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Research Article

Ketorolac

Comparative evaluation of ketorolac and morphine in central and visceral model of analgesia in Rats

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Introduction: Morphine produces analgesic actions through their actions in central nervous system. It provides better analgesia and greater patient satisfaction but the problem of adverse effects remains. Ketorolac is commonly used drug mostly in the perioperative setting. There are evidences that analgesia provided by 30 mg parenteral ketorolac may be as effective as 12 mg parenteral morphine .Hence, the study was planned compare Ketorolac and Morphine's analgesic action in central and visceral model of analgesia. **Methods:** Albino rats of either sex under standard laboratory conditions were subjected to two methods of analgesia i.e. Tail flick method and Writhing method. Effect of Ketorolac and Morphine were noted down in both these methods subjected to rats and the readings were analysed before and after the drug administration with a cut off time of 15 seconds. Percent analgesia was then calculated and the data was then subjected to statistical analysis. **Results:** In Radiant heat method Ketorolac showed a percent analgesia of 32.99% which was comparable to Morphine with percent analgesia of 34.29%. Similarly Morphine with percent inhibition of 30.56% was comparable to Ketorolac (26.79%) as shown in fig 1 and 2, respectively. This suggests that Ketorolac has good analgesic efficacy comparable to Morphin. **Conclusion:** Ketorolac is safe as compared to Morphine and has a comparable efficacy to Morphine and thus, it can be utilised as an alternative to Morphine in various pain management requiring short duration of therapy such as postoperative.

Keywords: Ketorolac, Morphine, Tail Flick method, writhing

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Introduction

Morphine produces analgesic actions through their actions in central nervous system [1, 2]. The use of Opioid analgesic i.e. Morphine provides better analgesia and greater patient satisfaction [3]. In perioperative setting, the use of opioid may contribute too early and delayed respiratory depression, confusion, nausea and vomiting, decreased gastrointestinal motility and pruritus [4]. Hence the problems of adverse opioid effects remain in these cases.

Ketorolac, a NonSteroidal Anti-Inflammatory Drug (NSAIDs) possesses potent analgesic with modest anti-inflammatory effects. Ketorolac, like other NSAIDs is a non-selective cyclooxygenase (COX) inhibitor which is responsible for synthesis of prostaglandin [5]. In other words, Ketorolac is an inhibitor of prostaglandin synthesis [6]. The widespread use is limited due to possibility of gastrointestinal and renal bleeding [5]. Ketorolac is commonly used drug mostly in the perioperative setting [7, 8]. There is evidences that analgesia provided by 30 mg parenteral ketorolac may be as effective as 12 mg parenteral morphine [9, 10, 11]. Hence, the study was planned compare Ketorolac and Morphine's analgesic action in central and visceral model of analgesia.

Aims & Objective

To evaluate and compare the effect of Ketorolac and Morphine in central and visceral pain models.

Materials and Methods

Animals: 30 Albino rats (150-250 gms) of either sex were used. Animals were housed under standard laboratory conditions with free access to food and water ad libitum. The rats were fasted from 8 am on the day of experimentation. The experimental protocol was approved by institutional animal ethics committee.

Drugs: Ketorolac (Dr Reddy's Lab), Morphine (Troikaa Pharmaceuticals) and and 4% NaCl (prepared freshly).

Drug Administration: All the drugs were administered by intraperitoneal route (i.p.) and subsequent subeffective doses (producing 20-30% response) were determined. All these Drugs were diluted in distilled water to prepare solutions of desired strengths.

Assessment of central nociception:

Tail flick test (radiant heat induced nociception): The hyperalgesic response in the tail withdrawal test (Analgesiometer) is generally attributed to central mechanism. Tail withdrawal latency from the radiant heat source was taken as endpoint. The intensity of the radiant heat was adjusted so that the baseline latency for tail withdrawal of rat was 4-5 seconds. A cut off time of 15 seconds was imposed to prevent any injury to tail. Analgesic response to both Ketorolac and Morphine was expressed as percentage analgesia and was calculated as follows:

$$\% \text{ analgesia} = \frac{\text{After drug} - \text{before drug}}{15(\text{cut of time in sec}) - \text{before drug}} \times 100$$

Assessment of visceral nociception:

Writhing method: The rats were given 0.4ml/100gm of freshly prepared 4% NaCl solution by intraperitoneal route. Within few seconds the rats showed characteristics writhes which was the contraction of abdomen with extension of hind limbs. The number of writhes before and after drug administration was counted for a period of 10 minutes for both Ketorolac and Morphine. Based on the number of writhes percentage inhibition was calculated by using the following formula:

$$\% \text{ inhibition} = \frac{\text{writhes with NaCl - writhes with NaCl after giving drug}}{\text{writhes with NaCl}} \times 100$$

Statistical Analysis: Results were expressed as mean ± SEM**.** Paired t test was used to compare reaction time before and after injecting the drugs as well as Percentage analgesia and percentage inhibition in ketorolac group (group I), Morphine (group II).

