

Evaluation of central and peripheral analgesic activity of amitriptyline in mice

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Received: 03 May 2019

Accepted: 31 May 2019

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ABSTRACT

Background: Pain is one of the most frequent reasons for visiting a doctor. Large-scale studies in Western countries have shown that a fifth of the adult population suffer from chronic pain. Treatment of pain, still a major problem in clinical practice. Despite several available analgesics, unrelieved pain remains a major health care issue. Amitriptyline is a tricyclic antidepressant drug, which is regarded as adjuvant analgesic. There is a common consensus among the researchers on analgesic effect of amitriptyline which is mediated by central pathway but for the peripheral mechanism no conclusive evidence exists till now.

Methods: To establish the analgesic mechanism of amitriptyline we tried to evaluate the analgesic activity on different mice models for central (Radiant heat tail flick test and Haffner's tail clip method) and peripheral analgesia (Writhing test). We also compare the effects of amitriptyline with standard drugs for central and peripheral analgesia.

Results: Both in Radiant heat tail flick test and Haffner's tail clip method we found that the amitriptyline showed significant ($p < 0.05$ to $p < 0.001$) activity as compared to control and diclofenac group. But in comparison to pentazocin group amitriptyline didn't show significant difference in the reaction time. In acetic acid induced writhing test amitriptyline group mice showed 41.09% reduction in number of writhes as compared to control group. While the standard control (Diclofenac) showed reduction of 65.17% as compared to control. So, amitriptyline showed comparable efficacy towards reduction in number of writhes with that of diclofenac.

Conclusions: The results revealed that amitriptyline has significant analgesic activity which is mediated by modulation of both the central and peripheral pathways.

Keywords: Amitriptyline, Analgesic activity, Central and peripheral pain mechanism

INTRODUCTION

In Greek word, pain means penalty. Plato said that pain arises from within the body and indicating that pain is more of an emotional experience. Task force on taxonomy

of the International Association for the Study of Pain defined pain as "any unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".¹ In recent times the concept of pain has evolved from one

dimensional to a multi-dimensional entity involving sensory, cognitive, motivational and affective qualities. Pain is a symptom of many diseases requiring treatment with analgesics. Pain is always subjective, and every individual use this word through their previous experience related to the injury. Pain is one of the most frequent reasons for visiting a doctor. About 9 out of 10 Americans regularly suffer from pain and pain is the most common reason for individuals seeking health care.^{2,3} Large-scale studies in Western countries have shown that a fifth of the adult population suffer from chronic pain. The treatment of pain, a major problem in practice because, it is a subjective sensation which cannot be measured objectively, and its intensity is not always a direct reflection of the nociceptive inputs provoking it. Despite several available analgesics, unrelieved pain remains a major health care issue. A study revealed that in USA the annual cost for medical treatment and lost productivity due to pain is 635 billion US dollar (Committee on Advancing Pain Research, 2011).^{1,4} Globally, it has been estimated that 1 in 5 adults suffer from pain and that another 1 in 10 adults are diagnosed with chronic pain each year.⁵

Treatments for pain can be broadly categorized as pharmacological and non-pharmacological. Still pharmacologic treatment is the mainstay of pain therapy. The pharmacological treatment is broadly categorized into non-opioid analgesics, opioid analgesics and adjuvant analgesics or co-analgesics.^{4,5} Despite several available analgesics, unrelieved pain remains a major health care issue. In 1986, World Health Organization (WHO) developed and introduced guidelines for pain management, called the WHO scheme or three-stage analgesic ladder. It has become the global standard for analgesic care.⁶ Amitriptyline is regarded as adjuvant analgesic while diclofenac is non-opioid analgesic.

Amitriptyline is a tricyclic antidepressant drug. Clinical evidences are growing about antidepressants are being frequently prescribed for conditions or health problems outside the field of psychiatry which include pain, dependence, other neurological conditions, gastroenterological conditions and urological conditions.^{7,8} There is a common consensus on analgesic effect of amitriptyline which is independent of its antidepressant effect. It may have beneficial effect in migraine, tension-type headaches, painful polyneuropathy, painful diabetic neuropathy, HIV- related neuropathies, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, non-specific low back pain and fibromyalgia.⁹⁻
¹¹ Diclofenac is a non-steroidal anti-inflammatory agent which has analgesic, antipyretic and anti-inflammatory activities. Its potency for cyclo-oxygenase-2 (COX-2) inhibition is substantially greater than that of Indomethacin, naproxen and several other NSAIDs. It is very useful in short-term management of postoperative pain, acute musculoskeletal pain and dysmenorrhea.¹² Pentazocine is a potent analgesic having agonist-antagonist action at opioid receptors. It has potent agonistic action on κ -receptor and weak antagonistic

