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Research Article

COMPARATIVE STUDY OF ANALGESIC EFFECT OF AMISULPRIDE WITH TRAMADOL IN MICE

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ABSTRACT

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. In view of the considerable side effects produced by the available analgesics, the search for a newer analgesic continues. The aim of this study is to anti nociceptive effects of various neuroleptics in animal models of pain have been described. The aim of our present study is to evaluate the analgesic activity of Amisulpride, an atypical antipsychotic in comparison with Tramadol, which is a synthetic opioid analgesic. The analgesic effect of Amisulpride was evaluated using Eddy's hot plate. The drugs were administered sub-cutaneously. In this test the reaction times i.e., the latency periods in the animals were recorded in all the three groups (control, standard and test groups) at 30 min, 60 min and 90 min time interval after drug administration. Each group contains 6 animals. The increase in reaction time in response to a drug denotes analgesic effect of the drug. The reaction times in the test group were compared with standard and control. Results were analyzed by ANOVA followed by post hoc Dunnett's test. According to Dunnett's test, the p value was very significant in Control vs test group at 90 min, which implies that Amisulpride (44 mg/kg) has significant analgesic effect at 90 min time interval after drug administration. P values were very significant at 30 min and 60 min and not significant at 90 min in Standard group versus Test group, which implies that the test drug (Amisulpride) has analgesic effect comparable to that of standard drug (Tramadol) at 90 min. This study suggests that Amisulpride has significant analgesic effect at 90 min. The analgesic effect of Amisulpride (44 mg/kg) is comparable to that of standard drug Tramadol (20 mg/kg) at 90 min.

Keywords: Anti nociceptive effect, Amisulpride, Atypical antipsychotic, Eddy's Hot plate, Reaction time, Tramadol.

INTRODUCTION

Pain is the most common reason patients seek medical care. Pain is an unpleasant sensation, ranging in intensity from slight through severe to indescribable. Pain is regarded as the normal protective response to mild tissue injury. At the other extreme in chronic pain conditions, the stimulus and pain are unrelated, which arise due to chronic pathological lesions or degenerative processes and in few cases no discernable pathology; according to the international association for the study of pain "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage"[1]. Pain is usually evoked by an external or internal noxious stimulus. It is a subjective experience which cannot be objectively defined or quantified satisfactorily. There are classically two components in pain perception: 1) the nociceptive component, which is a disabling, unpleasant sensation evoked by noxious stimuli conveyed to CNS by ascending path ways; and 2) the affective component, which is the psychological response towards the pain and conveyed from CNS to dorsal horn by descending pathways.[2] Pain is a warning signal primarily protective in nature but causes discomfort and suffering may even be unbearable and incapacitating. It is a symptom not a disease. As a symptom pain demands instant relief and in practice its dramatic relief highly impresses a lay man. Early treatment of pain is important as unrelieved pain can have profound psychological effects on the patient and acute pain that is poorly managed initially can degenerate into chronic pain, which may prove to be much more difficult to treat. It is important to assess and treat the mental and emotional aspects of the pain as well as its physical aspects. Although drug therapy is a mainstay of pain treatment, physical methods such as physiotherapy (including massage and the application of heat and cold), surgery, and nervous system stimulation techniques such as acupuncture and transcutaneous electrical nerve stimulation (TENS) are also used.[3] Analgesics are the drugs that selectively relieve pain by acting in the CNS or on peripheral pain mechanisms without significantly altering consciousness. Analgesics relieve pain as a symptom without affecting its cause. They are used when the noxious stimulus cannot be removed or as an adjutants to more etiological approach to pain. Until now there are many analgesics. Narcotic analgesics and NSAIDs are the most commonly used drugs. Narcotics produce considerable side effects like euphoria, depressant action on vital centers, addiction and tolerance etc. Therefore search for a new potent, safe and non toxic drug continues. Anti-nociceptive effects of various neuroleptics have been described and assessed in various animal models. But neuroleptics as a group do not have a well established place in the management of pain. The use of neuroleptics in treatment of pain is controversial, due to extrapyramidal symptoms and other side effects. These side effects are inevitable when treating psychosis but these effects outweigh benefit when treating pain. Moreover the clinical use of neuroleptics in combination with opiates is not uncommon. At present newer generation of neuroleptics with reduced profile of side effects are introduced. Thus, the possible use of these agents in treatment of pain is an issue which can be given a trial. There are studies showing augmenting effects of neuroleptic agents like risperidone (Schreiber *et al*.., 1997)[4] and also with atypical neuroleptic drugs clozapine and olanzapine (Schreiber *et al*., 1999)[5] on opioid induced anti-nociception. Amisulpride is an atypical antipsychotic agent, chemically a substituted benzamide. It is a selective blocker of dopamine D2 and D3 receptors with little affinity for other dopamine receptors (D1, D4, D5) or other neurotransmitter receptors (serotonin, histamine, muscarinic, adrenergic) (Schoemaker *et al* 1997)[6]. Its atypical profile depends on blockade of the mesolimbic dopaminergic tracts rather than nigrostriatal dopaminergic transmission and on a preferential blockade of dopamine D3 receptors in the limbic system. At low doses it has selective preference for pre-synaptic dopamine auto receptors, thereby increasing dopaminergic neurotransmission, thus having advantage in treating negative symptoms in schizophrenia. At higher doses it blocks postsynaptic dopamine receptors, thus controlling psychotic symptoms. In a study evaluating the interaction of the dopamineD3 receptor agonist (F) -7-hydroxy-dipropylaminotetralin (7-OH-DPAT) with the opioid system, Cook *et al*. (1999)[7] found it to induce a dose-dependent attenuation of the anti-nociceptive effects of morphine and dezocine. This finding suggests a possible

