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Research Article

STUDY OF ANALGESIC ACTIVITY OF CELECOXIB AND IBUPROFEN COMBINATION USING ALBINO RATS

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ABSTRACT

The present study was carried out to investigate the analgesic activity of Celecoxib (10 mg), a selective Cox-2 Inhibitor and Ibuprofen (10 mg), a non selective Cox Inhibitor for individual drug therapy and Celecoxib (5 mg) for combination therapy with Ibuprofen (10 mg) using Hot plate and Tail immersion methods. The Hot plate and Tail immersion test useful in the elucidating centrally mediated antinociceptive responses, which focused mainly on changes above the spinal cord level. All the test drugs significantly reduced the pain as compare to the control group in Hot plate ($p < 0.002$) and Tail Immersion ($p < 0.003$) methods. The results of pharmacological tests performed in the present studies suggest the combination of Celecoxib and Ibuprofen possess potent analgesic activity.

Keywords: Analgesic , Celecoxib, Cox-2 Inhibitor, Ibuprofen.

INTRODUCTION

Analgesia is a survival mechanism that serves as a warning sign of ongoing or impending tissue damage. Pain is an unpleasant sensory and produced by the excitation of particular receptors. Pain can classified as chronic or acute. The difference between acute & chronic pain is not based on its duration of feeling, other than the nature of the pain itself. Acute pain is symptom of pain. But chronic pain was the " disease of pain''.

The generation of pain in response to tissue injury involves four basic elements

- **Transduction**
  A occupation of nociceptors that convert noxious stimulation to nociceptive signals.
- **Transmission**
  A process to sends nociceptive signals along nerve fibers from the site of injury to the central nervous system (CNS).
- **Transformation or plasticity**
  A mechanism that modulates nociceptive signals at synaptic sites and at the level of the CNS through ascending, descending, or regional facilitation and inhibition.
- **Perception**
  Important component of the clinical pain experience that integrates cognitive and affective (emotional) responses.[1]

The perception of pain is due to activation of nociceptive receptor by the neurotransmitters. Three receptor has been identified for the pain perception, mu, kappa, and delta. They initiate the synthesis of either prostaglandin I or prostaglandin II or sometime both. Analgesic dugs block them either selectively or none selectively to the COX-II receptor.[2,3]

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and edema by suppressing the formation of prostaglandins, by inhibiting the activity of the enzyme Cyclooxygenase (COX-1 and COX-2). However, prostaglandins are key mediators of several components of GI mucosal defense,

so suppression of synthesis of prostaglandins (PGs) by NSAIDs greatly reduces the resistance of the mucosa to injury as well as interfering with repair processes. Selective COX-2 inhibitors were thought to be the solution to this conundrum as it is required that NSAIDs suppress prostaglandin synthesis at sites of inflammation, and not in the GI tract. However, it is now clear that both COX-1 and COX-2 isoforms contribute to mucosal defense. Selective COX-2 inhibitors elicit less GI damage and bleeding than conventional NSAIDs, although the magnitude of this reduction continues to be contested in the literature. As widely reported in the lay-press, the selective COX-2 inhibitors also cause significant adverse effects in the renal and cardiovascular systems, possibly more serious than those caused by conventional NSAIDs. The market for NSAIDs is expanding rapidly because of an aging population in developed countries and the associated increase in the prevalence of diseases like arthritis. Use of Aspirin is also increasing because of its utility in reducing the incidence of a number of common disorders including stroke, myocardial infarction, Alzheimer's disease and cancer.[4]

MATERIALS AND METHODS

Selection of Drugs and Chemicals

For the purpose of this work we selected Celecoxib (Selective COX – 2 inhibitor) and Ibuprofen (Conventional NSAID) drugs.

Preparation of drugs and Chemical solutions

Celecoxib (10mg/kg body weight) was dissolved in sufficient quantity of solvent in normal saline and use in the treatment. Celecoxib (5mg/kg) and Ibuprofen (10mg/kgbody weight) was dissolved together in sufficient quantity of solvent(normal saline).