action on μ -receptor. Analgesic activity is mediated by κ -agonistic action. It has half analgesic activity and shorter duration of action as compared to morphine.¹³ On the basis of above background, we tried to find out analgesic activity of amitriptyline and its probable mechanism.

METHODS

Study protocol was approved by Institutional Animal Ethical Committee (IAEC), NIMS University, Jaipur (India) on 13/09/2014 (Ref. number-NIMSUR/IAEC/CERT/2014/09/07). All animal experiments were carried out as per the rules and regulations of IAEC and CPCSEA under the "Guidelines for Care and Use of Animals in Scientific Research" (INSA 1992 and 2000). The study was conducted in the Department of Pharmacology, NIMS Medical College, NIMS University, Jaipur, India.

Chemicals and drugs

All chemicals and drugs used were of analytical grade. Acetic acid of 0.6% strength purchased from CDH laboratories, Delhi. Amitriptyline and pentazocine were purchased from a local pharmacy store. All the Amitriptyline tablets used in experiments were of same batch number similar precaution taken for diclofenac and pentazocine injections also.

Animals

The study was carried out on swiss albino mice of either sex obtained from institute's animal house, as they are easy to maintain in the laboratory conditions, much easier to handle and relatively sensitive analgesic model. Total 24 adult swiss albino mice of 3-4 months age (20-30g) were used, which were divided into three groups each containing 6 mice. Mice were placed in polypropylene cage under standard laboratory conditions and fed on standard pellet diet and water ad libitum. Each cage contained 3 mice and was appropriately labeled. In each cage the animals were identified by appropriate markings. The floor of the cages was stack with grain husk which were replaced every second day. The animals were inspected frequently to rule out any infection.

Study design

The mice were randomly divided into 4 groups (G1, G2, G3 and G4) each containing 6 mice.

- G1: Vehicle control group- received distilled water
- G2: Standard control group- received Diclofenac (10mg/kg intraperitoneally single dose)¹⁴
- G3: Standard control group- received pentazocine (10mg/kg intraperitoneally single dose)¹⁵
- G4: Test group- received Amitriptyline (10mg/kg orally single dose)^{16,17}

Evaluation of analgesic effect

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

- Radiant heat tail flick method (Thermal method)
- Haffner's tail clip method (Physical method)
- Writhing test (Chemical method)

All the mice in the groups were undergone through above all evaluation methods. First radiant heat tail flick method was performed followed by Haffner's tail clip method and lastly writhing test. After each test there was a wash out period of one week followed by the next method for evaluation of analgesic activity.

Radiant heat tail flick method¹⁸⁻²¹

This method is used for evaluation of central analgesics. An analgesiometer was used for this purpose, which has nichrome wire as source of radiant heat. The wire heated when current of 5 ampere passed and temperature was kept constant at 52±0.5°C. The distance between the heating source and the tail was kept around 1.5 cm and cut-off reaction time was fixed at 15 sec to prevent the tail injury. For the assessment of tail flick response mice were kept in cylindrical holder in such way that its tail came out through the cut hole in the shutter at the rear end of the holder. An initial reading before drug administration at 0 minute was taken then, drug was administered. Next readings were taken at 30 minutes, 60 minutes and 90 minutes after drug administration.

Haffner's tail clip method^{17,21,22}

This test is used for evaluation of central analgesics. Pain was produced by mechanical pressure on the tail by artery clip, the tips of which was covered with rubber tubing to avoid damage. The clip was applied around 1 cm away from the base of tail. The mice quickly responded to noxious stimuli by biting the clip or the tail near the location of the clip. The time between application of clip and response is measured by a stopwatch. Cut off time was kept 15 seconds. Readings were noted before the drug

administration at 0 minute and after drug administration at 30 minutes, 60 minutes and 90 minutes.

