A comparative study of Central Analgesic activity of potential Antidepressants

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ABSTRACT

Pain is an ill-defined, disabling accompaniment of many medical conditions. It is often evoked by an external and internal noxious stimulus. It affects millions of people suffering with depression and other psychiatric disorders. Most of the antidepressants are having analgesic capacity to treat the pain by inhibiting nociceptive stimuli by increasing the seratonergic and noradrenergic transmission in CNS.

Objectives: The Present study carried out to investigate the central analgesic activity of potential antidepressants like Fluoxetine, Imipramine, Amitriptyline and to compare the analgesic activity with standard central analgesic Pentazocine.

Methods: Analgesic activity was evaluated by using hot plate and tail immersion models in mice. Fluoxetine (10 mg/kg), Imipramine (20 mg/kg), Amitriptyline(20 mg/kg) were used as test drugs and Pentazocine (10 mg/kg) was used as standard drug.

Results: In tail immersion model of analgesic activity Fluoxetine possess significant analgesic activity (*p<0.05 at 60 min interval, ***p<0.001 at 90 and 120 min interval) Amitriptyline also showed significant analgesic activity (**p<0.01) at 90 min interval and ***p<0.001 at 120 min interval. Imipramine is the least effective analgesic in this study showed mild analgesic activity (*p<0.05 at 90 min interval and **p <0.01 at 120 min interval).

In hot plate analgesic model Fluoxetine and Amitriptyline possess significant analgesic activity (***p<0.001 at 120 min interval), Imipramine same like above said model less effective, doesn't shown significant analgesic activity.

Conclusion: All the test drugs significantly reduce the painful stimuli when compared to the control group in both the models. These results suggest that the antidepressants which increase the monoamine transmission in the brain posse's significant antidepressant activity and might be useful as potent analgesics.

Keywords: Pain, Antidepressant, Hotplate, Tail immersion, Imipramine, Fluoxetine, Amitriptyline

INTRODUCTION

Pain is whatever a person says it is and exists where ever a person says that it exists. There are two main classes of pain: i) integument pain (superficial related to skin, muscle and joint) and visceral pain (deep seated related to heart, stomach, kidney and gall bladder). The physiological pain receptors are free nerve endings which gets sensitised by different nociceptive substances like bradykinin, histamine, interleukins, substance P etc. Analgesics are the drugs which posses significant pain relieving properties by acting in the CNS or on peripheral pain receptors without significantly affecting consciousness.

There are two classes of analgesics

1. NSAIDS (non steroidal anti inflammatory drugs)
2. Narcotic or Central analgesics.

NSAIDS are used for treatment of integumental pain and central analgesics are used for treatment of visceral pain [1].

Adjuvant analgesic drugs like antidepressants also used in treatment of chronic pain. Tricyclic antidepressants such as Imipramine, Amitriptyline and SSRI like Fluoxetine are preferred antidepressants for treatment of neuropathic pain associated with depression and anxiety [2].

The previous studies conducted on animals and human beings for evaluation of analgesic activity of these antidepressants having conflict results. The present study evaluated for analgesic activity and mainly focused on the comparative study of potency

of these antidepressants with reference to Pentazocine [3].

Objectives:

- To evaluate the analgesic activity of Amitriptyline, Imipramine, Fluoxetine.
- To compare the analgesic activity with Pentazocine.

MATERIALS AND METHODS

Selection of drugs and chemicals:

For the purpose of this we selected Amitriptyline, Imipramine, Fluoxetine procured from sigma. Suitable oral formulations made in 0.5% w/v Na-CMC.

Selection of animals:

Healthy male Swiss albino mice (25-30g body weight) used in this study. Animals were procured from National Institute of Nutrition Hyderabad. All the animals are housed in poly propylene cages with proper diet and animals are maintained according to CPCSEA guidelines [4].

Grouping and Randomization of animals:

TABLE 1: EXPERIMENTAL DESIGN

Groups	Treatment	Dose(mg/kg)	Route of administration
Group- I	Control (distilled water)	-------	Oral
Group- II	Fluoxetine	10	Oral
Group- III	Imipramine	20	Oral
Group- IV	Amitriptyline	20	Oral
Group- V	Pentazocine (standard)	10	Oral

30 Male Swiss albino mice (25-30g body weight) were selected randomized according to body weight and divided in to 5 groups each group containing 5 animals.