Selection of Experimental Animals

Healthy Wistar albino rats of either sex weighing 180-200g were used in this study. All the animals were obtained from Animal house of Hindu College of Pharmacy, Acharya Nagarjuna University, Guntur, Andhra Pradesh. The animals were housed comfortably in a group of six in a single clean plastic cage with a metal frame lid on its top. They were housed under standard environmental conditions of temperature (24±1°C) and relative humidity of 30-70 %. A 12:12 h light dark cycle was followed. All animals had free access to water and standard pelletized laboratory animal diet *ad libitum*. All the experimental procedures and protocols used in this study were reviewed and approved via the Approval No. 17/09/IAEC/SOAU by the Institutional Animal Ethical Committee (IAEC) of Hindu College of Pharmacy, Acharya Nagarjuna University, Guntur, Andhra Pradesh (Regd. No. 1171/C/08/CPCSEA) constituted in accordance with the guidelines of the CPCSEA, Government of India.

Evaluation of Analgesic Activity

Hot plate method in rats[5,6]

The paws of mice and rats are very sensitive to heat at temperatures which are not damaging the skin. The responses are jumping, withdrawal of the paws and licking of the paws. The hot plate, which is commercially available, consists of a electrically heated surface. The temperature is controlled for 55° to 56 °C. This can be a copper plate or a heated glass surface. The animals are placed on the hot plate and the time until either licking or jumping occurs is recorded by a stop-watch. Wistar albino rats weighing between 180-200g were used for evaluation of analgesic activity; in each group six albino rats were kept. Test - 1 : A solution of Celecoxib (10mg/kg), Test - 2 : A solution of buprofen(10mg/kg), Test - 3 : A solution of Celecoxib (5mg/kg) in combination with Ibuprofen (10mg/kg) was prepared in 10ml of normal saline water. Wistar albino rats of either sex were divided into four different groups each containing six animals, the animals were marked individually. Food was withdrawn 12 hours prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. The test and standard drugs were given orally. After 60 minutes, the animals are placed on the hot plate and the observations were recorded and at the time interval of 90, 120 and 180 minutes. The results of Hot plate method in rats was tabulated in Table-1.

Tail immersion Method[7,8]

Analgesic activity was also checked in wistar albino rats by the caudal immersion[7].The procedure is based on the observation that morphine-like drugs are selectively capable of prolonging the reaction time of the typical tail-withdrawal reflex in rats induced by immersing the end of the tail in warm water of 55 °C. The lower 5 cm portion of the tail is marked. This part of the tail is immersed in to the water bath of exactly 55 °C. Within a few seconds the rat reacts by withdrawing the tail. The reaction time is recorded in 0.5 s units by a stopwatch. After each determination the tail is carefully dried. The reaction time is determined before and periodically after oral administration of the test and control substance. The cut off time is

15sec. Wistar albino rats weighing between 180-200g were used for evaluation of analgesic activity; in each group six albino rats were kept. Test - 1 : A solution of Celecoxib (10mg/kg), Test - 2 : A solution of buprofen(10mg/kg), Test - 3 : A solution of Celecoxib (5mg/kg) in combination with Ibuprofen (10mg/kg) was prepared in 10ml of normal saline water. Wistar albino rats of either sex were divided into four different groups each containing six animals, the animals were marked individually. The animals were weighed and numbered appropriately. The test and standard drugs were given orally. After 60 minutes, the observations were recorded and at the time interval of 30,60, 90 and 120 minutes. The results of tail immersion test in rats was tabulated in Table-2.

