 times in each animal before stating the experiment. Average of 5 readings taken as mean reaction time at 0 minutes. After recording of normal reaction time normal saline was administered (intra peritoneally) to control group, etoricoxib was administered (intra peritoneally) to test group. Reaction time after the drug given was recorded at 5 minutes, 15 minutes and 30 minutes. All recordings were tabulated separately.

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

**Result shows**

- 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. (Table-4)
- Before the experiment in standard group showed mean reaction time was 10.13 with SE of 0.329. Whereas in the group showed mean reaction time was 10.062 with SE of 0.325. (Table-4)
- After 5 minutes of drug administration, in standard group with etoricoxib 10 mg/kg body weight showed mean reaction time was 15.83 with SE of 0.833.Whereas in test group with venlafaxine 10 mg/kg body weight showed mean reaction time was 12.83 with SE of 0.477. (Table-5)
- After 15 minutes of drug administration, in standard group with etoricoxib 10 mg/kg body weight showed mean reaction time was 17.83 with SE of 1.013. Whereas in test group with venlafaxine 10 mg/kg body weight showed mean reaction time was 14.33 with SE of 0.557. (Table-6)
- After 30 minutes of drug administration, in standard group with etoricoxib 10 mg/kg body weight showed mean reaction time was 18.66 with SE of 0.954. Whereas in test group with venlafaxine 10 mg/kg body weight showed mean reaction time was 14.5 with SE of 0.670. (Table-7)
- In comparison between standard and test drug, it was found mean reaction time was increased gradually after 5 minutes, 15 minutes and 30 minutes of drug administration. Better results observed with the Etoricoxib than with Venlafaxaine.

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**Table 1:** Treatment with normal saline, Control: 0.2 ml of normal saline

| Sl.No | Normal reaction time (Sec) | | | | | Reaction time after drug given (in Sec) | | |
|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | After 5min | After 15 min | After 30 min |
| 1. | 11 | 10 | 11 | 10 | 10 | 10 | 11 | 10 |
| 2. | 10 | 11 | 9 | 10 | 11 | 9 | 11 | 10 |
| 3. | 10 | 11 | 10 | 11 | 10 | 10 | 9 | 10 |
| 4. | 10 | 11 | 10 | 9 | 10 | 9 | 10 | 11 |
| 5. | 10 | 9 | 11 | 9 | 10 | 10 | 11 | 10 |
| 6. | 11 | 10 | 11 | 10 | 11 | 11 | 10 | 9 |
| Mean | 10.33 | 10.33 | 10.33 | 9.83 | 10.33 | 9.83 | 10.33 | 10 |
| S.D. | 0.516 | 0.816 | 0.816 | 0.752 | 0.516 | 0.752 | 0.816 | 0.632 |
| S.E. | 0.210 | 0.331 | 0.331 | 0.306 | 0.210 | 0.306 | 0.331 | 0.257 |

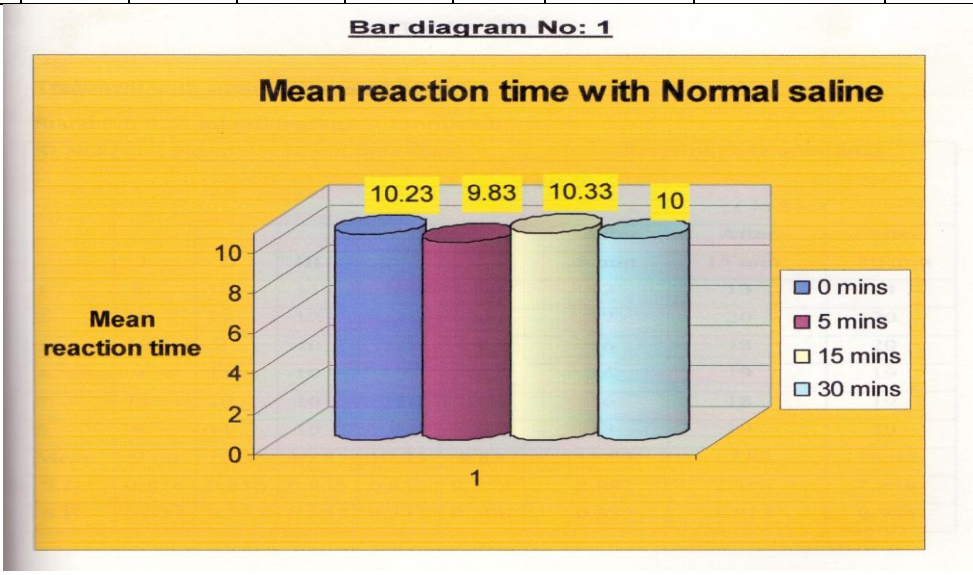


**Table 2: Comparison of mean responses at effective doses of drugs at 5 minutes by analgesiometer.**

| Name of the drug | Dose | Mean reaction time | Std.Dev | Std.Error |
|---|---|---|---|---|
| Normal saline | 0.2 ml | 9.83 | 0.752 | 0.306 |
| Etoricoxib | 10 mg/kg | 15.83 | 2.041 | 0.833 |
| Venlafaxine | 10 mg/kg | 12.83 | 1.169 | 0.477 |

