Study of possible Analgesic activity of Buspirone.

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Abstracts: Background: Pain results from complex interactions in peripheral and central synapses.[1]The majority of current approaches to treating pain are based on the idea that increasing the level of inhibitory drive or tone at key central nervous system (CNS) regions in the pain pathway can alter pain perception[2,3,4,5] Lot of neurotransmitters are implicated in it including 5-HT. Thus we were interested If buspirone is having analgesic effect.Our aim was to assess if buspiron has analgesic effect. And if comparative efficacy to drugs used today. Methodology**:** After appropriate IAEC clearance ,Hotplate , tail flick analgesiometer methods and acetic acid writhing test were employed. Comparative drugs used were amitriptyline and ibuprofen . Buspirone was used in doses of 2,4 ,mg/kg. Results: Our study showed a comparable efficacy of buspirone to ibuprofen in hot plate test while superior efficacy as an analgesic against amitriptyline at dose of 4mg/kg. Conclusion**:** 5-HT is considered pronociceptive but has shown differential activity in CNS and at peripheral tissues. Buspirone is a partial 5-HT $_{1A}$ agonist and antianxiety drug. Due to the complex interactions at centers in CNS it was proposed to have analgesic action.Our study evaluated this theory with three analgesic models. Our results show that at doses 2 & 4mg/kg it has comparable effect to ibuprofen 20 mg/kg dose. At the same dose it shows superiority to amitriptyline 40mg/kg. Thus it shows promise in treatment of pain associated with anxiety induced depression or other psychiatric problems.[Limaye R NJIRM 2015; 6(2):44-49]

Key Words: Buspirone ,analgesic, neuropathic , psychiatric, pain.

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Introduction: Pain is a complex and highly modifiable sensory experience.. The current paradigm is that pain results from the complex interaction of a variety of synaptic inputs in a pathway that begins at peripheral receptors, ascends the neural axis, and finally reaches the cerebral cortex and limbic structures, such as the amygdale [1]

Buspirone, is a partial 5-HT$_{1A}$ receptor agonist which is widely used for treating anxiety.[6, 7] 5-HT$_{1A}$ receptors are located presynaptically on cell bodies in the raphe nuclei (somatodendritic receptors) and postsynaptically in 5-HT forebrain projecting areas. By activating somatodendritic receptors, 5-HT and 5-HT$_{1A}$ receptor agonists decrease the firing of 5-HT neurons in the raphe, and, consequently decrease 5-HT terminal release.[8] Drugs acting on 5-HT receptors and the serotonin reuptake inhibitors clomipramine.[9] and fluoxetine [10] have been shown to exhibit analgesic and anti-inflammatory activity in animal models. Hence the study was aimed at finding out whether Buspirone has any effects in animal models of pain.

Aims and objectives:

1. To find out if there is any analgesic activity of Buspirone.
2. To compare the analgesic activity of Buspirone with NSAIDs.
3. To compare analgesic activity of Buspirone with Amitriptyline.

Material and Methods: Study was carried out in 5 groups of mice(6 mice /group) of either sex for analgesic tests at Dept. of pharmacology and central animal house, Bharati Vidyapeeth Deemed University, Medical College and Hospital Sangli.

The protocol was discussed in IAEC (Institutional Animal Ethical Committee), IAEC approved the project,IAEC approval registration no. – **BVDUMC& H/Sangli/CAH/IAEC/2012-13/04 Animals-**

Male and female (non pregnant) Swiss albino mice weighing (20-25 g) of body weight were used. They were housed under standardized conditions (temperature 25^0 Celsius, relative humidity 60% & 12 hour light/dark cycle). They had access to standard pellet diet and water ad. libitum. Experiments were conducted between 9:00 to 16:00 hour. All animal procedures were in accordance with the recommendations for the proper care and use of laboratory animals. The doses of drugs employed in the study were based

upon the human dose after conversion to that of mice .[11]

Drugs: All the drug solutions were freshly prepared on the day of the experiment and used the same day.

For all tests: At the end of this study, no animal showed grave injury or permanent disability after 2 weeks. During the recovery period the animals were followed up by standard procedures as outlined by CPCSEA guidelines.