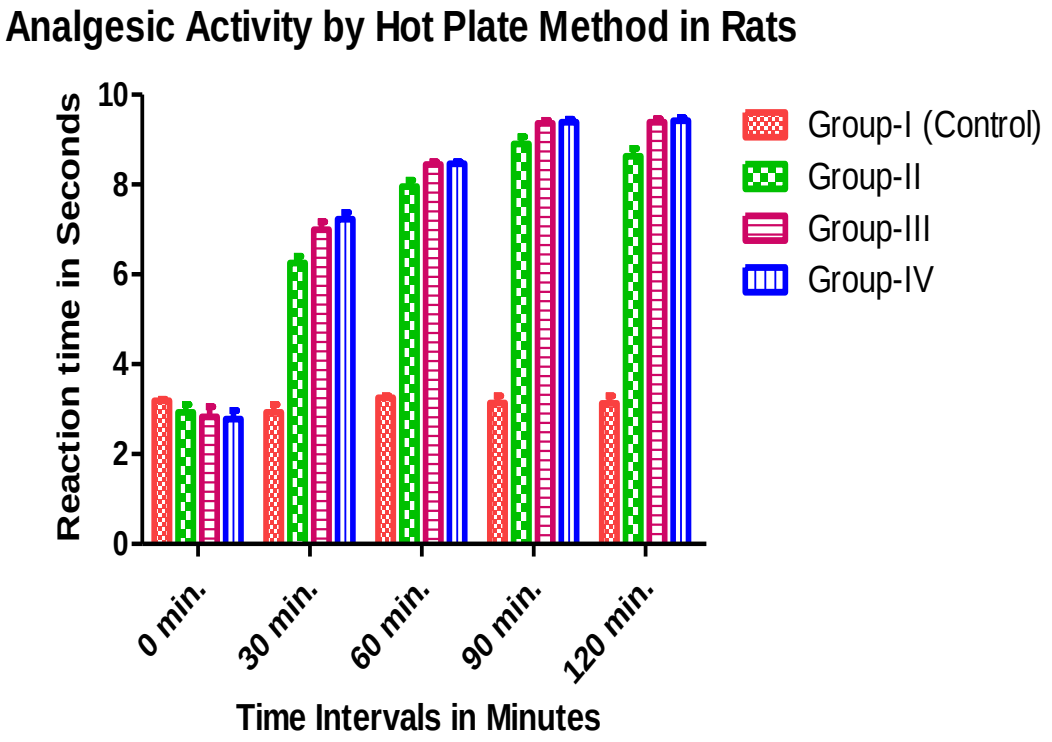
RESULTS AND DISCUSSION

The Hot plate and Tail immersion tests are useful in the elucidating centrally mediated antinociceptive responses, which focuses mainly on changes above the spinal cord level.

Table 1: Analgesic Activity by Hot Plate Method in Rats

Group	Treatment Dose (mg/kg)	Dose (mg/kg)	Reaction time in seconds at time (minutes) (mean ± sem)				
			0	30	60	90	120
Control	Normal Saline	--------	3.18 ± 0.041	2.93 ± 0.179	3.25 ± 0.047	3.14 ± 0.160	3.13 ± 0.162
Test – 1	Ibuprofen	10	2.93 ± 0.177	6.25 ± 0.155*	7.95 ± 0.150*	8.90 ± 0.161*	8.13 ± 0.176*
Test – 2	Celecoxib	10	2.83 ± 0.224	6.99 ± 0.182*	8.45 ± 0.051*	9.36 ± 0.070*	9.39 ± 0.070*
Test – 3	Celecoxib + Ibuprofen	5 + 10	2.78 ± 0.195	7.23 ± 0.145*	8.46 ± 0.041*	9.38 ± 0.073*	9.42 ± 0.067*

Each value is the mean ± SEM for 6 rats, * P < 0.02 compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's Multiple Comparison test