EXPERIMENTAL PROCEDURE:

The study was conducted on 5 groups of mice separately for hotplate model and tail suspension model. First group served as control just received distilled water. Second (Fluoxeteine), third (Imipramine) and fourth (Amitriptyline) groups are served as test compounds given orally. Fifth group was known as standard group, given Pentazocine orally. Effects of these anti depressants were studied on nociception when compared to the standard central analgesic Pentazocine [5].

Hot Plate Method:

The commercially available Eddy's hot plate consists of an electrically heated surface. It is used for evaluation of central analgesic activity of test compounds. The temperature is controlled at 55-56˚C. The animals are placed on the hotplate and the time until either licking or jumping occurs is recorded by a stop watch. The latency is recorded (in seconds) 0, 30, 60, 90, 120 minutes after drug administration [6], [7].

Tail Immersion Method:

The rodent tail withdrawal reflex can be elicited by immersion of tail in hot water at 55˚C. This test is specific for evaluation of central analgesic activity. Mice were selected and last 2 cm portion of tail was marked. And this part of the tail is immersed in a cup of freshly filed water at exactly 55˚C. The compounds were administered to respective groups through oral route and basal reaction time (tail withdrawal) was recorded 0, 30, 60, 90, 120 minutes after drug administration [6], [7].

Statistical Analysis:

The values obtained are expressed as mean±SEM. The groups were compared by using One way ANOVA followed by dunnets test. Probability (P) value <0.05 taken as the level of significance.

RESULTS AND DISCUSSION

The previous studies conducted on animals and human beings for evaluation of analgesic activity of these antidepressants having conflict results. So in the present study analgesic activity of Imipramine, Fluoxetine, Amitriptyline were evaluated for nociceptive activity and comparative study with Pentazocine by hotplate method and tail immersion method [5], [6], [7].

TABLE 2: BASAL REACTION TIME (TAIL WITHDRAWAL) BY TAIL IMMERSION MODEL

Groups	Treatment	Dose(mg/kg)	Basal Reaction Time in seconds at time (Minutes) mean±SEM			
			0 min	60 min	90 min	120 min
Group I	Control	-------	0.65±0.1	0.55±0.2	0.61±0.1	0.82±0.4
Group II	Fluoxetine	10	0.62±0.20	2.0±0.15*	3.7±0.31***	4.3±0.19***
Group III	Imipramine	20	0.55±0.1	1.1±0.3	2.6±0.17*	2.8±0.50**
Group IV	Amitriptyline	20	0.66±0.6	1.8±0.2	4.3±0.8**	4.6±0.1***
Group V	Pentazocine (standard)	10	0.75±0.2	3.02±0.1***	5.2±0.4***	5.8±0.2***

Each value is the mean ± SEM for 6 rats, * P < 0.05; ** P < 0.01; ***P < 0.001 compared with control. Data were analyzed by using Two-way ANOVA followed by Dunnett's test.

In Tail immersion model of analgesic activity it was shown that Fluoxetine possess significant analgesic activity (*p<0.05 at 60 min interval, ***p <0.001 at 90 and 120 min intervals), Amitriptyline had shown significant analgesic activity (**p<0.01 at 90 min interval and ***p<0.001 at 120 min interval). Imipramine is the mild analgesic agent in this study, showed less significant analgesic activity (*p <0.05 at 90 min interval and **p <0.01 at 120 min interval). The standard drug Pentazocine had shown significant analgesic activity (***p<0.001 at 60, 90 and 120 min interval) [8].

By study with Hot Plate analgesic model it was found that Fluoxetine and Amitriptyline possess significant analgesic activity (***p<0.001 at 120 min interval). Imipramine is the least effective analgesic agent doesn't shown significant analgesic activity. The standard drug Pentazocine had shown significant analgesic activity (*p <0.05 at 90 min interval and ***p<0.001 at 120 min interval).

TABLE 3: BASAL REACTION TIME (PAW LICKING OR JUMPING) BY HOT PLATE MODEL

Groups	Treatment	Dose(mg/kg)	Basal Reaction Time in seconds at time (Minutes)			
			0 min	60 min	90 min	120 min
Group I	Control	-------	3.6±0.8	4.2±1.6	4.5±0.5	3.7±1.5
Group II	Fluoxetine	10	4.02±2.2	7.02±2.2	8.45±2.2	13.35±2.0**
Group III	Imipramine	20	2.25±1.25	4.25±1.5	6.08±3.09	6.76±1.25
Group IV	Amitriptyline	20	3.36±2.2	7.08±1.3	9.25±3.2	12.55±2.0**
Group V	Pentazocine (standard)	10	3.04±1.9	8.02±3.6	10.45±2.2*	15.35±1.0***

Each value is the mean ± SEM for 6 rats, * P < 0.05; ** P < 0.01; ***P < 0.001 compared with control. Data were analyzed by using Two-way ANOVA followed by Dunnett's test.

