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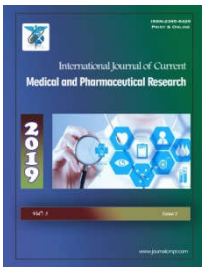

EXPERIMENTAL EVALUATION OF ANALGESIC ACTIVITY OF FLUPIRTINE USING HOT PLATE METHOD

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ABSTRACT

Introduction: International Association for the Study of Pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage**.** 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.

Material and Methods: In vivo model used - Hot plate method. Flupirtine (27 mg/kg p.o) was administered in rats either alone or in combination with pentazocine (10 mg/kg i.p.).
The analgesic activity was studied by recording the reaction time after administration of the drug at frequent intervals up to 3 hrs. The results were analysed 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. Its action started at 30 min. with a peak at 60 min. Pentazocine and the combination group showed significant increase in reaction time as compared to flupirtine at all the time intervals.

Conclusion: Flupirtine showed analgesic activity in this experimental model of pain. Its onset of action was similar to that of pentazocine. However, the degree of analgesia was significantly less than that of pentazocine. Combination of the two drugs resulted in potentiation of analgesia.

INTRODUCTION

Pain is a protective, warning signal which causes discomfort and suffering. It is the most important symptom for which an individual seeks physician's attention. The International Association for Study of Pain (IASP) defines pain as: "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[1] Although $NSAID_S$ and opioids have been used for relief of pain, they are associated with significant adverse effects like gastric erosions/ulcers and dependence liability respectively. Hence, there is an unmet need for new analgesic drugs with equal or greater efficacy, fewer side effects and minimum abuse liability. Flupritine is a centrally acting non-opioid analgesic that belongs to triaminopyridine class. Its spectrum of action includes analgesia, muscle relaxation and neuroprotection. It is a potential analgesic which can be used as an alternative to $NSAID_S$ and opioids, especially in cases where there is insufficient response to these drugs. However, there are few studies on experimental evaluation of flupirtine. Hence, this study was undertaken.

Aim and objectives

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

Objectives

1. To evaluate the analgesic activity of flupirtine.
2. To compare the analgesic activity of flupirtine with pentazocine.
3. To evaluate the analgesic activity of co-administration of flupirtine and pentazocine.

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.[2]

Animals used

Sprague-Dawley rats, experimentally naïve, of either sex, weighing between 150-250 g were selected for the study. They

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were procured from the animal house of Dr. D.Y. Patil Medical College, Hospital & Research Centre, Pimpri, Pune-411018.

Animal feed

Food: Animals were fed with commercially available 'Nutrimex Std-1020' manufactured by Baramati Agro Ltd. acquired from Nutrivet Life Sciences, Pune. The nutrition provided by the pellet feed was as follows:

Energy: 3620 kcal/kg, Crude protein: 22.15%, Ash: 5.11%, Sand silica: 1.15%

Water: Drinking tap water supplied by local municipal corporation was provided to the rats through the feeding bottles with stainless steel nozzle in each cage.

Both food and water were replenished once daily in the morning, and were available to the rats ad libitum.

Animal housing

Rats were housed in groups of four, in a standard big polypropylene cage measuring 40 x 27.5 x 13.5 cm, having wire mesh top with provision for drinking water and space for pellets. Corn cob was used as bedding material in each cage. Standard conditions of temperature (25^0C ± 5^0 C), relative humidity (55 ± 10%) and 12/12-hour light / dark cycle was maintained. Apart from daily replenishment of food and water, rats were left undisturbed.

Study drugs: Flupirtine (Source**:** Lupin Pharmaceuticals Limited, Pune) was the test drug. Pentazocine (Source**:** Dr. D. Y. Patil Medical College Pharmacy, Pimpri, Pune) was used as standard analgesic.

The method used

Hot plate method- The method described by Eddy NB & Leimbach D was used. Rats were placed on a hot plate (Eddy's hot plate analgesiometer) heated to 55 ± 0.5 °C.[3] The time taken after placing the animals on hot plate till the onset of response (licking/shaking of the paws, jumping) was taken as reaction time. It was recorded with the help of a stopwatch. The rats showing the reaction time less than 30 seconds were selected. Reaction times were recorded before and after administration of the test at 0, 30, 60, 90, 120, 180 min.

Animals were grouped (n=8 each) into four groups viz.

I.Control
II.Flupirtine
III.Pentazocine .
IV.Flupirtine + Pentazocine.

Flupirtine was administered in the dose of 27mg/kg (p.o.), pentazocine was given in the dose of 10mg/kg (i.p.) while control group received distilled water 1ml/rat (p.o.). Drug doses were calculated by extrapolation from human dose.[4,5]

Statistical analysis

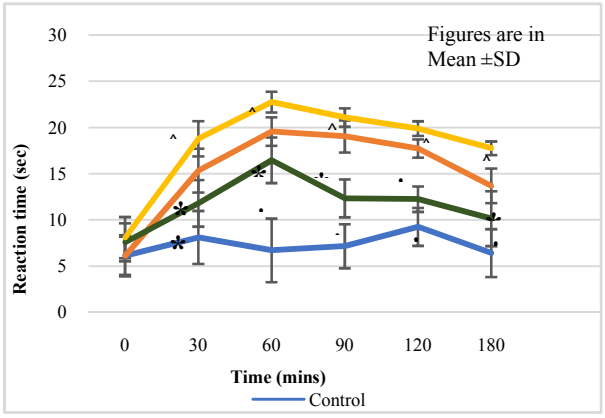
The data were compiled and analyzed using the statistical package, Primer of biostatistics, (version 7.0). Results were expressed as Mean ± SD and statistical significance between means was analysed using one-way analysis of variance (ANOVA) and Bonferroni's test was applied for multiple comparisons. P value < 0.05 was considered statistically significant.