**Analysis**

| | Normal saline Vs Etoricoxib | Normal saline Vs Venlafaxine | Etoricoxib Vs Venlafaxine |
|---|---|---|---|
| t value- | 4.66 | 3.38 | 3.23 |
| P value- | <0.001 (Statistically significant) | <0.05 (Statistically significant) | <0.05 (Statistically significant) |

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**Bar diagram No: 2**

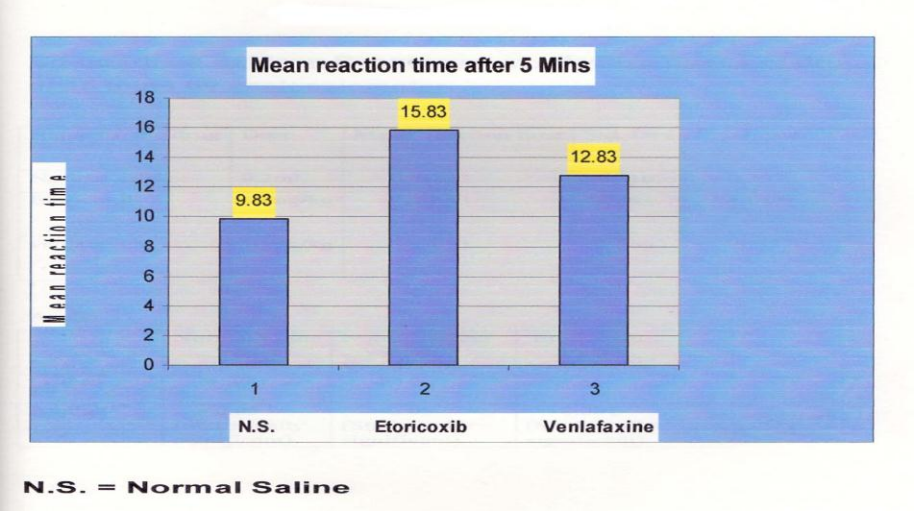


**Table 3: Comparison of mean responses at effective doses of drugs at 15 minutes by analgesiometer.**

| Name of the drug | Dose | Mean reaction time | Std.Dev | Std.Error |
|---|---|---|---|---|
| Normal saline | 0.2 ml | 10.33 | 0.816 | 0.331 |
| Etoricoxib | 10 mg/kg | 17.83 | 2.483 | 1.013 |
| Venlafaxine | 10 mg/kg | 14.33 | 1.366 | 0.557 |

**Analysis**

| | Normal saline Vs Etoricoxib | Normal saline Vs Venlafaxine | Etoricoxib Vs Venlafaxine |
|---|---|---|---|
| t value- | 4.59 | 4.14 | 4.66 |
| P value- | <0.05 (Statistically significant) | <0.05 (Statistically significant) | <0.001 (Statistically significant) |