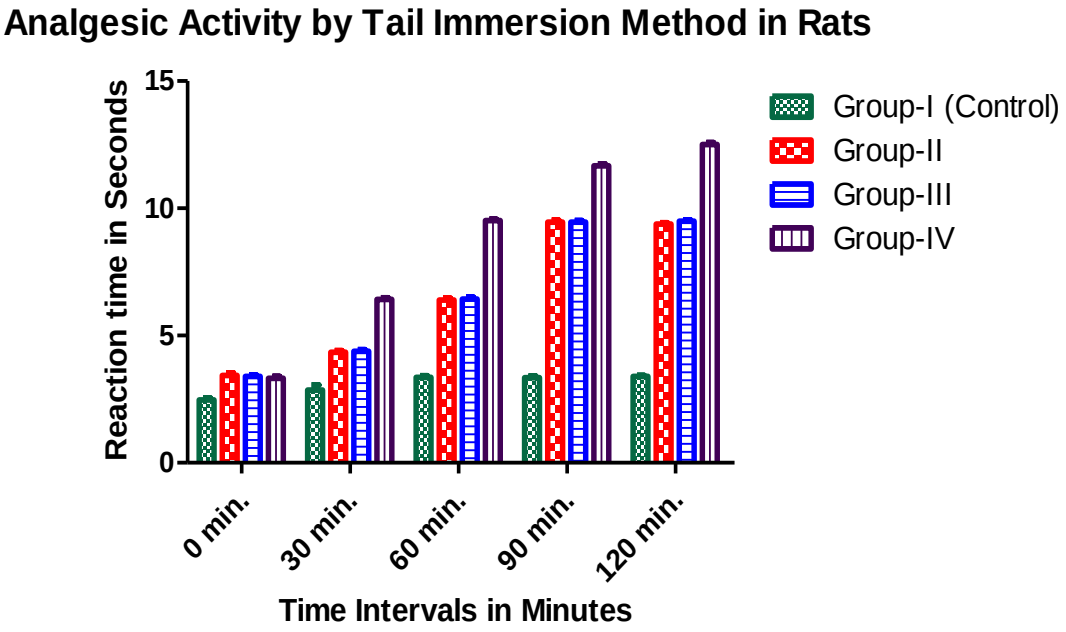
Here,

Group-I – Control, Group-II – Celecoxib (10mg/kg), Group-III – Ibuprofen (10mg/kg) and Group-IV - Celecoxib (5mg/kg) + Ibuprofen (10mg/kg)

Table 2: Analgesic Activity by Tail Immersion Method in Rats

Group	Treatment Dose (mg/kg)	Dose (mg/kg)	Reaction time in seconds at time (minutes) (mean ± sem)				
			0	30	60	90	120
Control	Normal Saline	--------	2.46 ± 0.076	2.85 ± 0.194	3.36 ± 0.054	3.34 ± 0.057	3.39 ± 0.043
Test – 1	Ibuprofen	10	3.42 ± 0.107	4.34 ± 0.059 ^{ns}	6.39 ± 0.073 ^{ns}	9.46 ± 0.064 ^{ns}	9.37 ± 0.047 ^{ns}
Test – 2	Celecoxib	10	3.39 ± 0.052	4.38 ± 0.061^{ns}	6.42 ± 0.077 ^{ns}	9.45 ± 0.065 ^{ns}	9.49 ± 0.059 ^{ns}
Test – 3	Celecoxib + Ibuprofen	5 + 10	3.32 ± 0.070	6.42 ± 0.063*	9.51 ± 0.059*	11.67 ± 0.072*	12.5 ±0.080*

Each value is the mean ± SEM for 6 rats, * P < 0.03 compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's Multiple Comparison test



Here, Group-I – Control, Group-II – Celecoxib (10mg/kg), Group-III – Ibuprofen (10mg/kg) and Group-IV - Celecoxib (5mg/kg) + Ibuprofen (10mg/kg)

All the test groups significantly ($p<0.002$) reduce the pain as compare to the control group in Hot Plate method. Ibuprofen increased the reaction time from 2.9sec to 8.90 sec and Celecoxib increased the reaction time from 2.8 sec to 9.36 sec, whereas the combination of Celecoxib and Ibuprofen showed the increased reaction time from 2.7 sec to 9.38 sec for the thermal stimuli. When Compared to Group – II, the Group – III and Group – IV showed more significant effect and Group-IV when compare to the Group – III showed significant effect at 30, 60, 90 and 120 minutes.

In Tail immersion method all the test drugs significantly ($p<0.003$) reduce the pain as compare to the control. Ibuprofen increased the reaction time from 3.42sec to 9.37 sec and Celecoxib increased the reaction time from 3.39 sec to 9.49 sec, whereas the combination of Celecoxib and Ibuprofen showed the increased reaction time from 3.32 sec to 12.5 sec for the thermal stimuli. Group – IV showed significant effect compared to Group – II and Group – III at 30, 60, 90 and 120 minutes time intervals. But there is no significant difference between Group – II and Group – III.

CONCLUSION

Here in this research work we found that Celecoxib is more effective than the conventional NSAID Ibuprofen. The low dose combination of Celecoxib with Ibuprofen has more effective for analgesic activity as compare to the individual Celecoxib and Ibuprofen (conventional NSAIDs). Here we conclude that the combination product was more effective than the single drug, it may be due to different mechanism of actions of different drugs in combined products. But the

chances of side effects of combination products are more as compare to the single drug. More study on combination drug therapy may overcome these problems.

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