

TO EVALUATE THE ANALGESIC EFFECT OF DULOXETINE AND ITS INTERACTION WITH MORPHINE AND NALOXONE IN ALBINO RATS

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Summary

The present study evaluates the probable site of the anti-nociceptive action of Duloxetine and its interaction with Morphine and Naloxone.

The anti-nociceptive activity of Duloxetine was studied using Tail flick method in the absence and presence of Naloxone in rats. Morphine 1mg/kg, Duloxetine 10mg/kg and Naloxone 1mg/kg administered intraperitoneally to study their interaction on Tail flick latency. Duloxetine 10mg/kg did not cause a significant increase in tail flick latency. A dose of 1mg/kg morphine produced a significant increase in Tail flick latency at 30mins that persisted during the entire test period. Combination of Duloxetine 10mg/kg and Morphine 1mg/kg produced an additive effect. Naloxone pretreatment did not affect the anti-nociception produced by Duloxetine. It is not yet known whether the analgesic action of SNRI(duloxetine) involves an interaction with opioid system similar to tricyclic antidepressants but the present study suggest opioid system does not contribute to the effect of duloxetine.

Key words: Anti nociceptive, Analgesia, SNRI, opioids.

Introduction

Pain is an abstract notion referring to a personal feeling of hurt, a damaging stimulus that leads to tissue damage and series of reaction that occurs in order to protect the individual from further injury.^[1] The principal objective of the treatment of pain is to remove or abolish the cause of pain. But it is not always possible to do so. Hence analgesics are used for symptomatic treatment of pain. Clinically, it has been recognized that antidepressant drugs are efficacious and have been widely used in the management of chronic pain conditions.^[2, 3] Firm evidence has shown that tricyclic antidepressants(TCA) should be considered the gold standard for neuropathic pain.^[4, 5] It has also been reported that the analgesic effect of antidepressants is independent of their antidepressive action and occurs at lower doses with a faster onset of action in a clinical situation.^[6, 7] This effect can be explained by several pharmacological mechanisms. Some TCAs block sodium channel, which may contribute to their antihyperalgesic efficacy.^[8] They also apparently block calcium ion channels.^[9, 10] However, it has also been considered that antidepressants modulate pain perception by blocking the reuptake of monoaminergic neurotransmitters in noradrenergic and serotonergic systems, which originate from brain stem and project to the spinal cord dorsal horn.^[11] Moreover, the antihistaminergic action of TCA may have a general analgesic effect.^[12] Recent findings have shown that antidepressants interact with the opioidergic system^[13] and that they act as NMDA receptor antagonists.^[14] SNRIs are used to treat anxiety disorders including generalized anxiety disorder, obsessive compulsive disorder, and attention deficit hyperkinetic disorder. However, very few studies have investigated the relationship between the analgesic effect of antidepressants and changes in emotionality under a chronic pain like state.

Duloxetine hydrochloride is a potent and selective serotonin and norepinephrine reuptake inhibitor^[15] that lacks significant affinity for muscarinic, histaminergic, adrenergic, serotonergic, dopaminergic and ion channels including sodium ion channel.^[16] Because of the proposed role of serotonin and norepinephrine as key mediators of descending pain pathways, duloxetine was evaluated in animal models of persistent and neuropathic pain and in models of acute nociceptive pain.

Therefore the present study was planned

- 1) to evaluate the analgesic effect of duloxetine,
- 2) to study any interaction of duloxetine and morphine,
- 3) to study the probable site of analgesic action of duloxetine.

Material and Methods

Albino rats of either sex weighing between 150-200gms maintained in well ventilated animal house will be used for the study. The animals were allowed access to water ad libitum and standard pellet diet. The animals were divided into six groups of six animals each.

Group 1 received vehicle(distill water), Group 2 received duloxetine 10mg/kg, Group 3 received morphine 1mg/kg, Group 4 received duloxetine 10mg/kg and morphine 1 mg/kg, Group 5 received naloxone 2mg/kg, Group 6 received duloxetine 10mg/kg and naloxone 2mg/kg. All drugs were administered intraperitoneally.