Analgesic study Models :-

1. Hot-plate method [12,13,14]: The hotplate test was performed on mice by using an electronically controlled hotplate heated to 55-56 degree Celsius. Groups of 6 mice each were given buspirone at doses of 2, 4 mg/kg ,i.p[15], saline (control), & ibuprofen (20 mg/kg i.p.) and amitriptyline (40 mg/kg i.p.)[16] 30 min prior to testing. The animals were placed on the hot plate and the time until either licking or jumping occurs was recorded by a stop-watch. The latency was recorded before and after 30 minutes following intraperitoneal administration of the control and test drugs . Cut off time for mice is 15-20 seconds.

2. Tail electric stimulation method [17]: Groups of 6 mice each were given buspirone (2, 4 mg/kg, i.p.), and ibuprofen (20mg/kg i.p.), amitriptyline (40mg/kg i.p.) and saline (control). Animal was placed into small holder leaving the tail exposed. A constant current was passing through the wire of the instrument. Tail was kept on the platform to expose it to be radiant heat and the reaction time was noted by stop watch. Time between placing the tail of the mice on the radiant heat source and sharp withdrawal of the tail was recorded as "reaction time". Same procedure was performed and reaction time was noted after 30 ,60 min. Cut off time for mice is 15-20 seconds.

3. Acetic acid-induced writhing[13]: Groups of 6 mice each were given saline(control), Buspirone (2, 4 mg/kg, , i.p.) ,ibuprofen (20mg/kg i.p.) and amitriptyline (40mg/kg i.p.). An Acetic acid 0.2 ml of 0.6% was administered intraperitoneally in each animal. Each mouse was placed individually into glass chamber and number of writhes in each animal was recorded over a period of 10 min.

Statistical Analysis: Statistical analysis was carried out using one way ANOVA (Analysis of variance) for significance between groups. Data was expressed as mean ±S.E. The level of significance between individual groups was detected using unpaired "t" test. For all tests, effects with a probability of $P < 0.05$ were considered to be significant.

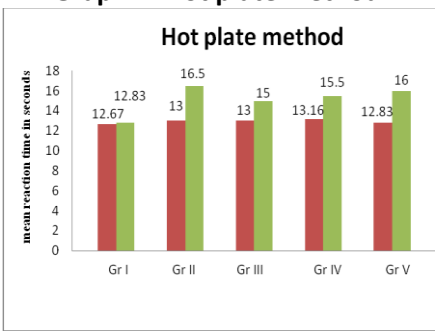
Results:

Table 1: Effect of various treatments on hot plate method

Drug N=6 animals per group	Mean Reaction time in seconds at each observation	
	Pre drug (0 min)	Post drug (30 min)
[I]Control (0.2 ml NS)	12.67 +/- 0.211	12.83+/-0.167
[II]Ibuprofen (20 mg/kg)	13.00+/- 0.258	16.50+/-0.342 *
[III]Amitriptyline (40 mg/kg)	13.00+/- 0.366	15.00+/-0.25* #
[IV]Buspirone (2 mg/kg)	13.16+/- 0.308	15.50+/-0.342*
[V]Buspirone (4 mg/kg)	12.83+/- 0.307	16.00+/-0.25 * $

p<0.05 is significant *p<0.05 compared with control p <0.001 is highly significant # p<0.05 compared with Ibuprofen $ p<0.05 compared with Amitriptyline ^ p<0.05 compared with Buspirone 4mg/kg

Graph 1: Hot plate method



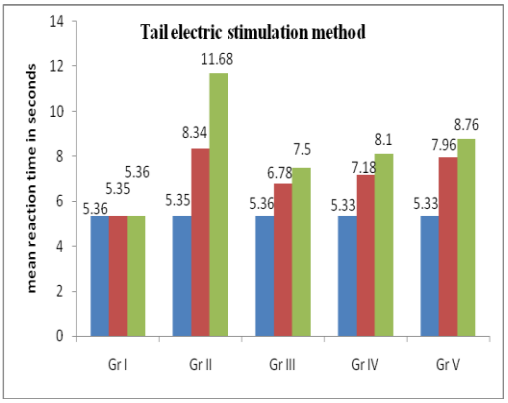
Gr I Control 0.2 ml NS ; Gr II Ibuprofen 20 mg/kg ; Gr III Amitriptyline 40 mg/kg ; Gr IV Buspirone 2mg/kg ; Gr V Buspirone 4 mg/kg