modulation of anti-nociception of morphine, mediated through the dopamine D3 receptor. Since amisulpride involves dopamine D3 receptor blockade, it is hypothesized that it would exert an anti-nociceptive effect. Furthermore, in previous studies it was found that different dopamine receptor subtypes mediate anti-nociception by different interactions with the opioid system (Schreiber *et al*., 1997, 1999)[4,5], thus assessing the anti-nociceptive properties of a drug that interacts both with dopamine D2 and D3 receptors (amisulpride) may shed some light on the different effects of dopamine D2 and D3 receptor subtypes on opioid regulation. It was found that the sensitivity of amisulpride-induced anti-nociception is mediated through selective involvement of all three opioid receptor subtypes. Based on previous studies with risperidone, clozapine and olanzapine this global interaction with the opioid system of amisulpride is attributed to amisulpride's action at the dopamine D2 receptor sites. As this drug Amisulpride has a lesser adverse effect profile when compared to that of typical anti-psychotics, its possible use for anti-nociception has to be considered. The aim of the present study is to evaluate the analgesic effect of amisulpride in comparison with tramadol, which is a synthetic opioid analgesic.

MATERIALS AND METHODS

Drugs and chemicals

Amisulpride was obtained from Optimus Pharma Private Limited; Tramadol was obtained as injection form 100 mg/2 ml, Aldaccoryza. Normal saline and ethanol mixed in a ratio of 80:20, was used as control. Tramadol was used as a standard drug and was dissolved in Normal saline. Amisulpride was dissolved in Normal saline and ethanol in 80 : 20 ratio. The drugs were diluted to provide appropriate doses for injections.

Equipment

Eddy's hot plate, animal weighing balance, insulin syringes, 2ml syringes, glass beakers, stirrers, petridish, cotton, spirit, marker pens, stop watch

Animals

Albino mice of either sex, weighing 20-25 g were used. 18 mice were procured from Central animal house, Osmania medical college. The study was approved by the Institutional Animal Ethics committee (ID no; IAEC/Pharma/OMC/21/2013). The mice were maintained at 12 hour light/ 12 hour dark cycles with food and water available *ad libitum*.

Experimental design

Eighteen healthy albino mice were divided into three groups of 6 animals in each group as follows;

- Control group; received a mixture of Normal saline and ethanol in 80 : 20 ratio, 10 ml/kg subcutaneously.
- Standard group; received Tramadol 20 mg/kg subcutaneously.
- Test group; received Amisulpride 44 mg/kg subcutaneously.

Anti-nociceptive assessment

Mice were tested using Eddy's hot plate method[8,9]. Hot plate analgesia apparatus (Techno) consists of a thermostatically controlled electrical heated plate, heated by a thermode or a boiling liquid (Woolfe and Mac Donald 1994; Eddy Leimbach 1953), surrounded by a transparent square box with a flexible lid on its top. The plate is heated to a constant temperature of 45-50^{0}C. To test for the analgesic effect of the drug, the animal is placed on the hot plate at 30 min, 60 min and 90 min time intervals after drug administration. The post treatment latency periods or reaction times were determined after 30 min, 60 min and 90 min for each animal. The time taken for responses like paw licking and withdrawal of paws to appear after placing the animal on hot plate was taken as reaction time. The cut off time i.e., the maximum time to keep the animal on hot plate was taken as 15 seconds, to minimize tissue damage. After recording the reaction time each mouse was immediately transferred to a petridish containing water to prevent thermal injury. The reaction times of each animal in all the groups were thus determined using hot plate method and noted down and were subjected to statistical analysis.