Schedules of drug administration.

In all the groups the antinociceptive test was performed at time intervals 0, 30, 60 and 90mins after the administration of drugs/vehicle. However, naloxone was administered 10mins prior to the administration of duloxetine.

Determination of antinociceptive activity.

Antinociceptive activity was measured by the tail flick method using Analgesiometer. The rats were exposed to noxious stimuli (radiant heat) and tail flick latencies (time required for flicking of the tail that is the reaction time, generally varies between 3-4secs) were recorded. The strength of the current passing through naked nichrome wire will be kept constant 6amps. The distance between the heat source and the tail skin will be 1.5cms and the site of application of the radiant heat in the tail will be maintained at 2.5cms measured from the root of the tail. In order to prevent tissue injury, a cut off time of 10 seconds will be maintained.^[17]

Drugs and chemicals.

Duloxetine hydrochloride (Wockhardt limited ,Gujarat), Morphine (Sree Jayadeva Institute of Cardiovascular Sciences & research centre and Bangalore Medical College and research Institute)

Statistical analysis.

The results are expressed as mean \pm SEM, significance is assessed at 5% level of significance ($p < 0.05$). Analysis of Variance (ANOVA) has been used to find the significance of study parameters between three or more groups. Repeated measures ANOVA has been performed to find the significance of changes over the study period with in each group.

Results

The results are shown in Table 1 and Figure 1

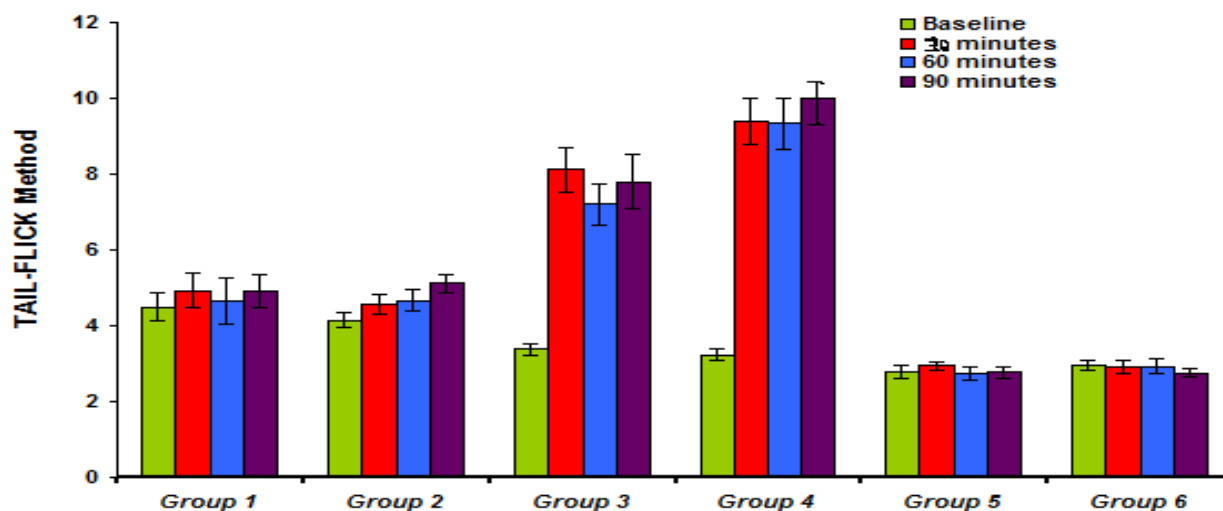
1. Effects of Distilled water treatment
In distilled water treated animals there were no significant changes in the tail flick latency during the entire test period of 90mins.
2. Effects of Duloxetine treatment
Duloxetine (10mg/kg) showed no significant effect on tail flick latency.
3. Effects of Morphine treatment
Morphine (1mg/kg) produced significant increase in reaction time ($p < 0.01$) as compared to baseline values.
4. Effects of combination treatment with duloxetine and Morphine.
The combination of Duloxetine (10mg/kg) and Morphine (1mg/kg) produced significant (< 0.001) increase in reaction time.
5. Effects of Naloxone treatment
Naloxone (1 mg/kg) had no significant effect on tail flick latencies
6. Effects of combined treatment of Naloxone and Duloxetine
Combined treatment of Naloxone (1mg/kg) and Duloxetine (10mg/kg) did not produce significant change in tail flick latency during entire test period.

