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RESEARCH ARTICLE

COMPARISON OF ANALGESIC ACTIVITY OF TRICYCLIC ANTIDEPRESSANTS AND SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN MICE

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ABSTRACT:

Objectives: Depression is frequently found in patients with chronic pain syndrome. It has also been noted that some depressed patients suffer from various types of pain. From studies it has been found that variations in brain serotonin level as common pathogenesis for both depression and chronic pain syndrome. So we proposed to study analgesic activity of some tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) in mice.

Design & Interventions: Healthy albino mice are grouped as healthy control (Normal saline, Gum acasia), TCA(Nortriptyline, Amitriptyline), SSRI (Fluoxetine, Sertraline), Standard (Acetyl salicylic acid) and test carried are physical method(tail pinch),chemical method(writhing),thermal method (radiant heat).All drugs are administered by oral route half hour before test .

Outcome Measures & Results: Results are analyzed by using student's `t` test. In our study TCA showed higher control over pain ($p<0.001$) than SSRI (0.02). Amitriptyline showed higher analgesia ($p<0.001$) than other drugs. Nortriptyline showed less control ($p<0.01$) over pain than amitriptyline. SSRI showed significant control of pain by radiant heat and tail pinch methods ($p<0.02$). Fluoxetine ($P<0.001$) has higher control over pain than Sertaline ($p<0.05$).

Conclusion: From our observations, we conclude that higher analgesia is produced by tricyclic antidepressants (amitriptyline, nortiptyline) than selective serotonin reuptake inhibitors (fluoxetine, sertaline).

Key Words: Analgesia, Tricyclic antidepressants, Selective serotonin reuptake inhibitors

INTRODUCTION:

Depression is frequently found in patients with a chronic pain syndrome and interestingly, it has also been noted that some depressed patients also suffer from various types of pain.[1] The strict correlation between these two problems has led to the opinion that there might be a common pathogenesis. Sternbac et al[2] discussed the variations in brain serotonin level as the common pathogenesis for both depression and chronic pain syndrome. Sternbac[2] maintains that chronic pain ,changes the brain neurotransmitter levels and especially reduces the level of serotonin in the dorsal raphe nucleus.This view is supported by the facts that the pain aggrevates as it becomes chronic and that it is frequently followed by depression and this circle can be broken by antidepressants that affect the serotonergic system.

Till now no antidepressants have been prescribed for chronic pain syndromes with successful results. The analgesic effect of Tricyclic antidepressants is also seen in patients suffering from different types of pain syndromes without accompanying depression.[3]

Serotonin uptake inhibitors is a new class of antidepressants introduced in 1970's.They have less side effect profile than Tricyclic antidepressants like cardiac effects and anticholinergic effects.[4,5] Hence they are preferred as antidepressants.

So we proposed to study the analgesic effects of tricyclic antidepressants and selective serotonin reuptake inhibitors and compare that with standard analgesic drug.

MATERIAL AND METHODS:

Albino mice of either sex weighing 20-30 Gms. are made available from animal house of Government medical college. Animals are kept on standard diet and housing condition.

A dis-coordination test, to test intact CNS activity, is carried out to exclude the possibilities of false positive results. In which animals are placed on a slow rotating drum covered with a wire mesh. The animals that fall off are considered as discoordinated.

For evaluation of analgesic activity following three different methods are used.

1. Radiant heat method (Thermal method):

The method of `D` Amour & Brooke[6] as modified by Bass and Sander Brooke is used. Pain is produced by using radiant heat from the wire (heated electrically) in an apparatus called analgesiometer . The animal is kept in holders and the tail is kept on the platform provided .A constant current is passed to heat the wire and the time for tail flick response is noted . For this study mice are selected, who show tail flick response within 10 seconds. Drugs are administered half an hour before the actual test.

2. Tail pinch method (physical method):

The method of Bianchi and Franceschini[7] is used .Pain is produced by mechanical pressure on the tail by pinch cork, the tips of which are covered with rubber tubing. They are applied 2 cm away from the base of tail .The mice making an attempt to remove the forceps within 20 seconds are selected .Drugs were administered half an hour before actual test. Reaction time for onset of efforts to remove the pinch is noted.

3. Writhing test (chemical method):

The method of Seigmund et al[8] is used .Pain is produced by injecting 0.6% of acetic acid intraperitoneally in mice. This produces a series of contractions that travels along the abdominal wall. Someimes this is accompanied by turning movements of body and extension of hind limbs. There is extension of back with abdomen touching the surface. This response is known as writhing.

After half an hour of administration of drugs , 0.2 ml of 0.6% acetic acid was injected intraperitoneally. In this study protection from writhing was observed.