Statistical analysis

The results were expressed as Mean ± SEM. Statistical analysis was done using one way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. $P < 0.05$ was considered significant.

OBSERVATIONS AND RESULTS

Table 1: The reaction times expressed as Mean ± Standard error of mean of different groups at 30 minutes time interval

Group	Number of animals	Mean ± Standard error of mean (SEM)
Control (normal saline + ethanol) 10 ml/kg	6	6.67 ± 0.33
Standard (Tramadol, 20 mg/kg)	6	11.50 ± 0.62
Test (Amisulpride, 44 mg/kg)	6	6.67 ± 0.33

Number of animals in each group (n) is 6

Table 2: The reaction times expressed as Mean ± Standard error of mean of different groups at 60 minutes time interval

Group	Number of animals	Mean ± Standard error of mean (SEM)
Control (normal saline + ethanol) 10 ml/kg	6	6.33 ± 0.33
Standard (Tramadol, 20 mg/kg)	6	12.0 ± 0.58
Test (Amisulpride, 44 mg/kg)	6	6.83 ± 0.17

Number of animals in each group (n) is 6

Table 3: The reaction times expressed as Mean ± Standard error of mean of different groups at 90 minutes time interval

Group	Number of animals	Mean ± Standard error of mean (SEM)
Control (normal saline + ethanol) 10 ml/kg	6	6.67 ± 0.49
Standard (Tramadol, 20 mg/kg)	6	12.83 ± 0.65
Test (Amisulpride, 44 mg/kg)	6	11.17 ± 0.48

Number of animals in each group (n) is 6

Table 4: Percentage increase in reaction time in standard and test groups on comparison with control group, at different time intervals

Group	30 min	60 min	90 min
Standard	72.41 %	89.57 %	92.35 %
Test	No effect	7.89 %	67.46 %

Percentage increase in reaction time when compared to control group is calculated at different time intervals by using the following formula = mean reaction time in test group – mean reaction time in control group × 100

Mean reaction time in control group

Table 5: Statistical Analysis showing comparison of reaction time between different groups at different time intervals

Time interval	Groups	Mean ± SEM	F value*	Significance
30 min	Control	6.67 ± 0.33	38.294	S
	Standard	11.5 ± 0.62		
	Test	6.67 ± 0.33		
60 min	Control	6.33 ± 0.33	62.711	S
	Standard	12 ± 0.58		
	Test	6.83 ± 0.17		
90 min	Control	6.67 ± 0.49	33.906	S
	Standard	12.83 ± 0.65		
	Test	11.17 ± 0.48		

*F value calculated using one way ANOVA, S- significant

Table 6: p values and statistical significance on comparison of reaction times between different groups using Dunnett's test

Groups	Time intervals	t value	P < 0.05*	Significance
Control vs Standard	30 min	7.580	Yes	S
	60 min	10.113	Yes	S
	90 min	7.957	Yes	S
Control vs Test	30 min	0	No	NS
	60 min	0.892	No	NS
	90 min	5.813	Yes	S
Standard vs Test	30 min	7.580	Yes	S
	60 min	9.221	Yes	S
	90 min	2.144	No	NS

*Statistical significance calculated using Dunnett's test., S – Significant, NS – not significant, Number of animals in each group (n) is 6