Table 1 : Effect on the tail flick latency after treatment with duloxetine alone, combination of duloxetine with morphine and duloxetine with naloxone in Tail Flick Method

Results expressed as Mean ± SEM, n=6, + p<0.10,*p <0.05, **p<0.01 significant compared to baseline

GROUPS	DRUG DOSE mg/kg	Pre-drug reaction time (Mean ± SEM)	POST DRUG TIME (mins) REACTION TIME IN sec (Mean± SEM)			p VALUE
			30	60	90	
1	CONTROL (Distilled water)	4.50 ± 0.35	4.92 ± 0.45	4.69 ± 0.61	4.92 ± 0.44	0.908
2	DULOXETINE (10mg/kg)	4.15 ± 0.21	4.57 ± 0.27	4.67 ± 0.27	5.12 ± 0.23	0.105
3	MORPHINE (1mg/kg)	3.37 ± 0.15	8.12 ± 0.59	7.20 ± 0.54	7.80 ± 0.73	<0.001**
4	DULOXETINE (10mg/kg) + MORPHINE (1mg/kg)	3.23 ± 0.16	9.40 ± 0.60**	9.33 ± 0.67**	10.00 ± 0.0**	<0.001**
5	NALOXONE (1mg/kg)	2.77 ± 0.18	2.95 ± 0.11	2.73 ± 0.17	2.77 ± 0.15	0.775
6	NALOXONE + (1mg/kg) DULOXETINE (10mg/kg)	2.95 ± 0.14	2.92 ± 0.16+	2.93 ± 0.19	2.75 ± 0.11*	0.705

Fig 1. Histogram showing the effect of duloxetine alone, combination of duloxetine with morphine, and duloxetine with naloxone in Tail Flick Method



Discussion

Pain is an unpleasant sensory or emotional experience associated with actual or potential tissue damage. Pain is always a subjective feeling. Many people report pain in the absence of tissue damage or any likely pathophysiological cause. One of the objectives of treatment is to remove the cause of pain. Opioids have been the mainstay of pain treatment for thousands of years and remain so even today. Opioids exert their therapeutic effect by mimicking the action of endogenous opioid peptides at opioid receptors.^[18]

Several clinical and laboratory studies have reported antinociceptive activity of antidepressants.^[19,20,21] Antidepressants are reported to be more effective than opioid analgesics in treating neuropathic or deafferentiation pain.^[22] Inhibition of the reuptake of monoamines is considered to be a major effect of antidepressants.^[23] Some studies have disputed the affinity of SSRIs (Selective Serotonin Reuptake Inhibitors), a class of antidepressants like fluoxetine for opioid receptors.^[21,24] It is not clear whether or not opioid receptors are involved in the analgesic activity and if so to what extent.

However, SSRIs have not proven to be as effective against neuropathic pain as anticipated.^[25] In general, the SSRIs are less effective in the treatment of diabetic neuropathy, compared with TCAs.^[25] The TCAs have been used for the treatment and management of neuropathic pain for some 25 years.^[25,26,27,28] The mechanism of action in relieving of neuropathic pain by the TCAs is thought to be due to the inhibition of reuptake of serotonin and norepinephrine or just norepinephrine within the central nervous system; however, other possible mechanisms of action include α -adrenergic blockade, sodium channel effects, and NMDA receptor antagonism. Nevertheless, the side effect profile of the TCAs, including sedation, hypotension, anticholinergic, and cardiovascular liabilities, has limited their use in the treatment and management of neuropathic and other persistent pain states. Thus, the more selective dual uptake inhibitors may offer a safer alternative.