Drugs like tricyclic antidepressants (Nortriptyline and Amitriptyline),Selective serotonin reuptake inhibitors (Fluoxetine and Sertaline) and standard analgesic (Acetyl salicylic acid) are obtained in pure powder form from manufacturer.

Drug	Dose for 20 gm mouse (mg)	Vehicle
Amitriptyline	0.39	Normal saline
Nortriptyline	0.26	Normal saline
Fluoxetine	0.15	Gum Acasia
Sertaline	0.26	Gum Acasia
Acetyl salicylic acid	0.78	Gum Acasia

All drugs are administered 30 minutes before test by oral route.

Statistics:

Paired 't' test was used to analyze results of tail flick & tail pinch methods while unpaired 't' test was used to analyze results of writhing test. $P < 0.05$ was taken to be significant.

RESULTS:

Table 1: Analgesic activity by radiant heat method

Name of drug	Mean reaction time (sec.)before treatment	Mean reaction time (sec.)after treatment	Probability by student paired `t` test
Amitriptyline	8.4 ± 0.45	14.1 ± 0.91	P<0.001
Nortriptyline	7.6 ± 0.65	9.3 ± 0.92	P<0.05
Fluoxetine	7.4 ± 0.89	11.5 ± 1.38	P<0.02
Sertaline	8.0 ± 0.50	11.2 ± 0.62	P<0.05
Acetyl salicylic acid	7.1 ± 0.52	13.7 ± 1.08	P<0.001

[Values are expressed as mean ± SEM]

Table 2: Analgesic activity by tail pinch method

Name of drug	Mean reaction time (sec.)before treatment	Mean reaction time (sec.)after treatment	Probability by student paired `t` test
Amitriptyline	7.2 ± 0.95	11.4 ± 0.76	P<0.001
Nortriptyline	14.9 ± 1.48	17.8 ± 1.79	P<0.01
Fluoxetine	5.0 ± 0.53	8.6 ± 0.63	P<0.02
Sertaline	5.8 ± 0.46	9.2 ± 0.48	P<0.05
Acetyl salicylic acid	7.7 ±0.61	14.4 ±1.03	P<0.001

[Values are expressed as mean ± SEM]

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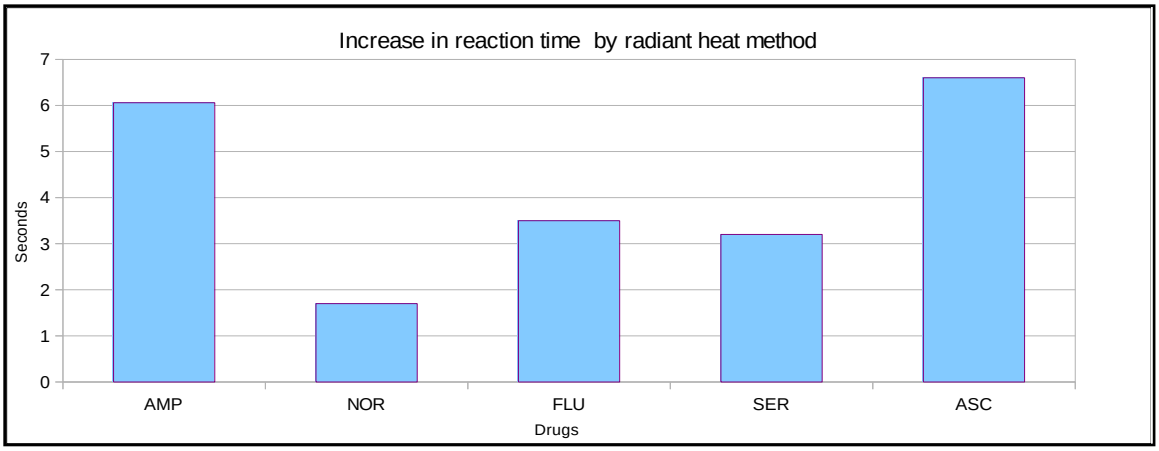
Table No. 3: Analgesic activity by writhing method