Writhing test^{14,17,21,23}

It is an acute pain animal model in which writhes are produced by 0.6% acetic acid. Writhes are series of contractions that travels along the abdominal wall sometimes accompanied by turning movements of body, extension of back and hind limbs. Drugs were administered 30 minutes before the administration of 0.6% acetic acid. 0.6% acetic acid was administered intraperitoneally at a dose of 10 ml/kg body weight. Then the mice were placed in a transparent glass cage. After 5 minutes, total numbers of writhes were counted for 20 minutes and expressed as percent protection. The percentage protection against acetic acid was calculated using the following formula

$$\% \text{ protection} = \frac{(N_c - N_t)}{N_c} \times 100$$

Where N_c- Number of writhes in control group,

N_t- Number of writhes in test group.

Statistical analysis

Results were presented as mean±SEM. Data were analyzed by using one-way ANOVA followed by Bonferroni post-hoc test for multiple comparisons between the groups. P-value <0.05 was considered significant.

RESULTS

In radiant heat tail flick method it was found that the reaction time was increased in all groups after drug treatment as compared to pre-treatment values except in control group. Further, the rats treated with amitriptyline showed a significant increase in reaction time at 0 min (p<0.05), 60 and 90 minutes (p<0.001) as compared to control group. When it was compared with the diclofenac group it showed significant (p<0.001) increase in reaction time at 60 and 90 minutes.

Table 1: Effect of amitriptyline on radiant heat tail flick reaction time.

Groups (n=6)	Tail flick reaction time (Seconds)			
	Pre-treatment values at 0 minute	Post-treatment values		
		At 30 minutes	At 60 minutes	At 90 minutes
G1 (Control)	3.98±0.43	4.33±0.21	4.17±0.31	4.00±0.51
G2 (Diclofenac)	4.20±0.30	6.73±0.33*	7.23±0.13*	8.00±0.36**
G3 (Pentazocin)	4.07±0.31	8.82±0.22**	12.17±0.17**	11.67±0.12**
G4 (Amitriptyline)	3.93±0.35	7.17±0.30*	11.33±0.33**##	10.11±0.34**##

Values were expressed as Mean±SEM. p<0.05- significant *indicates p<0.05, ** indicates p<0.001 when compared to the control group. # indicates p<0.05, ## p<0.001 when compared to the Diclofenac group. \$ indicates p<0.05 when compared with the Pentazocin group.

But the test group didn't make a significant difference in reaction time at any time interval as compared to pentazocin group instead of that the values were almost comparable to pentazocin group. (Table 1).

Analgesic activity evaluation by Haffner's tail clip method showed that there is no significant change in reaction time in control group after administration of distilled water while in other groups there was increase in reaction time post-treatment. In all the groups there were significant

increase in reaction time at all time intervals after respective drug administration as compared to control group ($p < 0.05$).

In the amitriptyline group there was a significant increase in reaction time at 90 minutes as compared to diclofenac group ($p < 0.05$). Albeit, there were no significant difference in the reaction time in amitriptyline group as compared to pentazocin group but the reaction time values were almost comparable. (Table 2).

Table 2: Effect of amitriptyline on tail clip reaction time.

Groups (n=6)	Tail clip reaction time (Seconds)			
	Pre-treatment values at 0 minute	Post-treatment values		
		At 30 minutes	At 60 minutes	At 90 minutes
G1(Control)	3.16±0.33	3.08±0.42	2.96±0.31	3.06±0.52
G2 (Diclofenac)	3.67±0.29	8.33±0.33*	9.66±0.12**	8.51±0.36*
G3 (Pentazocin)	3.43±0.17	8.14±0.21*	10.11±0.13**	13.07±0.08**
G4 (Amitriptyline)	3.17±0.36	7.50±0.30*	9.33±0.33**	12.16±0.34**#

Values were expressed as Mean±SEM. $p < 0.05$ - significant *indicates $p < 0.05$, ** indicates $p < 0.001$ when compared to the control group. # indicates $p < 0.05$ when compared to the Diclofenac group. \$ indicates $p < 0.05$ when compared with the Pentazocin group.

Writhing test is one of the important methods for screening of peripheral analgesia. In present study we found that maximum decrease in number of writhes seen in diclofenac group so, diclofenac provides maximum protection from acetic acid induced writhes (65.17%). In amitriptyline and pentazocin groups this decrement is by 41.09% and 14.38% respectively. So, both in amitriptyline and pentazocin protection against acetic acid induced writhing is less as compared diclofenac. (Table 3).