Above two models tail immersion and hot plate evaluates central analgesic activity of opiods (ex: Pentazocine). Significant analgesic activity of Fluoxetine, Amitriptyline and Imipramine through this methods pointed that above said compounds have central analgesic activity. The comparative analgesic study of these antidepressants with Pentazocine showed that Fluoxetine and Amitriptyline produces significant analgesic activity.
Comparative study by both the models, among these three antidepressants Fluoxetine and Amitriptyline were shown potent central analgesic activity when compared to the Imipramine. [8], [9].
Various literature was described the analgesic activity of antidepressants. The possible mechanism for central analgesic activity of these antidepressants might be due to blockade of serotonin and nor adrenaline transporters and agonistic action μ opiod receptors.

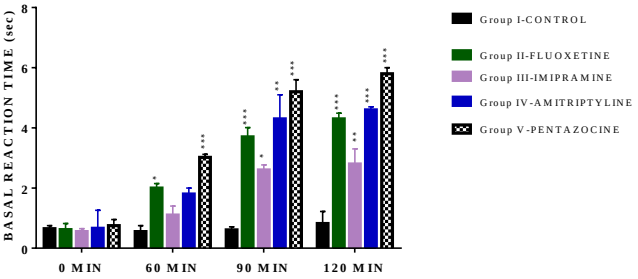

FIGURE 1: COMPARISON OF BASAL REACTION TIME IN TAIL IMMERSION METHOD

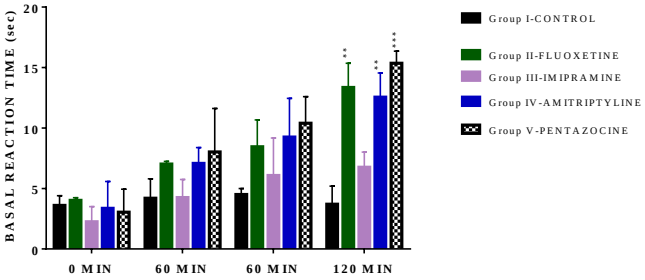

FIGURE 2: COMPARISON OF BASAL REACTION TIME IN HOT PLATE METHOD

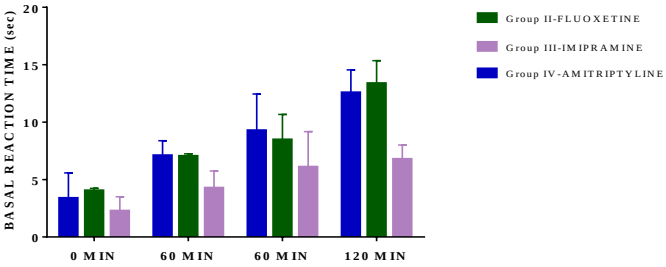

FIGURE 3: COMPARATIVE ANALGESIC ACTIVITY OF DIFFERENT ANTIDEPRESSANTS BY HOT PLATE METHOD

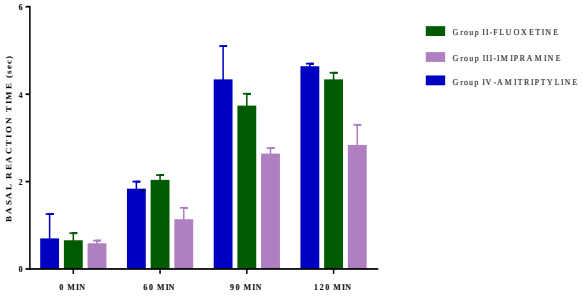

FIGURE 4: COMPARATIVE ANALGESIC ACTIVITY OF DIFFERENT ANTIDEPRESSANTS BY TAIL IMMERSION METHOD

CONCLUSION

Chronic pain in depressed patients is a major condition which can decrease the quality of life. The traditional opiods or central analgesics are preferred for treatment of chronic pain but these drugs have huge high side effect profile. Various literature was described the analgesic activity of antidepressants. So the drugs which are used for treatment of depression (antidepressants) are investigated for central analgesic activity.

Fluoxetine is an SSRI most common prescribed antidepressant posse's analgesic activity by blocking the serotonin transporters. Imipramine and amitriptyline are the tricyclic antidepressants (TCA) increase the monoamine transmission in the brain and agonistic activity on the opiod receptors.

In both the models these antidepressants showed significant analgesic activity which might be useful for treatment of chronic pain in depressed patients with fewer side effects.

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