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Antinociceptive Evaluation of Antidepressants (Citalopram, Duloxetine and Amitriptyline) in a Mouse Model of Acute Pain

[1]Sidra Shah, [2]Mudassara Saqib, [3]Azka Khan

ABSTRACT

Introduction: Acute pain is a pervasive and debilitating symptom affecting the general population as well as depressed patients who suffer even more from pain and fatigue.
Aims and Objectives: To evaluate the antinociceptive effect induced by antidepressants (Citalopram, Duloxetine and Amitriptyline) in acute pain induced in mice.
Place and Duration of study: Animal Research Laboratory of University of Lahore. Study Period: 2018- 2019
Material and Methods: An experimental animal study was carried out on 25 albino mice. The mice were divided into 5 groups; Group 1: Positive Control (PC), Group 2: Ibuprofen (IBO) (Standard) 80mg/kg, Group3: Citalopram (CTP)3mg/kg, Group 4: Duloxetine (DXT) 25mg/kg, Group 5: Amitriptyline (AMT) 15mg/kg. Groups 2-5 were administered drugs orally through a feeding tube as per group designation while Group 1: Control was given an equivalent amount of normal saline. One hour post treatment with test drugs, all Groups (1-5) were injected 10 ml/ kg of 2% acetic acid I/P and number of writhing movements consisting of contraction of abdominal muscles leading to extension of hind limb and periodic arching of body as well as paw licking behavior were counted for 20 minutes at 5-minute interval, using hand tally counter. Degree of analgesia was calculated by using formula of percentage effectiveness. Data was entered and analyzed utilizing SPSS version 21, $p \leq 0.05$ was taken as significant.
Results: Ibuprofen completely eliminated the nociceptive outcome of diluted acetic acid in writhing and licking of experimental animals. Citalopram, showed maximum decreasing effect (95%-96%) in writhing in 5-20 min. However, its effect in paw licking was low. Duloxetine showed 70% to 90% decrease in writhing at 5-20 min whereas 100 % inhibition of paw-licking was observed at 5 to 20 minutes. The writhing effect of amitriptyline was 77%-90% at 5-20 min and paw licking effect was 80-90 % at 5-20 min.
Conclusion: Amitriptyline, duloxetine and citalopram have significant effect in reducing the acute nociceptive pain and may be utilized as analgesic in acute state of pain.

Key Words: Antidepressant drugs, antinociceptive effect, mice

INTRODUCTION

Acute pain is a sudden short-lived response of body to an injury or medical condition. Pain is an enormous global health problem affecting general public as well as depressed patients. More than 75% of depressed patients suffer from painful symptoms with increasing severity and a less favorable outcome of depression. Studies proposed the role of neurotransmitters and neuronal pathways in pain and depression. The ascending serotonergic and noradrenergic pathways control a number of psychological activities that may enhance chronic pain and depression. Conversely, the descending pathways are involved in inhibition of nociception. This gives rationale for the utilization of re-uptake inhibitors (serotonin or norepinephrine), in relieving the pain. Antidepressants like Citalopram, Duloxetine and Amitriptyline may be used in the treatment of painful signs with depression[1,2,3]. Studies demonstrate that depression and pain are highly entwined and may aggravate physical & psychological symptoms. It is known that norepinephrine and serotonergic antidepressants are commonly used to alleviate pain. Literature shows that pain & depression impact each other and have an important role in the progression and continuation of some other chronic signs and symptoms. Antidepressants persistently play an important role in managing acute/chronic pain[4]. Studies on brain imaging found that different parts

[1]*Department of Pharmacy, Continental Medical College, Lahore.*
[2]*Department of Pharmacology and Therapeutics, Shaikh Zayed Medical Complex, Lahore.*
[3]*Department of Pharmacology, Rashid Latif Khan University & Medical College, Lahore.*

Correspondence:
Sidra Shah, *Head of Department, Continental Medical College, Lahore.*
E-mail: sidrashah_86@yahoo.com

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of the brain take part in the process of independent painful, sensory, affective, motor, cognitive, and inhibitory actions. This comes close to, the neuromatrix theory of pain which proposes that perception of pain uses a nociceptive process and that pain is due to the activation of neural network and rapid generation of neuroplastic problems[5]. Citalopram is known to have antidepressant characteristics with minor side effects. Experimental studies in animals proved its analgesic effects. However, it is controversial in human studies. Many studies showed significant effect of Selective Serotonin Reuptake Inhibitors (SSRI) including citalopram, escitalopram etc. and may be the good SSRI[6]. Amitriptyline is tri-cyclic antidepressant (TCA) drug and blocks the reuptake of both norepinephrine and serotonin neurotransmitters. Amitriptyline is more numbing and has more anticholinergic activities than other classes of TCAs. The drug is used to treat chronic pain syndrome, insomnia and anxiety. The most known side effects of Amitriptyline include increased body weight, gastrointestinal issues like constipation, headache, dizziness, and somnolence. The clinical signs and symptoms of Amitriptyline toxicity are neurological, cardiac, and anticholinergic reactions. Due to such side effects, it is not used as a first-line drug to treat depression[7,8].

