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A COMPARATIVE STUDY OF ANTINOCICEPTIVE ACTIVITY OF FLUPIRTINE WITH DICLOFENAC IN SWISS ALBINO MICE

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ABSTRACT

There is a need for new effective analgesic drugs with fewer side effects and minimum drug abuse liability. Flupirtine is a centrally acting, non-opioid analgesic agent with unique pharmacological properties. Materials and Methods: Tail flick (thermal method), tail clip (physical method) and writhing test (chemical method) were used as in-vivo model. Flupirtine (10 and 20 mg/kg i.p.) was administered as test drug in mice and compared with diclofenac (10 mg/kg i.p.) as standard drug. The analgesic activity was studied by recording the reaction time after administration of the drug at frequent intervals up to 90 minutes. The results were analyzed by ANOVA and Bonferroni's test. P value < 0.05 was considered as significant. Results: Administration of flupirtine showed significant increase in reaction time as compared to control at all the time intervals. Flupirtine inhibited the nociceptive responses induced by chemical, thermal and mechanical stimuli in rodents. Conclusion: Flupirtine has good analgesic activity in this experimental model of pain.

Keywords :- Analgesia, Flupirtine, Diclofenac, Opioids.

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INTRODUCTION

Pain is the most common reason for patients to refer health-care center and is the most common reason given for self-medication. Nociceptive pain is due to direct stimulation of peripheral nerve endings (e.g. wounds, fractures, burns). It is inflammatory pain which is associated with tissue damage and the infiltration of immune cells.Nociceptive pain may also be divided into deep somatic pain and visceral pain. Analgesics are group of drugs used to relieve pain. Analgesic drugs act in various ways on peripheral and central nervous systems;they include the non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.[1] The treatment of pain is a major problem in practice because it has been complicated by many factors including the significant adverse effects like gastric erosions/ulcers and dependence liability by the use of NSAIDs and opioids respectively. [2] Hence, there is an unmet need for new analgesic drugs with equal or greater efficacy, fewer side effects and minimum abuse liability. Most NSAIDs are commonly indicated for the relief of only mild to moderate pain. In addition, NSAIDs are contraindicated in patients with peptic ulcer disease, renal impairment, and tendency for bleeding. Opioids are highly effective for acute and chronic pain, but their use is limited by nausea, vomiting, constipation, and sedation,

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as well as the possibility of addiction and dependence. [2] In the present study flupirtine, a centrally acting non-narcotic analgesic has been selected and its efficacy has been compared with a potent analgesic, diclofenac. Flupirtine is indirect NMDA receptor antagonist and is the first representative of a pharmacological class of selective neuronal potassium channel opener. [3] Flupirtine is a centrally acting nonopioid analgesic that belongs to triaminopyridine class. Its spectrum of action includes analgesia, muscle relaxation and neuroprotection. [4] It is a potential analgesic which can be used as an alternative to NSAIDS and opioids, especially in cases where there is insufficient response to these drugs. However, there are few studies on experimental evaluation of flupirtine. [5-7] Keeping the above facts in mind this study was undertaken.

The study has been carried out on animal using albino mice. For analgesic study, tail flick (thermal method), tail clip (physical method) and writhing test (chemical method) were employed. The present study was undertaken to explore the possibility of use of flupirtine as a potent analgesic, when compared with diclofenac. This study may enable us to know the efficacy of flupirtine with respect to diclofenac.

AIM AND OBJECTIVES

Aim: To evaluate the analgesic activity of flupirtine in mice.

Objectives

1. To evaluate the analgesic activity of flupirtine.
2. To compare the analgesic activity of flupirtine with diclofenac.

MATERIALS AND METHODS

Ethical Considerations

The study was commenced after Institutional Animal Ethics Committee (IAEC) approval was granted and was conducted in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines.

