

## To compare the analgesic activity of Diacerein, Etoricoxib and Meloxicam in rats by using analgesiometer

<sup>1</sup>Dr.Neeraja.K, <sup>2</sup>S.K.D.Swathi.Remella, <sup>3</sup>Hanumanth N

<sup>1</sup> (Professor, Dept. of Pharmacology/NRI Medical College/ India)

<sup>2</sup> (Tutor, Dept. of Pharmacology/NRI Medical College/ India)

<sup>3</sup> (Statistician, Dept. of Community Medicine, Dr PSIMS & RF, India)

### Abstract:

**Introduction:** Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is not a disease by itself in fact it is a warning signal of noxious stimulus. Pain is a subjective experience, it occurs only in consciousness, in the mind. Pain can be experienced in response to both external perceived events and can sometimes follow from nociception. Analgesics are the drugs which possess significant pain relieving properties by acting in the CNS or on peripheral pain receptors without significantly affecting consciousness.. The main aim of this study is to compare analgesic effect of Diacerein with standard drugs like Meloxicam (preferential COX2 inhibitor) and Etoricoxib (selective COX2 inhibitor).

**Objectives:** To study the analgesic effect of Diacerein. 2.To compare the analgesic effect of Diacerein, Meloxicam and Etoricoxib in albino rats, using digital analgesiometer.

**Methodology:** A Randomized controlled trail was conducted in the Dept. of Pharmacology, Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance. Total rats were randomly divided into 4 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 test drug and treated with Diacerein at doses of 1.4mg/kg, 2.8mg/kg, and 4.2 mg/kg body weight. Third group were considered as standard 1 and treated with Etoricoxib at doses of 5mg/kg, 10mg/kg and 15 mg/kg. , Fourth group were considered as standard 2 and treated with Meloxicam at doses of 0.214mg/kg, 0.428mg/kg, and 0.642 mg/kg.

**Conclusion:** Diacerein an Interleukin-1 inhibitor drug is having analgesic property but Meloxicam and Etoricoxib are having more analgesic property when compared to Diacerein. However the above preclinical experiments only give us an idea about the analgesic effect of Diacerein but large scale clinical trials are necessary for final assessment.

### I. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is not a disease by itself in fact it is a warning signal of noxious stimulus. Pain is a subjective experience, it occurs only in consciousness, in the mind. Pain can be experienced in response to both external perceived events and can sometimes follow from nociception. 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<sup>[1]</sup>.

Pain is believed to be the earliest sign of morbidity by which a person judges the existence of disease in him that makes the person to consult the doctor. When the cause of pain cannot be removed, then drugs are generally used to relieve it<sup>[2]</sup>. Analgesics are the drugs which possess significant pain relieving properties by acting in the CNS or on peripheral pain receptors without significantly affecting consciousness. Analgesic drugs are divided into two groups. They are 1. Narcotic/ Opioid analgesics. 2. Non narcotic analgesics/Non steroidal anti inflammatory drugs (NSAIDs). Opioid analgesics are mainly used to treat deep seated visceral pain.NSAIDs are used to treat integument pain. NSAIDs act by inhibition of COX enzyme. 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.e; either COX-1 or COX-2. Selective COX-2 inhibitors are now a day's widely using for pain relief. These are associated with less side effects compared to non selective COX inhibitors.

**Diapered in:** Diacerein is an Disease modifying antiarthritic drug. Diacerein has anti-inflammatory effect and has small effect in improving pain<sup>[3]</sup>. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) diacerein inhibits IL-1 instead of acting on the cyclooxygenase (COX) enzymes. **Mechanism of Action<sup>[4]</sup>:** Diacerein is a Disease modifying antiarthritic drug. Diacerein is an interleukin-1 inhibitor. It works by inhibiting interleukin-1. Interleukin-1 plays an important role in inflammation and pain. Diacerein also inhibits the Interleukin-1 produced by synovial cells and chondrocytes which causes cartilage destruction.