**Bar diagram No: 3**

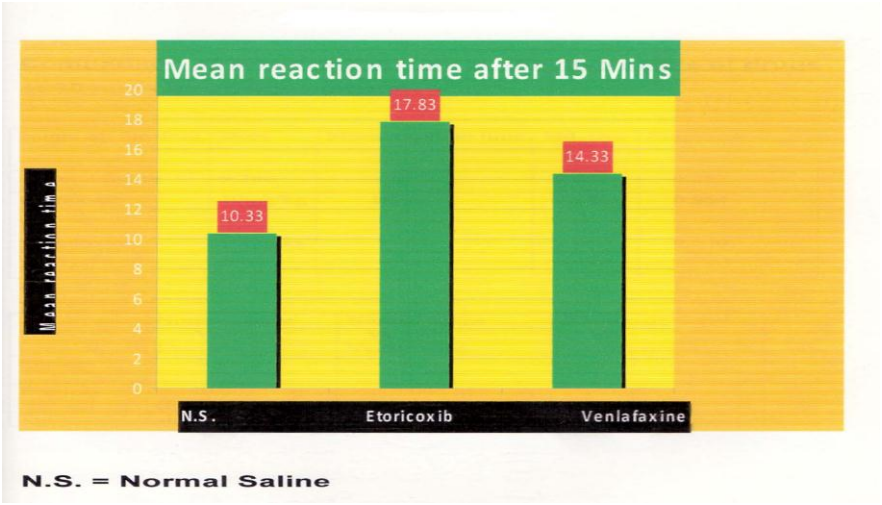

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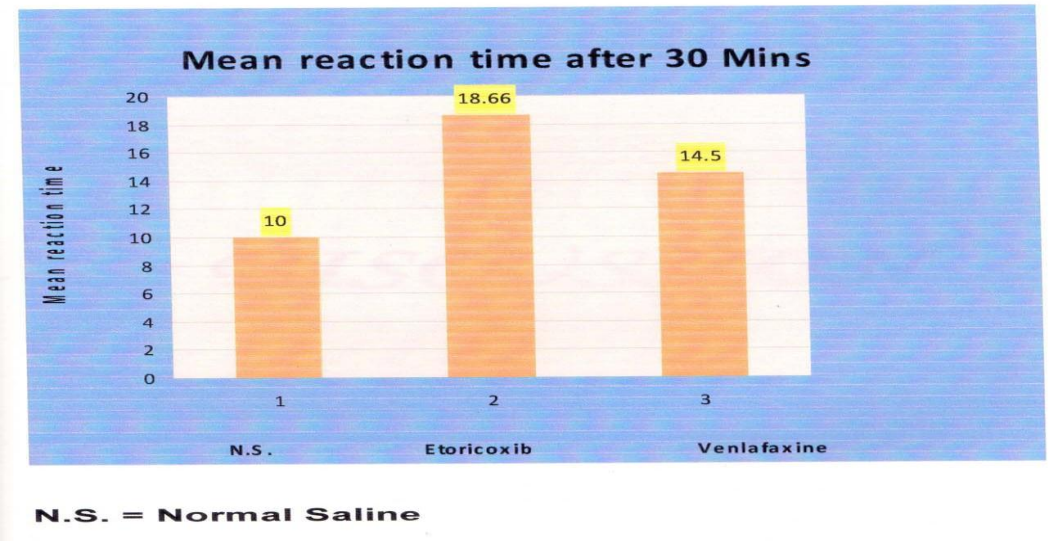
**Table 4: Comparison of mean responses at effective doses of drugs at 30 minutes by analgesiometer**

| Name of the drug | Dose | Mean reaction time | Std.Dev | Std.Error |
|---|---|---|---|---|
| Normal saline | 0.2 ml | 10 | 0.632 | 0.257 |
| Etoricoxib | 10 mg/kg | 18.66 | 2.338 | 0.954 |
| Venlafaxine | 10 mg/kg | 14.5 | 1.643 | 0.670 |

**Analysis**

| | Normal saline Vs Etoricoxib | Normal saline Vs Venlafaxine | Etoricoxib Vs Venlafaxine |
|---|---|---|---|
| t value- | 5.40 | 5.69 | 3.47 |
| P value- | <0.005 (Statistically significant) | <0.005 (Statistically significant) | <0.05 (Statistically significant) |

**Bar diagram No: 4**




## DISCUSSION

Antidepressants, as a class, include diverse structures and represent several phases of development (e.g., tricyclic, tetracyclic and heterocyclic antidepressants, selective serotonin reuptake inhibitors, selective noradrenaline reuptake inhibitors) [13]. The earliest focus, with regard to mechanism of action, was the ability of antidepressants to inhibit biogenic amine reuptake; interest subsequently developed in altered biogenic amine receptor sensitivity after the chronic alteration of biogenic amine levels in the synapse [14]. It has, however, become increasingly apparent that this class of drugs exhibits diverse pharmacological properties, with individual agents within a class exhibiting such effects to variable degrees, and this may account for differing specific pharmacological profiles between agents. Pain is a complex neurobiological phenomenon, with a diversity of neurochemical factors contributing to both peripheral and central pain-signalling mechanisms. Accordingly, a range of antidepressant

actions may contribute to the mechanisms by which pain suppression occurs. The contribution of these mechanisms to central and peripheral analgesia was compared with a standard COX-II inhibitor Etoricoxib in this study.

Most of the published guidelines on neuropathic pain still recommend the TCAs as first-line drugs. Some have also more recently elevated the newer SNRIs to this same level [15-17].

A recently published review of randomized control trials of venlafaxine, duloxetine, and milnacipran versus the TCAs provides some guidance in this area. Watson and colleagues[18] found multiple RCTs that established the analgesic effects of venlafaxine and duloxetine in patients with diabetic neuropathic pain, postherpetic neuralgia, and fibromyalgia, and for prophylaxis of migraine and tension-type headache. Duloxetine was found to be beneficial for osteoarthritic pain and low back pain. The studies on milnacipran are essentially limited to those focusing on fibromyalgia.

Unfortunately, there are few studies that compare the newer SNRIs with one another or with the TCAs. Based on those that are available, Watson et al [18] conclude that TCAs are at least as analgesic as venlafaxine, duloxetine, or milnacipran, and that overall TCAs may actually be more efficacious than the newer drugs.

In our study, venlafaxine showed antinociceptive effect at 10 mg/kg**.** Various other studies, viz. Lang et al., [19] also suggested the antinociceptive effect of venlafaxine in mitigating thermal hyperalgesia in animals. Songer and Schulte [20] showed the analgesic effect of venlafaxine in radicular back pain associated with depression; also, Bradley et al.[21] showed its effect in migraine, chronic back pain, and chronic regional pain syndrome (CRPS), and Dwight et al.[22] in fibromyalgia with axis I psychiatric disorders.

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