Duloxetine is a balanced serotonin and noradrenaline reuptake inhibitor used to treat anxiety, depression, nerve pain and fibromyalgia. Additionally, duloxetine affects the brain, management of acute and postoperative pain. The efficacy of the drug is mainly due to its modulating effect on the descending inhibitory pain pathways and the perpetuation of the nociceptive effect. Duloxetine's binding capacity to the human serotonin and norepinephrine transporters shows a 100 times greater potency as compared with another SNRI, Venlafaxine. Its side effects are headache, dry mouth, and dizziness (similar to other antidepressants, but less common). Three risks found with the use of duloxetine are hepatic, suicidal issues and bleeding problems [9, 10].

Constant utilization of non-steroidal anti-inflammatory medicines &opioids are related with inflamed gastric mucosa and medicine reliance. Recent studies on use of antidepressants for acute pain relief are unavailable while, most studies provide data on antidepressants utilization in chronic pain [4]. So, there is a need to investigate use of antidepressants in acute pain in the experimental model first. The purpose of our study was to find the antinociceptive effect induced by antidepressants (Citalopram, Duloxetine and Amitriptyline) in the treatment of acute pain in group of mice.

MATERIAL AND METHODS

This experimental work was carried out with prior approval by Institutional Review Board number vide 53/IRB/CMC Dated:09/01/2024. Male albino mice weighing 20-30 gm. were taken from animal dwelling of The University of Lahore. Duration of study was one year (2018-2019). Animals were kept at 22±20 ºC and humidity maintained both day & night. Foodstuff was given ad libitum. Animals were kept on fast 12 hours prior to experimentation.

Animals:

Mice were divided into five groups (n= 5) each. Group 1: Positive Control (PC), Group 2: Ibuprofen (IBO) (standard), Group 3: Citalopram (CTP), Group 4: Duloxetine (DXT) & Group5: Amitriptyline (AMT)

Chemicals & Drugs:

Sodium Chloride& acetic acid were purchased from Sigma Company. Ibuprofen (IBO), Amitriptyline (AMT) & Citalopram (CTP), were provided by Unison Chemical, Lahore. Duloxetine (DLX) was obtained from Laboratories of High Noon, Lahore.

Acute Pain Model: Acetic Acid Induced Writhing and Paw licking Test:

Mice were divided into 5 groups (five mice/ group); Group no: 1 was maintained as Positive Control group on normal saline while groups 2-5 were given oral drugs prepared in normal saline and administered through a feeding tube as follows: Group no 2(Standard): IBO with dose of 80mg/kg, Group no 3: CTP with dose of 3mg/kg, Group no 4: DXT with a dose of 25mg/kg, Group no 5: AMT with dose of 15mg/kg. One hour post oral treatment, all Groups 1-5 were injected 10 ml/ kg of 2% acetic acid I/P. Number of writhing movements consisting of contraction of abdominal muscles leading to extension of hind limb and periodic arching of body as well as paw licking behavior were counted for 20 minutes at 5-minute interval, using hand tally counter. Degree of analgesia was calculated by using formula of %age effectiveness[11].

% Effectiveness = (Number of writhes in positive control group – Number of writhes in treated group /Number of writhes in control) × 100

Statistical Analysis:

Data was entered and calculated by SPSS version 21. Data was expressed as variable mean and Standard error mean. ANOVA (one-way) was applied to find the probability of significance between the groups. The value of $p \leq 0.05$ was taken as significant.

RESULTS

The antinociceptive effect of Citalopram, Duloxetine and Amitriptyline antidepressants on acetic acid induced writhing / paw-licking actions over a 5–20-minute period are shown in Table-1. It was observed that IBO (80 mg/kg) eliminated (100%) the nociceptive outcomes of diluted acetic acid in writhing & licking problem. The drug CTP (3mg/kg), showed highest reducing effect (96%-94 %), in writhing in 5-20 min. However, its effect in paw licking was low (57%-78%) in 5-20 min. DXT with dose of 25mg/kg showed 90%-70% decrease in writhing at 5-20 min whereas (50% to 100 %) decrease of paw-licking was observed at 5 - 20 min. The writhing effect of AMT (15 mg/kg) was 77%-90 % in 5-20 min and paw licking effect was 80%-90 % in 5-20 min.