Table 3: Effect of amitriptyline on acetic acid induced writhes.

Groups (n=6)	Number of writhes in 20 minutes duration (Mean±SEM)	Percentage protection (%)
G1(Control)	41.09±0.92	-----
G2(Diclofenac)	14.31±0.84	65.17
G3(Pentazocin)	35.18±0.69	14.38
G4(Amitriptyline)	26.23±0.78	41.09

DISCUSSION

In present study authors tried to evaluate the analgesic effect of amitriptyline by different analgesic models in mice. Among the different models used, two models are for central analgesia (Radiant heat tail flick method and Haffner's tail clip method) and one model for peripheral analgesia (Writhing test).

Authors used two standard drug one for peripheral analgesia and another for central analgesia which were diclofenac and pentazocin respectively. Authors results revealed that amitriptyline has significant analgesic activity in all analgesic models used in present study.

If authors look at the results individually in different analgesic models authors found that amitriptyline showed more analgesic activity in central analgesia models. In central analgesic models authors found that amitriptyline has significant analgesic activity as compared to control group as well as the analgesic activity is comparable with that of pentazocin which is a standard drug for central analgesia. This signifies that amitriptyline showed analgesic activity mainly through central analgesic mechanism which is similar to the results found in previous studies.²⁴⁻²⁷ In authors study we also found that amitriptyline showing analgesic activity through peripheral mechanism as evidenced by decrease in number of writhes in mice, although this decrement was not as good as diclofenac. But authors can't completely disagree with this fact that it partially improved pain through peripheral mechanism also.

It is well established fact that central analgesia is mainly mediated by opioid receptors which are modulated by opioid peptides like enkephalins, dynorphins and endorphins.²⁸ Besides this other pathway like noradrenergic and serotonergic pathways also involved in pain modulation.²⁷

Amitriptyline is an important member of tricyclic antidepressant group, which primarily inhibits the reuptake of serotonin and norepinephrine in the presynaptic membrane. This results in increase in concentration of serotonin and norepinephrine in the synaptic cleft. Both serotonin and norepinephrine enhance the inhibitory descending pathway of pain.^{29,30} Amitriptyline also has the capability to modulate opening of potassium channels (Kvoltage-gated, KATP and KCa2+). It is also a known fact that at the level of post-synaptic membrane opening of potassium channels results in hyperpolarization as a result of which decrease in action potential generation.³¹ So, the central analgesic activity of amitriptyline is probably mediated by increasing the serotonergic and noradrenergic transmission at post-synaptic membrane as well as by opening of potassium channels.

Fattahian E et al, reported that amitriptyline has anti-inflammatory effect in ulcerative colitis rats. They found that amitriptyline decrease the inflammation extent as well as it decrease the oxidative stress.³²

Rafiee L et al, reported in-vitro and in-vivo studies that amitriptyline decrease the inflammatory mediators especially the different adhesion molecules which accumulate during inflammation.³³ Manning J et al, reported that reduced inflammation and cytokines in mdx mice model of Duchenne muscular dystrophy.³⁴ Another study by Hajhashemi V et al, reported the anti-inflammatory effect of amitriptyline in carrageenan induced paw edema in rats.³⁵ In present study authors found that acetic acid induced writhes were decreased in amitriptyline group, which signifies the peripheral analgesic action of amitriptyline. This finding also strengthens the above mentioned studies both direct and indirect way. So, peripheral analgesic action could be the result of decrease in mediators at inflammatory site.

CONCLUSION

Present study findings suggested that amitriptyline has analgesic activity which is mediated by both central and peripheral mechanism. Further studies require elucidating the molecular mechanism of amitriptyline as an analgesic.

ACKNOWLEDGEMENTS

Authors would like to thank the efforts of Prof. Ashok Kumar Dubey, Prof. Manjula Bhargava and Dr Neha Shrama.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by Institutional Animal Ethical Committee (IAEC), NIMS University, Jaipur, India on 13/09/2014 (Ref. number-NIMSUR/IAEC/CERT/2014/09/07).

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Cite this article as: Ahmad I, Hasan MN, Mishra KA. Evaluation of central and peripheral analgesic activity of amitriptyline in mice. *Int J Basic Clin Pharmacol* 2019;8:1622-7.