Study drugs and chemicals

The test drugs flupirtine and the standard drug diclofenac were used. The drugs were purchased from local pharmacy and were manufactured by following manufacturers–

- Flupirtine by Lupin Pharmaceutical Ltd., Jammu,
- Diclofenac by Novartis India Ltd., Mumbai.

Experimental animals

The study was carried out on Swiss albino mice. Adult mice of either sex with age group of 3 to 4 months were used. They were housed in polypropylene cages under standard laboratory conditions in a well-ventilated room and fed standard pellet diet. They had free access to diet and water except at the time of experiment. They were placed in clean, neatly labeled cages, each containing 3 mice. The floor of the cages was stack with grain husk which were replaced every second day. The animals were inspected frequently to rule out infections. In each cage the animals were identified by appropriate markings.

Inclusion Criteria

- Albino mice of either sex weighing between 20-25 g.
- Age 3-4 months.
- Healthy with normal behavior and activity.

Exclusion Criteria

- Mice <20 g or >25 g and aged <3 months or >4 months.
- Pregnant mice or those who have recently delivered.
- Animals previously used in other experiments.

STUDY DESIGN

Study Groups

The mice were placed in 4 groups (G1-G4) containing 6 mice each. (24 mice in total)

- G1- were the control group received only Distilled water.
- G2 - were the standard group received Diclofenac (10 mg/kg i.p.)
- G3- were the test group received test drug Flupirtine (10mg/kg i.p.)
- G4 - were the test group received test drug Flupirtine (20 mg/kg i.p.)

METHODS

Analgesic activity of flupirtine (10 mg/kg, 20 mg/kg) was evaluated in graded dose and compared with diclofenac by

1. Radiant heat method (Thermal method),
2. Tail clip method (Physical method),
3. Writhing test method (chemical method).

Statistical analysis

Results are presented as Mean ± SEM. One way ANOVA was used for multiple comparisons followed by Bonferroni's test post hoc test for comparison between groups. For all the test s "p" value of 0.05 or less was considered for statistical significance.

RESULTS

Table 1. Effect of different drugs on tail flick response in mice

Parameter	Control (n=6) M ± SEM (second)	Diclofenac (n=6) M ± SEM (second)	Flupirtine at 10mg/kg (n=6) M ± SEM (second)	Flupirtine at 20mg/kg (n=6) M ±SEM (second)
Pre-treatment	5.45±.577	5.25±.618	5.50±.438	5.47±.432
At 30min.	5.33±.463	6.25±.399	6.83±.585*	8.67±.345*#
At 60min.	5.43±.463	9.27±.501	9.07±.605*	11.11±.500*#
At 90min.	5.36±.598	7.58±.512	10.80±.623*#	13.62±.736*#

Data were presented as mean ± SEM. Analysis was done using one-way ANOVA followed by post hoc Bonferroni's test. The * depicts comparison with control, # depicts comparison with diclofenac, * P<0.05, # P<0.05.

Table 2. Effect of different drugs on tail clip-induced pain in mice

Parameter	Control (n=6) M ± SEM (second)	Diclofenac (n=6) M ± SEM (second)	Flupirtine at 10mg/kg (n=6) M ± SEM (second)	Flupirtine at 20mg/kg (n=6) M ± SEM (second)
Pre-treatment	4.13±.599	4.52±.633	3.92±.601	4.17±.427
Post-treatment	4.32±.458	12.00±.660	12.40±.555*	15.75±.501*#

Data were presented as mean ± SEM. Analysis was done using one-way ANOVA followed by post hoc Bonferroni's test. The * depicts comparison with control, # depicts comparison with diclofenac. * P<0.05, # P<0.05.