Groups	Writhing/ Twitching		Paw Licking		P value
	5-10 (minutes)	15-20 (minutes)	5-10 (minutes)	15-20 (minutes)	
Positive Control group	5.34 ± 0.89	7.1 ± 0.87	5.24 ± 0.87	7.10 ± 0.88	-
IBO group (80 mg/kg)	0 ± 0 (100 %)	0 ± 0 (100 %)	0 ± 0 (100 %)	0 ± 0 (100%)	-
CTP group (3 mg/kg)	0.21 ± 0.21* (96.17 %)	0.40 ± 0.25* (94.45%)	2.21 ± 0.20* (57.71%)	1.60 ± 0.61* (77.79 %)	<0.05
DXT group (25mg/kg)	0.41 ± 0.40 (92.30%)	2.0 ± 0.54* (72.21%)	2.61 ± 1.9 (50.01%)	0 ± 0 (100 %)	<0.05
AMT (15 mg/kg)	1.21 ± 0.71* (76.91%)	0.81 ± 0.30* (88.90 %)	1.0 ± 0.71* (80.78 %)	0.21 ± 0.21* (97.21 %)	<0.05

Table-1: Outcome of Antidepressant Drugs' on Acetic Acid induced Paw-Licking /Writhing actions in Group of Mice

Data was showed as Mean ± SEM, No = 05. * $P \leq 0.05$, in comparison with the values of controls. Values of % age effectiveness is given in parentheses. (Ibuprofen IBO, Citalopram CTP, Duloxetine DXT, Amitriptyline AMT)

DISCUSSION

Acute pain relief is aimed at treating the underlying cause and interrupting the nociceptive signals. Present study was carried out on acute pain relief while most of the studies were carried out on chronic pain. The writhing effect of AMT (15 mg/kg) was 77%-90 % in 5-20 min and paw licking effect was 80-90 % in 5-20 min. Number of studies were carried out to find the pain-relieving effect of anti-depressant drugs. It is in accordance with a study in which oral administration of antidepressant ammoxetine (0.625-10 mg/kg) have showed decrease in writhing and paw licking of mice in dose-dependent manner. Ammoxetine has effectively relieved continuous pain related to inflammation and even pain due to neuropathy and fibromyalgia in animal models, which is caused by enhanced neurotransmission of 5-HT and NE in the descending inhibitory systems[12].Same is with duloxetine which exhibit simultaneous noradrenergic/sero-tonergic neuro-transmitter outcomes. Due to these effects, its role in pain management is assumed. It is believed that dysregulation of neurotransmitter scheme is common to mediation of pain and depression[13]. In another study citalopram which is serotonergic inhibitors found to be more effective in the hot-plate test than in the writhing test[14] ,while in our study , The drug citalopram showed highest reducing effect (96%-94 %), in writhing in 5-20 min although its effect in Paw licking is low (57%-78%) in 5-20 min.

Amitriptyline cream or gel as Local application was proved to be an effective method of drug delivery in conditions with inflammatory pain in mice . It was found that amitriptyline can produce a local peripheral antinociceptive action most probably mediated by interacting with endogenous adenosine leading to inhibition of the cellular uptake of adenosine on sensory nerve terminals.[15]

Our findings were that Duloxetine (DXT) with dose of 25mg/kg showed 90%-70% decrease of writhing at 5-20 min whereas a decrease of (50% to 100 %) of paw-licking was observed at 20 min.

Experimental studies found that noradrenaline is very important for treating pain. High levels of noradrenaline in the spinal cord directly block pain via alpha 2 adrenergic inhibitor. Additionally, noradrenaline improves the function of impaired noradrenergic inhibitory scheme. Serotonin along with dopamine may strengthen the noradrenergic outcomes to block neuropathic pain[2,] Antidepressants due to inhibition of serotonin and norepinephrine reuptake in presynaptic terminals leads to increase in concentration of these neurotransmitters in the synaptic cleft and improvement in pain. In our study, acetic acid is used which is causing acute pain[16] due to synthesis of pain mediators and antinociceptive effects of antidepressant drugs are seen while other studies are carried out in chronic pain conditions. The authors declare no conflict of interest.

CONCLUSION

Amitriptyline, duloxetine and citalopram own significant ability to produce acute analgesic effect in nociceptive arc/ pain, and possibly utilized to relieve acute pain. However there is a need of multi-centric pre clinical and clinical trials in populations that possibly reveal the superiority of either drug.

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The Authors:

Sidra Shah,
Head of Department (HOD),
Department of Pharmacy,
Continental Medical College, Lahore.

Dr. Mudassara Saqib,
Associate Professor,
Department of Pharmacology and Therapeutics, Shaikh Zayed Medical Complex, Lahore.

Dr. Azka Khan,
Assistant Professor,
Department of Pharmacology,
Rashid Latif Khan University & Medical College, Lahore.

Authorship:

SS: Designed, Performed Experiment
MS: Manuscript Writing
AK: Statistics & Proof Reading