RESULTS

With the administration of pentazocine (10mg/kg), there was a significant increase in reaction times at all the time intervals starting from 30 min. as compared to control (P<0.05). (see table - 1 and graph - 1)

Administration of flupirtine (27mg/kg), also resulted in significant increase (P<0.05) in reaction times as compared to control. Its action started at 30 mins and lasted up to 180 mins. The increase in reaction times with flupirtine was significantly less as compared to that resulting after administration of pentazocine.

Administration of combination of flupirtine and pentazocine, resulted in significantly (P<0.05) more prolongation of reaction times than either drug alone at all the time intervals.



*,#,^ = P<0.05

* Comparison with control
\# Comparison of Flupirtine with Pentazocine
^ Comparison of Pentazocine+Flupirtine with either Pentazocine or Flupirtine

Table 1 Effect of different treatments on reaction times using hot plate method in rats

TIME → GROUPS↓	Reaction times (in seconds) at given time interval					
	0 min	**30 min**	**60 min**	**90 min**	**120 min**	**180 min**
I –Control	6.12±2.06	8.11±2.86	6.70±3.44	7.15±2.38	9.25±2.05	6.41±2.59
II-Pentazocine	6.11±2.23	15.35±2.37*	19.57±1.54*	19.05±1.74*	17.74±0.99*	13.69±1.87*
III- Flupirtine	7.59±2.06	11.8±2.52*#	16.46±2.45*#	12.34±2.06*#	12.25±1.38*#	10.14±2.97*#
IV-Pentazocine + Flupirtine	8.09±2.23	18.80±1.91^	22.77±1.13^	21.09±1.00^	19.89±0.79^	17.76±0.74^

Figures are in Mean ±SD

*, # ,^ = P<0.05

* Comparison with control
\# Comparison of Flupirtine with Pentazocine
^ Comparison of Pentazocine+Flupirtine with either Pentazocine or Flupirtine

Pentazocine, flupirtine and combination group showed its peak effect at 60 mins as shown in the graph.

DISCUSSION

Administration of pentazocine resulted in significant increase in reaction time, which validated the model used. Similarly, administration of flupirtine resulted in significant increase in reaction times at various time interval, suggesting the analgesic activity of this drug. The onset, peak and duration of flupirtine and pentazocine were similar, indicating that flupirtine can be used at similar time intervals. Flupirtine alone was less effective than pentazocine alone. However, their combination resulted significantly more analgesia than either drug alone, suggesting the synergistic effect, which might be due to the different mechanisms of action of these drugs.

It has been observed previously, that flupirtine was equally effective as compared to pentazocine, diclofenac, naproxen, ketoprofen and paracetamol. Also, concomitant administration of flupirtine maleate at a single low dose enhanced the antinociceptive activity of paracetamol, acetylsalicylic acid and ibuprofen in the acetic acid writhing test, acetylsalicylic acid in the hot plate test and paracetamol, acetylsalicylic acid and ibuprofen in the Randall-Selitto test.[6]

Nickel B. *et al*. compared the analgesic activity of flupirtine with pentazocine, morphine and codeine. Flupirtine was found to be as potent as pentazocine in electro stimulated pain test in mice as well as in dogs, whereas in hot plate method it was half as potent as morphine. The maximal antinociceptive activity of flupirtine was observed 30 min after dosing and analgesia lasted for at least 75 min.[7]

In a previous study done by Kolosov *et al*. (2012), prostate cancer cells were injected into the right tibia of male Wistar rats, leading to development of hyperalgesia to noxious heat. Hyperalgesia was assessed by measurement of paw flick latency (PFL) to application of radiant heat. Both morphine (ED_{50} = 0.74 mg/kg) & flupirtine (ED_{50} = 3.32 mg/kg) caused dose-related anti-hyperalgesia. There was a synergistic interaction between flupirtine and morphine, as suggested by significant decreases in ED_{50} of both morphine (0.74 to 0.08 mg/kg) and flupirtine (3.32 to 0.31 mg/kg).[8] In another study done by Goodchild CS *et al*. (2008) complete reversal of carrageenan-induced hyperalgesia was caused by 10 mg/kg flupirtine (i.p.) in combination with 0.4 mg/kg morphine (i.p.).[9]

In the diabetic neuropathy model, a lower dose of morphine (1.6 mg/kg, i.p., ineffective when given alone) in combination with flupirtine 10 mg/kg (i.p.) caused highly significant anti-nociceptive effects causing complete reversal of hyperalgesia caused by diabetic neuropathy.

The results of present study were comparable to the previous studies as on combining flupirtine with opioid (pentazocine), significantly more analgesia was noticed at all time intervals.

This study demonstrated that flupirtine can be used as an adjuvant to the other standard analgesic drugs or can be used alone as an analgesic.

CONCLUSION

Administration of flupirtine (27mg/kg p.o.) increased the reaction time thereby suggesting its analgesic activity in hot plate model of acute pain.

Its onset of action and duration were similar to that of pentazocine; while the degree of analgesia was significantly less than pentazocine. The efficacy of co-administration of flupirtine with pentazocine was significantly better than the individual drugs, showing the synergistic effect of the two drugs.

In this study, flupirtine was used in single dose. Its mechanism of action and side effects were not assessed. Therefore, more studies are required for the same.

In conclusion, flupirtine - a new analgesic, may be used alone or as an add on analgesic drug to currently available analgesics.

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