Results

Both these results, suggests that Ketorolac has good analgesic efficacy comparable to Morphine.

In Radiant heat method Ketorolac showed a percent analgesia of 32.99% which

Was comparable to Morphine with percent analgesia of 34.29%. Reaction time before and after drug after application of paired t test showed a significant p value of 0.0192 for Ketorolac and p value of 0.0152 for morphine. Similarly Morphine with percent inhibition of 30.56% was comparable to Ketorolac (26.79%) as shown in fig 1 and 2, respectively. Reaction time before and after drug after application of paired t test showed a significant p value of 0.01 for Ketorolac and p value of 0.0047 for morphine.

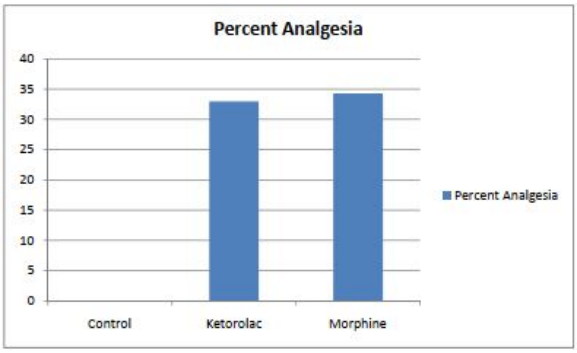

Fig 1: Figure showing Percent Analgesia of Ketorolac and Morphine in Tail flick method in Albino Rats.

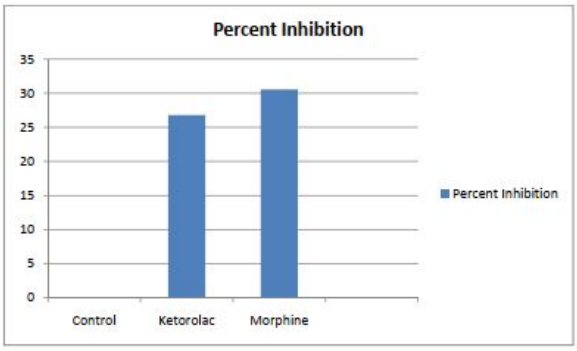

Fig 2: Figure showing Percent Inhibition of Ketorolac and Morphine in writhing method in Albino Rats.

Discussion

Radiant heat method and 4% NaCl induced writhing method are recognized screening tests for potential antinociceptive properties of central and visceral nociception, respectively[12,13]..Used together these two complimentary tests detect antinociceptive actions of all major analgesic drugs in clinical use.

NSAIDs are known to provide effective relief of hyperalgesia associated with inflammation [14]. The antinociceptive action of ketorolac is through inhibition of prostaglandin synthesis which occurs through reversible inhibition of cyclo-oxygenase enzyme [3]. These laboratory observations in rats support the antinociceptive activity of ketorolac in man [5]. Although ketorolac have antinociceptive and anti-inflammatory actions but cannot be used for long term treatment as analgesic because of few shortcomings like gastrointestinal and renal bleeding as adverse effects and hypersensitive reactions in sensitive persons. Beside analgesic action, opioids also relieve hyperalgesia in periphery in situations involving inflammation or prolonged nociceptive stimulation [1, 2]. Morphine is a potent μ opioid receptor agonist that acts centrally. In contrast to these ketorolac exerts its effects by inhibiting COX enzymes involved in prostaglandin synthesis which are mediators of pain and inflammation.

The results of this study suggest Ketorolac has comparable efficacy against Morphine in both central and visceral pain models. Our study goes in flow with other study by Safdar B.et al which stated that there was no difference in reduction of pain score between Ketorolac and Morphine which suggests equal efficacy between Ketorolac and Morphine [15]. Another study with a different opioid Pethidine suggested Ketorolac appeared safer than pethidine, while pethidine appeared more effective analgesic than Ketorolac in the management of post-operative pain [16]. So, the question of safety and efficacy remains debatable. Ketorolac is safe as compared to Morphine and has a comparable efficacy to Morphine and thus, it can be utilised as an alternative to Morphine in various pain management requiring short duration of therapy such as postoperative pain.

Conclusion

Ketorolac is safe as compared to Morphine and has a comparable efficacy to Morphine and thus, it can be utilised as an alternative to Morphine in various pain management requiring short duration of therapy such as postoperative pain.

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