Table 2:- Effect of various treatments on Tail electric stimulation method

Drug N=6 animals per group	Mean Reaction time in seconds at each observation		
	Pre drug (0 min)	Post drug (30 min)	Post drug (60 min)
[I]Control (0.2 ml NS)	5.36+/- 0.033	5.35+/- 0.034	5.36+/- 0.072
[II]Ibuprofen (20 mg/kg)	5.35+/- 0.042	8.34+/- 0.003*	11.68+/- 0.060*
[III]Amitriptyline (40 mg/kg)	5.36+/- 0.042	6.78+/- 0.005* #	7.50+/- 0.036* #
[IV]Buspirone (2 mg/kg)	5.33+/- 0.042	7.18+/- 0.005* # $ ^	8.10+/- 0.036* # $ ^
[V]Buspirone (4 mg/kg)	5.33+/- 0.049	7.96+/- 0.012* # $	8.76+/- 0.049* # $

p<0.05 is significant * p < 0.05 compared with control p <0.001 is highly significant # p < 0.05 compared with Ibuprofen $ p < 0.05 compared with Amitriptyline ^ p< 0.05 compared with Buspirone 4mg/kg

Graph 2:-Tail electric stimulation method



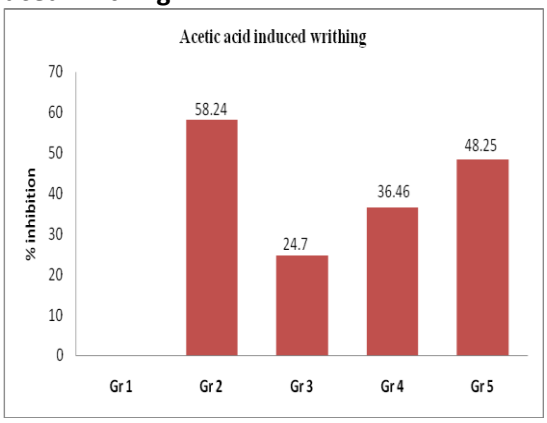
Gr I Control 0.2 ml NS ; Gr II Ibuprofen 20 mg/kg ;Gr III Amitriptyline 40 mg/kg ; Gr IV Buspirone 2mg/kg ; Gr V Buspirone 4 mg/kg

Table 3:- Effect of various treatment on Acetic acid induced writhing

Drug N=6 animals per group	Writhing response(no. of abdominal constrictions)	% inhibition
[I]Control (0.2 ml NS)	28.33+/- 0.333	0
[II]Ibuprofen (20 mg/kg)	11.83+/- 0.307*	58.24
[III]Amitriptyline (40 mg/kg)	21.33 +/- 0.333* #	24.70
[IV]Buspirone (2 mg/kg)	18.00 +/- 0.365 * # $ ^	36.46
[V]Buspirone (4 mg/kg)	14.67 +/- 0.333* # $	48.25

p<0.05 is significant * p < 0.05 compared with control,p<0.001 is highly significant # p < 0.05 compared with Ibuprofen $ p < 0.05 compared with Amitriptyline ^ p< 0.05 compared with Buspirone 4mg/kg

Graph 3:- percentage inhibition of Acetic acid induced writhing



Gr I Control 0.2 ml NS ; Gr II Ibuprofen 20 mg/kg ; Gr III Amitriptyline 40 mg/kg ; Gr IV Buspirone 2mg/kg ; Gr V Buspirone 4 mg/kg

Discussion: Buspirone is a $5HT_{1A}$ receptor partial agonist and mainly used in the treatment of anxiety and depression. [18] The tricyclic antidepressants have been used for many years to suppress certain types of pain, including diabetic neuropathy ,postherpetic neuralgia ,headaches ,arthritis, chronic back pain ,cancer pain and phantom limb pain.[19]Watson et al, reported the effect of amitriptyline in the treatment of postherpetic neuralgia.[20]

It is observed that besides prostaglandins, bradykinin ,histamine and other autocoids , serotonergic modulatory pathway is proposed to be involved in pain. 5-HT either facilitate or inhibit nociceptive transmission. [11]