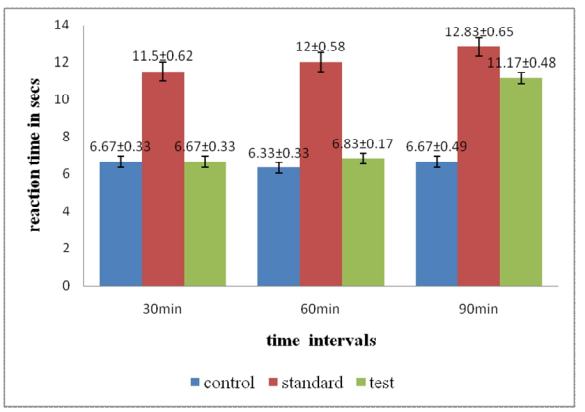

Figure 1: Variations in reaction times at different time intervals

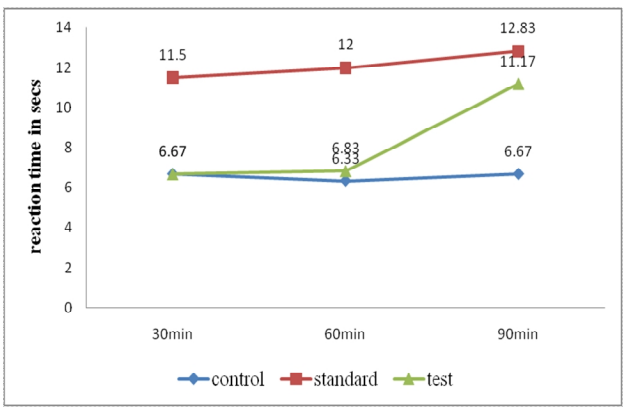

Figure 2: Variations in reaction times at different time intervals

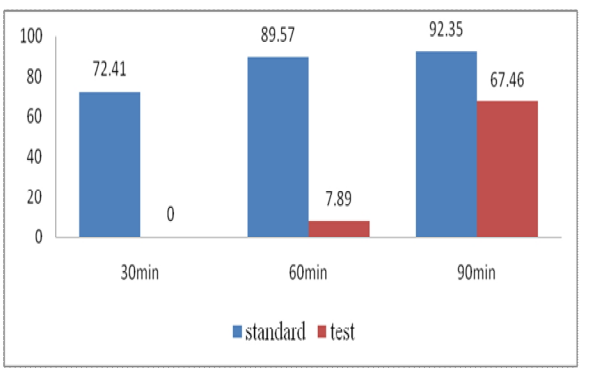

Figure 3: Percentage increase in reaction time in different groups at 30 min, 60 min and 90 min when compared to control group

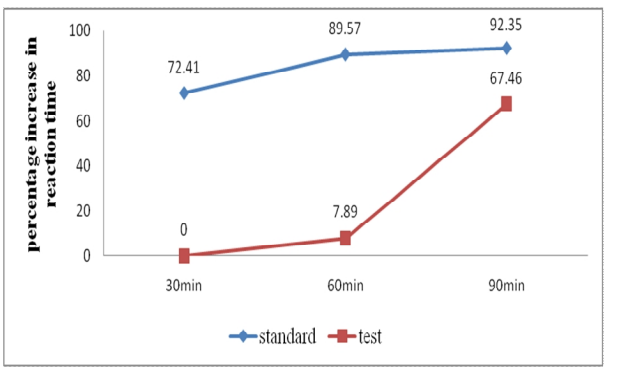

Figure 4: Percentage increase in reaction time in different groups at 30 min, 60 min and 90 min when compared to control group

DISCUSSION

The present study evaluated the analgesic activity of Amisulpride, by using Eddy's hot plate method. The results have been compared with that of standard drug Tramadol. The anti-nociceptive activity of Amisulpride mediated through opioid mechanisms has been established in previous studies by Weizman *et al*. Their research has found Amisulpride to be a potent analgesic agent in the mouse tail flick assay, with an ED_{50} of 36.6 mg/kg, and its analgesic activity is mediated through involvement of all three opioid receptor subtypes[10]. Our present study compared the centrally mediated analgesic effect of Amisulpride with Tramadol, which is a synthetic opioid analgesic (centrally acting analgesic). Hot plate method was chosen for the study as it is model of central analgesia. The increase in the reaction time in response to a drug denotes analgesic effect of the drug. The results of hot plate method were expressed as Mean ± SEM. From the Table 1, the mean reaction times of the three groups at 30 min were, control group - 6.67 ± 0.33, standard group - 11.5 ± 0.62, test group - 6 .67 ± 0.33. At 30 min time interval Standard group showed an increase in mean reaction time when compared to control and the mean reaction time in test group is almost equal to that of control group. At 60 min time interval, the mean reaction times were, control group – 6.33 ± 0.33, standard group – 12 ± 0.58, test group - 6.83 ± 0.17 (Table 2). At 60 min time interval, standard group showed an increase in mean reaction time and the test group showed a slight increase in mean reaction time, when compared to control. At 90 min time interval, the mean reaction times were control group - 6.67 ± 0.49, standard group - 12.83 ± 0.65, test group - 11.17 ± 0.48 (Table 3). It was observed that test group showed a significant increase in mean reaction time when compared