**MELOXICAM:** Meloxicam is a non steroidal anti-inflammatory drug with analgesic and antipyretic effect. Meloxicam is a derivative of oxicam and falls in the enolic acid group of NSAIDs. It is a preferential cyclooxygenase-2 (cox-2) inhibitor. **Mechanism of Action:** Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) derived from enolic acid, exhibiting selectivity for cyclooxygenase-2 (COX-2) over cyclooxygenase-1(COX-1) [5]. Its effects are due to the inhibitory actions on cyclo-oxygenases, which are involved in the synthesis of prostaglandins. Prostaglandins have an important role in the production of pain, inflammation and fever. In therapeutic doses it does not have any effect in platelet aggregation [6].

**Etoricoxib:** Etoricoxib exhibits anti-inflammatory, analgesic and antipyretic activities. Etoricoxib is a potent, orally active, highly selective cyclooxygenase-2 (COX-2) inhibitor [7]. Two isoforms of cyclooxygenase (COX) have been identified: COX-1 and COX-2. COX-1 is responsible for prostaglandin mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and platelet inhibition. 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 [8].

## II. Materials & Methods

A Randomized controlled trial was conducted in the Dept. of Pharmacology, Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation (Dr.PSIMS), Chinoutapalli, Krishna District, Andhra Pradesh with the institutional ethical committee clearance. Total rats were randomly divided into 4 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 test drug and treated with Diacerein at doses of 1.4mg/kg, 2.8mg/kg, and 4.2 mg/kg body weight. Third group were considered as standard 1 and treated with Etoricoxib at doses of 5mg/kg, 10mg/kg and 15 mg/kg. , Fourth group were considered as standard 2 and treated with Meloxicam at doses of 0.214mg/kg, 0.428mg/kg, and 0.642 mg/kg.

Tail flick time was considered as reaction time. Normal reaction time was noted for 5 times in each animal before starting the experiment. Average of 5 readings taken as mean reaction time at 0 mins. After recording of normal reaction time normal saline was administered (intra peritoneally) to control group, Diacerein was administered (intra peritoneally) to test group, Etoricoxib was administered (intra peritoneally) to standard 1 group, Meloxicam was administered (intra peritoneally) to standard 2 group and. Reaction time after the drug given was recorded at 5 minutes, 15 minutes and 30 minutes. All recordings were tabulated separately.

### Materials

**Equipments:** Digital analgesiometer, Insulin syringes, Measuring jar, Glass beaker, Animal weighing balance, Motor & pestle, Spirit, Cotton, Stop watch.

**Chemicals and solutions:** Diacerein, Etoricoxib, Meloxicam, Double distilled water, Normal saline, Dimethyl sulfoxide

**Animals:** Male Wistar Albino rats weighing about 200-250gms.

**Digital Analgesiometer** [9] **Instrument 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 nichrome 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. Analgesiometer operates on 220/230V, 50HZ.

**The Tail Flick Method** [10] **(Rat):** The tail flick procedure was originally described by D'amor & smith (1941) for testing analgesics in both rats and mice. Male Wistar Albino rats are selected for the experiments. Animals are weighed with the help of weighing machine. The animals weighing 250gms on average are selected for the experiment. The animals are divided into two groups. First group is control, second group is Test (Boswellia Serrata). Each group contains 6 animals. For identification each group is marked with different colours. A portion of the tail is darkened using ink, at approximately 3 cm from the tip of the tail. Control group of animals are marked with black ink and test group of animals are marked with red ink respectively. Prior to the experiment all animals normal reaction time for heat on analgesiometer is tested for at least 5 times and reaction is tabulated. The timer in the analgesiometer will automatically record the tail flick latency. The instrument is operated at 2.5 amps current throughout the experiment.

Data was collected, compiled and analysed using SPSS-V19. Statistical tools applied were means, SD, SE, Kruskal wallis H test, Friedman test, Mann-whitney test and Wicoxon test.