The hot plate test is one of the oldest and most widely used experimental methods to assess

nociception in rats and mice.[12]In present study ,buspirone (2 and 4 mg/kg) showed increased nociceptive threshold to thermal model of pain i.e. hot plate method .Observations in the present study are thus consistent with data reported by other studies including Various other 5- HT_{1A} agonists, exhibiting analgesic effects in the hot-plate test in mice[21,22] and in a rat model of surgical pain.[23]

The most likely mechanism is through descending inhibitory pathways that end in the dorsal horn of the spinal cord and affect sensory centripetal neurotransmission. Buspirone was reported without effect on tail flick latency and in hot plate test in rats but significantly inhibited morphine-associated analgesia in rats.[24] The analgesic effects of buspirone are likely to be mediated through an action on 5-HT_{1A} receptors[25], but might involve ATP-sensitive K^+ channels as well[22] or a non-opioid-adrenally mediated mechanism, since buspirone (5 mg/kg, i.p.) reportedly produced elevation in plasma norepinephrine and corticosterone. [26]

One data demonstrated that Ca^{2+} influx from extracellular fluid and release of Ca^{2+} from Ca^{2+}/caffeine-sensitive microsomal pools may be involved in buspirone induced antinociception.[27]

Galeotti et al. demonstrated the antinociceptive effect of buspirone, gepirone and 8-OHDPAT in the hot plate and writhing tests in mice.[21]According to data provided by Milan ,the mechanism of antinociceptive action of $5HT_{1A}$ agonists involve adrenergic receptor alpha 2 activation.[28]Buspirone has a weak affinity to the receptor alpha 2.[29]One study demonstrated that the 5-HT_{1A} receptor, not 5-HT_2 nor 5-HT_3 receptor, plays an important role in the descending pathway of anti-nociception from the brainstem to the spinal cord in intact rats, in rats with nerve injury and in rats with inflammation.[30] This may be the cause of its superiority to amitriptyline as an analgesic in all models in the present study.

In the present study hot plate latency of buspirone (2mg/kg) was similar to amitriptyline(40mg/kg). Tricyclic antidepressants have been the mainstay treatment modality for neuropathic pain. Thus opening a promising area for use of Buspirone as an analgesic, specially in neuropathic pain and may be pain associated with depression.[3]

In the present study, buspirone (2 and 4mg/kg) were without effect on tail electric stimulation and acetic acid induced writhing test. An earlier study reported analgesic activity of buspirone in tail flick method and acetic acid induced writhing models.[32] Previous studies had shown significant effect of buspirone (2,4 and 16 mg/kg) as analgesic in hot plate method ,tail flick method and acetic acid induced writhing respectively over indomethacin (18mg/kg)[15] .In our study Ibuprofen was used.

In hot plate model significant effect of buspirone (2 and 4mg/kg) as analgesic was observed when compared with ibuprofen (20mg/kg).While it was without significant effect on tail flick method and acetic acid induced writhing method.

The discrepancy of the results of different studies as regards the analgesic activity could be explained on the basis of the difference in animal models used, the dose, the time and the route of administration of buspirone and the control. Our study showed potential of buspirone to act as an analgesic even at low dose.

Present study indicate promise in the use of buspirone as analgesic agent, if the present findings could be extrapolated to clinical situations including neuropathic pain. Buspirone may also contribute to its analgesic activity in humans by decreasing anxiety associated with pain. Larger and longer studies are needed in animals and then humans to establish its usefulness.

Conclusion Analgesic activity of buspirone may involve descending inhibitory pathways that end in the dorsal horn of the spinal cord and affect sensory centripetal neurotransmission , action on 5-HT_{1A} receptors, ATP-sensitive K^+ channels, Calcium ions and activation of alpha-2 adrenergic receptors. [22,25,26]

To summarise, analgesic results of two doses of buspirone (2 and 4 mg/kg) were significant when compared with ibuprofen and results of buspirone (2 mg/kg) was significant when compared with

amitriptyline. Low dose of buspirone can be used in neuropathic pain.So advantage of this drug for patients suffering from anxiety would be reduction in pill burden and increased compliance.

From the present study we can conclude that buspirone in low dose shows analgesic activity. It is worthwhile to evaluate such preparations through clinical trials.

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