to control at 90 min time interval. Intergroup comparison using Dunnett's test showed that Amisulpride significantly increased the reaction time ($p < 0.05$) when compared to control at 90 min time interval (Table 6). Mice treated with Tramadol showed significant increase in reaction time ($p < 0.05$) at 30 min, 60 min and 90 min time intervals when compared to control (Table 6). However, at 90 min time interval, the increase in reaction times with Amisulpride (Test group) and Tramadol (standard group) were similar ($p > 0.05$) ,which implies a comparable analgesic effect of Amisulpride and Tramadol. The percentage increase in reaction time in test group (Amisulpride) is 67.46 % (Table 4), which implies that Amisulpride has significant analgesic effect at 90 min post drug administration. The onset of action was faster with Tramadol, i.e., the increase in reaction time occurred at 30 min post drug administration and showed a continuous increase in reaction time up to 90 min. Whereas, Amisulpride showed a significant increase in reaction time at 90 min post drug administration. However, since our observation period was only 90 min we cannot make any comment on the further course of action of Amisulpride. Thus the present work though of preliminary in nature suggests that Amisulpride in particular has good analgesic activity, comparable to that of Tramadol at 90 min. Synergistic, additive or antagonistic actions can be observed when two analgesics are given at the same time. In the context of synergistic interaction, the lower doses for each drug can be used to reach an equal or better analgesia with fewer overall side effects from individual compounds. In addition, the multiplicity of mechanisms involved in pain suggests that combination therapy can improve pain management. Thus, further studies on combination of Amisulpride and Tramadol are required.

CONCLUSION

In this study analgesic effect of Amisulpride was evaluated in comparison with Tramadol in albino mice using Eddy's hot plate method. In our study conclusions drawn are; the test drug Amisulpride (44 mg/kg) has analgesic effect at 90 min post drug administration, which is comparable to that of standard drug Tramadol (20 mg/kg) at 90 min time interval. Amisulpride which is basically an anti-psychotic drug has anti-nociceptive effect. It has analgesic effect at 90 min time interval. This study gives us an idea about the use of Amisulpride as an analgesic and also probable useful combination of Tramadol and Amisulpride as analgesic at lower doses there by reducing the side effects of individual drugs. Moreover when treatment of pain is needed in psychotic patients using Amisulpride, the dosage of Tramadol could be reduced, thus reducing its adverse effects. To obtain the final assessment, large scaleclinical trials regarding combination of Amisulpride and Tramadol are required.

REFERENCES

1. PN Bennett, MJ Brown. Clinical Pharmacology, Chapter- Pain and Analgesics. 10th edition; p. 293-307.
2. HL Sharma, KL Sharma. Principles of Pharmacology, Chapter- Opioid Analgesics and Opioid Antagonists, 2nd edition; p. 490.
3. Sean C Sweetman. Martindale: The Complete Drug Reference, 36th edition, Analgesics Anti-inflammatory Drugs and Antipyretics; p. 2.
4. Schreiber S Backer, M Weizman, R Pick CG. Augmentation of opioid induced anti-nociception by the atypical antipsychotic drug risperidone in mice. Neurosci.Lett 1997; 228: 25-28. http://dx.doi.org/10.1016/S0304-3940(97)00345-5
5. Schreiber S, Getslev MM, Backer M, Weizman R, Pick CG. The atypical neuroleptics clozapine and olanzapine differ regarding their anti-nociceptive mechanisms and potency. Pharmacol.Biochem.Behav 1999; 64: 75-80. http://dx.doi.org /10.1016/S0091-3057(99)00107-0
6. Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, Oblin A, Gonon F, Carter C, Benavides J, Scatton B. Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity.J. Pharmacol. Exp. Ther 1997; 280: 83-97.
7. Cook CD, Rodefer JS, Picker MJ. Selective attenuation of the anti-nociceptive effects of mu opioids by the putative dopamine D3 agonist 7-OH-DPAT.Psychopharmacology 1999; 144: 239-247. http://dx.doi.org/10.1007/s002130050999
8. SK Gupta. Drug screening methods, 2nded, chapter- Analgesic agents; p. 461-479.
9. MN Ghosh. Fundamentals of Experimental Pharmacology, 5thed, some common evaluation techniques; p. 151-53.
10. Tal weizman, Chaim G Pick, Maria M Backer, Tova Rigai, Miki Bloch, Shaul Schreiber. The anti-nociceptive effect of Amisulpride in mice is mediated through opioid mechanisms, European Journal of Pharmacology 2003; 478: 155-159.

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