In the present study analgesic effect of duloxetine, a balanced serotonergic and noradrenergic reuptake inhibitor, was evaluated using Tail flick test.

Nociceptive information is processed and integrated peripherally as well as at spinal and supraspinal levels within the central nervous system. In the present study, duloxetine had no effect in the tail-flick test, a spinally integrated nociceptive reflex. Thus, the present data suggest that duloxetine was without effect on the processing of acute noxious stimuli at the level of the spinal cord in rats. That duloxetine might have peripheral effects on the modulation of acute nociceptive stimuli seems unlikely but could not be determined from the present results. Previous studies have reported that direct acting serotonergic and noradrenergic receptor agonists such as MK212 and quipazine^[29] and the α_2 -adrenergic receptor agonists clonidine and oxymetazoline^[30] produced dose-related acute antinociceptive effects in the tail-flick test when given systemically. Taken together, the data suggests that duloxetine may not increase extracellular serotonin and norepinephrine sufficiently to stimulate the relevant serotonergic and/or noradrenergic receptors that modulate acute nociception, particularly at the spinal cord level.

Several studies, mainly investigating the analgesic effect of tricyclics, have shown that apart from the monoaminergic mechanism, tricyclic analgesia implies an activation of opioid system,^[31] even though tricyclics do not bind to opioid receptors. SNRIs do not bind to opioid receptors either, but it is not yet known whether the action of SNRIs involves interaction with the opioid system similar, to tricyclics.

SNRIs include venlafaxine, duloxetine and milnacipran. Regarding the antinociceptive effect of venlafaxine involving opioid system only few preclinical studies are available with apparently opposing results. There is no data available for other SNRIs duloxetine and milnacipran.^[32,33]

The action of morphine is mainly antagonized by opioid antagonist naloxone. Naloxone produces very little effect in normal subjects, but produces rapid reversal of effects of morphine and also the partial agonists such as pentazocine and nalorphine.^[34]

In the present study pretreatment with naloxone did not affect the reaction time in Tail flick method, so the results of the present study suggest that opioid system does not contribute to the analgesic effect of SNRIs.

Most antidepressants interact with other receptor systems, which have been characterised as cholinergic, muscarinic, histaminergic, noradrenergic and even GABAergic system.^[23, 35] In all instances some pathways carrying these receptors are able to elicit analgesic activity. So it would not be unreasonable to suggest that antidepressant drugs would involve at least some of these systems in mediation of their analgesic effect.^[36,37]

It has been suggested that the antinociceptive activity of antidepressants might be due to their antidepressant action. However, analgesic effect was observed at much lower doses than that required to achieve antidepressant effects. Therefore it is likely that opioid or opioid-like activity may be playing an important role in antidepressant mediated antinociception.^[21,37]

In the present study a combination of morphine and duloxetine produced a significant increase in reaction time both in tail- flick method suggesting additive antinociceptive action. Therefore the above combination therapy would theoretically minimize the dose requirements and thus the potential adverse effects, however further clinical studies are needed to prove the same.

Conclusion

This study showed that,

- Duloxetine had no effect in Tail flick method suggesting that duloxetine had no effect in processing of acute noxious stimuli at the level of spinal cord. Pretreatment with Naloxone did not affect the reaction time both in Tail flick method suggesting that opioid system does not contribute to the effect of Duloxetine.
- Combination of Morphine and Duloxetine produced a significant increase in reaction time in Tail flick method suggesting additive antinociceptive action

With the apparently opposing results it was not easy to make a definite conclusion especially when the data on acute nociceptive action of SNRIs is so limited. Hence more experimental and clinical study should be carried out on such an important field of research.

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