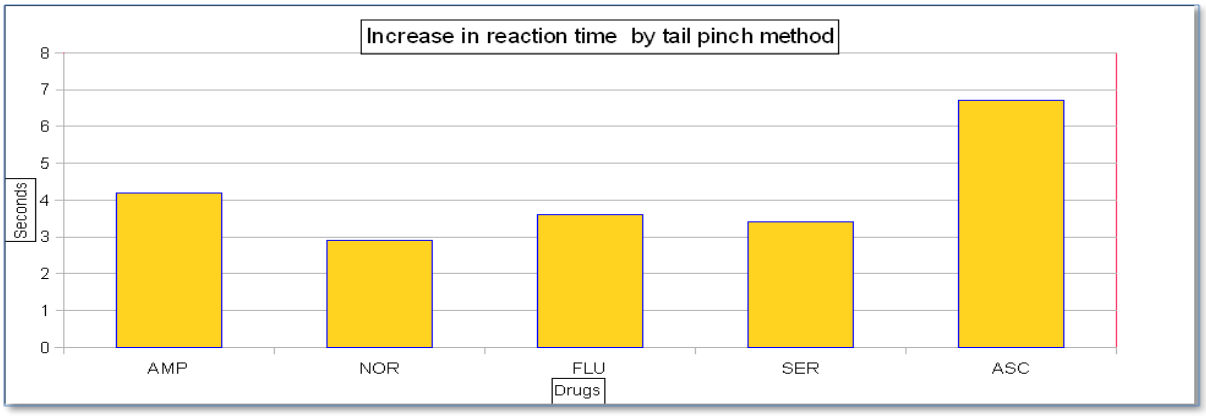
Name of the drug	Control group		Test group		Probability by student unpaired `t` test
	Mean onset (min.)	Mean No. of writhes in 5 min.	Mean onset (min.)	Mean No. of writhes in 5 min.	
Amitriptyline	5.0 ± 0.57	13.3 ± 0.81	9.7±1.43	18.0 ±1.18	P<0.001
Nortriptyline	7.8 ± 0.57	22.3 ± 1.08	9.1 ± 0.58	22.3 ± 1.12	p>0.05
Fluoxetine	7.5 ± 0.86	19.1 ± 1.94	7.2 ± 0.82	21.5 ± 1.62	p>0.05
Sertaline	7.4 ± 0.76	20.2 ± 0.96	5.0 ± 0.59	19.6 ± 0.88	P>0.05
Acetyl salicylic acid	5.1 ± 0.3	20.9 ± 1.30	10.7 ±0.66	10.5 ± 0.50	P<0.0001

[Values are expressed as mean ± SEM]

Graph 1: Increase in reaction time by radiant heat method



Graph 2: Increase in reaction time by tail pinch method



AMP- Amitriptyline, NOR-Nortriptyline, FLU-Fluoxetine, SER-Sertaline, ASC-acetyl salicylic acid

DISCUSSION:

Although antidepressants are imperfect analgesics because of limited efficacy and untoward effects , they may be the only avenue of relief for a painful condition .[9]

Chronic nonmalignant pain is often characterized by multiple treatment failures , a pattern of maladaptive behavior and depression . Narcotic analgesics, NSAIDS and Tricyclic antidepressants are commonly employed in patients with chronic pain.[10]

In our present study Amitriptyline showed higher analgesia (p<0.001) than other drugs in all three methods.This is comparable to standard drug , Acetyl salicylic acid (p<0.001) in radiant heat method and tail pinch method. Only Amitriptyline showed control of pain in writhing method significantly in comparison to standard drug.

Nortriptyline showed lower control of pain(p<0.05) than other drugs in radiant heat method and tail pinch method .

Fluoxetine showed significant analgesia in radiant heat method (p<0.01)and tail pinch method(p<0.02).This is higher than Sertaline (P<0.05) in both methods.

From previous studies on long term use of Amitriptyline it was found that analgesic effect was blocked by PCPA

(serotonin synthesis inhibitor).confirming role of serotonin in Tricyclic antidepressant analgesia.[11]

Serotonin is involved in the descending system (brain to spinal cord) that inhibits signals from peripheral nociceptors.[12] Further electrical stimulation of nucleus raphe magnus[13], brain stem area and transcranial electro-stimulation confirms role of serotonergic pathway in pain control.[14]

So in present study, we compared analgesic activity of Selective serotonin reuptake inhibitors with tricyclic antidepressants. And we found that Amitriptyline having higher analgesia because of it's action on both amines serotonin and norepinephrine .Nortriptyline showed less analgesia because of it's action only on norepinephrine .Fluoxetine and Sertaline showed significant analgesic activity which confirms role of serotonin in analgesia.

In this study selective serotonin reuptake inhibitors (like fluoxetine, sertaline) showed significant but less analgesic activity than tricyclic antidepressants. But as they have better efficacy and better tolerability(no anticholinergic and cardiac side effect), for various painful conditions with depression component like cancer pain , diabetic neuropathy, herpetic neuralgia, tension headache, migraine SSRI can be preferred over the tricyclic agents.[15,16,17]

CONCLUSION:

From our observations we can conclude that higher analgesia is produed by Amitriptyline but Selective serotonin reuptake inhibitors (Fluoxetine and Sertaline) also have significant analgesic activity.

Considering their better efficacy & tolerability, further studies are needed to establish the role of SSRI`S as clinically useful analgesics.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional animal ethical committee.

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