Table 3. Percent inhibition by different drugs on acetic-acid induced writhes in mice

Group n= 6	Average no. of writhes in 20 minute	Percent inhibition (%)
Control	47.500±1.258	-
Diclofenac 10 mg/kg	14.333±.667	69.8%
Flupirtine with 10 mg/kg	19.000±.577	60%
Flupirtine with 20 mg/kg	12.833±.601	73%

DISCUSSION

Evaluation of analgesics in animals although very crude, is highly predictive of clinical efficacy. In the present work, albino mice have been selected for the experiments. These animals are cheap, easy to handle, easily available and can be kept on laboratory diet at room temperature.

Any injury or tissue damage is associated with pain. Analgesics can act on peripheral as well as central nervous system. Peripherally acting analgesics act by blocking the generation of impulses at chemoreceptor site of pain, while centrally acting analgesics not only raise the threshold for pain, but also alter the physiological response to pain. [8]

In the present study, we have explored the antinociceptive actions of flupirtine in three models of pain. The analgesic effects of flupirtine have already been demonstrated in several studies using experimental pain models. Flupirtine, when administered intra-cerebroventricularly or intrathecally has been shown to possess analgesic activity in rodents. [9] The analgesic effect of flupirtine was not abolished by naloxone and it showed no affinity for opioid receptors. [10] These studies indicate that flupirtine induces analgesic effect through a central action in which opioid mechanisms play no role.

Radiant heat method (Thermal method):

Radiant heat method is known to evaluate centrally acting analgesics. In standard group with diclofenac, the mean reaction time increased, maximum at 60 minute, from 5.25±.618 to 9.27±.501. The mean reaction time also increased in test groups treated with flupirtine (10 mg/kg), maximum at 90 minute, from 5.50±.438 to 10.80±.623 .The maximum reaction time was 13.62±.736 seen with 20 mg/kg at 90 minute after post administration within test group.

As per statistical analysis, the mice treated with both flupirtine 10 mg/kg and 20 mg/kg have shown a significant ($p< 0.05$) increase in the reaction time compared to the control group. The mice treated with flupirtine 10 mg/kg have shown a significant ($p < 0.05$) increase in the reaction time compared to diclofenac at 90 minute. The mice treated with flupirtine 20 mg/kg have shown a significant ($p < 0.05$) increase in the reaction time compared to diclofenac at 30, 60 & 90 minute.

Tail clip method

In standard group with diclofenac, the mean reaction time increases, from 4.52±.633 to 12.00±.660. The mean reaction time also increased in test groups treated with flupirtine (10 mg/kg), from 3.92±.601 to 12.40±.555. The maximum reaction time was 15.75±.501 seen with 20 mg/kg after post administration within test group. The increase in reaction time with 20 mg/kg is comparable with diclofenac. As per statistical analysis, the mice treated with both flupirtine 10 mg/kg and 20 mg/kg have shown a significant ($p< 0.05$) increase in the reaction time compared to the control group. The mice treated with flupirtine 20 mg/kg have shown a significant ($p < 0.05$) increase in the reaction time compared to diclofenac.

Writhing test

The acetic acid induced writhing test described as a typical model for inflammatory pain, has long been widely used as a tool to screen for analgesic or anti-inflammatory properties of new agent. Acetic acid induced abdominal pain sensation by releasing arachidonic acid via cyclooxygenase and prostaglandin synthesis which plays a role in nociceptive mechanism. In this test, the average number of writhes in control group was 47.500±1.258. The mice treated with 10 mg/kg and 20 mg/kg of flupirtine produced 19.000±.577 and 12.833±.601 writhes respectively. The maximum percentage inhibition was 73% seen with 20 mg/kg after post administration within test group. The reduction in the number of writhes was significant ($p<0.05$) with dose 10 mg/kg and 20 mg/kg of flupirtine respectively as compared to the control group. There was a dose dependent reduction in number of writhes in the test animals treated with flupirtine.

CONCLUSION

The results obtained during this study suggest antinociceptive activity of flupirtine with all three pain models used. Flupirtine might represent a novel analgesic agent. Its atypical mechanism of analgesic action suggests that it might be effective against pain where traditional NSAIDs or opioids may not be effective.

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