### III. Results & Discussion

- 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 dose
  - Before the experiment in test Diacerein at dose of 1.4mg/kg group showed mean reaction time was 6.3 with SE of 0.123, Where as in standard1 Etoricoxib at dose of 5mg/kg group showed mean reaction time was 6.3 with SE of 0.161, Where as in standard 2 meloxicam at dose of 0.214mg/kg group showed mean reaction time was 6.3with SE of 0.145. Mean reaction time was not significant in all the groups comparison with normal saline at 0 minutes.
  - After 5 minutes of drug administration in test groups Diacerein showed mean reaction time was6.3 with SE of 0.15, Where as in standard1 Etoricoxib group showed mean reaction time was 6.8,with SE of 0.252,Where as in standard 2 Meloxicam group showed mean reaction time was 6.7 with SE of 0.165. No significant difference was observed in standard and test groups when compared to normal saline.
  - After 15 minutes of drug administration, in test Diacerein group showed mean reaction time was 6.8 with SE of 0.244, Where as in standard1 etoricoxib group showed mean reaction time was 9.3with SE of 0.675, Where as in standard 2 Meloxicam group showed mean reaction time was 8.5 with SE of 0.495. Significant results were observed in standard groups when comparison with normal saline but in case of test drug it was not significant.
  - After 30 minutes of drug administration, in test Diacerein group showed mean reaction time was 7.7 with SE of 0.334, Where as in standard1 Etoricoxib showed mean reaction time was 13.2 with SE of 1.482, Where as in standard 2 Meloxicam group showed mean reaction time was 10.7 with SE of 0.945. Standard and test groups were significantly differ with normal saline.
- 3) At medium doses
  - Before the experiment in test Diacerein at dose of 2.8mg/kg group showed mean reaction time was 6.3with SE of 0.129, Where as in standard1 Etoricoxib at dose of 10mg/kg group showed mean reaction time was 6.2with SE of 0.130, Where as in standard 2 Meloxicam at dose of 0.428mg/kg group showed mean reaction time was 6.3 with SE of 0.123. No significant difference was observed in standard and test groups when compared to normal saline.
  - After 5 minutes of drug administration in test Diacerein group showed mean reaction time was 6.5,with SE of 0.167, Where as in standard1Etoricoxib showed mean reaction time was 7 with SE of 0.247, Where as in standard 2 Meloxicam group showed mean reaction time was 6.7, with SE of 0.172. No significant difference was observed in standard and test groups when compared to normal saline.
  - After 15 minutes of drug administration, in test Diacerein group showed mean reaction time was 8.3, with SE of 0.461, Where as in standard1 Etoricoxib group showed mean reaction time was 10.8,with SE of 0.993 Where as in standard 2 Meloxicam group showed mean reaction time was 10.0, with SE of 0.818. Standard and test groups were significantly differ with normal saline.
  - After 30 minutes of drug administration, in test Diacerein group showed mean reaction time was 9.8 with SE of 0.786,Where as in standard1 Etoricoxib group showed mean reaction time was 15.8,with SE of 2.05. Where as in standard 2 Meloxicam group showed mean reaction time was 13.0, with SE of 1.450. Standard and test groups were significantly differ with normal saline.
- 4) At high doses
  - Before the experiment in test Diacerein at dose of 4.2mg/kg group showed mean reaction time was6.2, with SE of 0.095, Where as in standard1 Etoricoxib at dose of 15mg/kg group showed mean reaction time was 6.3 with SE of 0.172, Where as in standard 2 Meloxicam at dose of 0.642mg/kg group showed mean reaction time was 6.3 with SE of 0.172. No significant difference was observed in standard and test groups when compared to normal saline.
  - After 5 minutes of drug administration in test Diacerein group showed mean reaction time was 6.8,with SE of 0.195, Where as in standard1 Etoricoxib showed mean reaction time was 7.5, with SE of 0.311, Where as in standard 2 Meloxicam group showed mean reaction time was 7.5, with SE of 0.307. No significant difference was observed in standard and test groups when compared to normal saline.
  - After 15 minutes of drug administration, in test Diacerein group showed mean reaction time was 9.3, with SE of 0.690,Where as in standard1 Etoricoxib group showed mean reaction time was 11.8,with SE of 1.21. Where as in standard 2 Meloxicam group showed mean reaction time was 10.8, with SE of 1.0. Standard and test groups were significantly differ with normal saline.

- After 30 minutes of drug administration, in test Diacerein group showed mean reaction time was 11.5 with SE of 1.17, Whereas in standard 1 Etoricoxib group showed mean reaction time was 17.6, with SE of 2.442, Whereas in standard 2 Meloxicam group showed mean reaction time was 14.6, with SE of 1.8. Standard and test groups were significantly differ with normal saline.
- 5). In comparison between standards and test drug, it was found mean reaction time was increased gradually after 5 minutes, 15 minutes and 30 minutes of drug administration. No significant results were observed between standard drugs. Standard drugs were significantly differs with test drug at 30 min. Better results observed with standard drugs than with Diacerein.

#### **IV. Conclusion**

Diacerein an Interleukin-1 inhibitor drug is having analgesic property. Meloxicam and Etoricoxib are having more analgesic property when compared to Diacerein. However the above preclinical experiments only give us an idea about the analgesic effect of Diacerein but large scale clinical trials are necessary for final assessment.

#### **Acknowledgement**

Authors are very grateful to Dr.K.Neeraja, Professor, Dept. of Pharmacology for her valuable guidance for this study.

#### **References**

- [1]. Lynn, B "Cutaneous nociceptors" in Holden, AV & Winlow W., The neurobiology of pain. Manchester, UK: Manchester University Press, 1984, page no: 106.
- [2]. Vanderah TW. "Pathophysiology of pain". Medical clinics of North America., 2007, vol: **91** (1), page no: 1–12.
- [3]. Fidelix TS, Soares BG, Trevisani VF. "Diacerein for osteoarthritis". Cochrane database of systematic reviews (1) (2006): CD005117.
- [4]. Solignac M. Mechanisms of action of diacereine the first inhibitor of interleukin-1 in Osteoarthritis. Presse Med 2004, Vol: 33, Page no: S 10-2.
- [5]. Noble, S; Balfour, JA (Mar 1996). "Meloxicam". Drugs , Vol:**51** (3),Page no: 424–30; discussion 431–32.
- [6]. Panara MR, Renda G, Sciulli MG, Santini G, Di Giamberardino M, Rotondo MT, Tacconelli S, Seta F, Patrono C, Patrignani P: Dose-dependent inhibition of platelet cyclooxygenase-1 and monocyte cyclooxygenase-2 by meloxicam in healthy subjects. J Pharmacol Exp Ther. 1999 Jul, Vol: 290(1), page no: 276-80.
- [7]. Dallob A, Jawkey, CJ, Greenberg H, et al. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. J Clin Pharmacology 2003, Vol: 43, Page no: 573-585.
- [8]. Matsumoto AK, Cavanaugh PFJ: Etoricoxib, Drug today (Barc). 2004, vol: 40; page no: 395-414.
- [9]. John, P., Premendran, B., Jayasree, T., Siresha, J. V., Kota, K., Venkateshwarlu, P., & Sharma, V. "A comparative study of certain pharmacological effects of lidocaine and ropivacaine". 2012, Vol: 2 (4), page no:54-61
- [10]. Kolesnikov, Yuri A., Igor Chereshev, and Gavril W.Pasternak. "Analgesic synergy between topical lidocaine and topical opioids." Journal of Pharmacology and Experimental Therapeutics 2000, Vol: 295.2, page no: 546-551.