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Research Article

Evaluation of antidepressant and analgesic activity of tapentadol with mirtazapine: an experimental study

Pankaj K. Chaudhary[1], Atul Jain[1], Asha Pathak[1]*, Neha Sharma[2], Atul K. Mishra[3], Arvind K. Maurya[1], Vikas Gaur[4]

[1]Department of Pharmacology, U.P. Rural Institute of Medical Science & Research, Etawah, Uttar Pradesh, India, [2]Department of Pharmacology, NIMS Medical College, Jaipur, Rajasthan, India, [3]Medical Officer, U.P. Rural Institute of Medical Science & Research, Etawah, Uttar Pradesh, India, [4]Department of Psychiatry, NIMS Medical College, Jaipur, Rajasthan, India

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***Correspondence to:**
Dr. Asha Pathak,
Email: drasha_pathak@yahoo.co.in

ABSTRACT

Background: Data comparing tapentadol with an antidepressant is limited. A comparison of tapentadol with mirtazapine at different dose has not been performed, the other antidepressant in the same therapeutic class with a significant market share, has been undertaken. In the absence of relevant data to assess the place that tapentadol should occupy in the therapeutic arsenal, indirect comparisons are the most rigorous way to go. We conducted a study evaluate antidepressant and analgesic activity of tapentadol with mirtazapine at different doses in Swiss albino mice.
Methods: Tapentadol was administered at 10, 20 and 40 mg/kg (i.p) once daily for 14 days to swiss albino mice of either sex. The immobility period for antidepressant activity of mice were recorded in forced swim test and reaction time for analgesic activity of mice were recorded in tail flick test of the control and drug treated group. The antidepressant and analgesic activity of tapentadol (10, 20, 40 mg/kg i.p) was compared with that of mirtazapine (3, 5, 7 mg/kg i.p), administered for 14 days.
Results: Tapentadol produced better antidepressant at (20, 40 mg/kg), but less at 10 mg/kg and significant analgesic activity at all the three doses, as indicated by reduction in immobility times and increase in reaction time as compared to control. Mirtazapine produced no antinociceptive activity at 3 mg/kg, but significant at 5, 7 mg/kg and showed better antidepressant activity at all the three doses in mice. The result of this study indicates the better analgesic activity of tapentadol at all the doses and least antidepressant activity at 10 mg/kg, as compared to mirtazapine which has shown better antidepressant activity at all the three doses but no analgesic activity at 3 mg/kg.
Conclusion: It can be concluded that tapentadol is a better drug in case of depression associated with pain compared to mirtazapine in mice.

Keywords: Antidepressant, Analgesic, Tail flick test, Forced swim test, Tapentadol, Mirtazapine

INTRODUCTION

Depression

Depression is one of the leading causes of global disease burden and disability.[1] For instance, depression is the most important risk factor for suicide, which claims around 0.85 million lives annually, and is among the top three causes of death in young people ages 15-35.[2,3]

There are two types of depression mainly unipolar in which mood swings in only one direction and bipolar in which depressive episode alternate with mania. The symptoms include persistent sad, anxious, or "empty" feelings, feelings of hopelessness or pessimism, feelings of guilt, worthlessness, or helplessness.

The World Health Organization estimates that major depression is the fourth most important cause worldwide of

loss in disability-adjusted life years. An estimated 3-4% of India's 100 crore plus population suffers from major mental disorders and about 7.10% of the population suffers from minor depressive disorders.[4] The high prevalence of suicide in depressed patients (up to 15%), coupled with complications arising from stress and its effects on the cardiovascular system, have suggested that it will be the second leading cause of death by the year 2020 and studies show depression as a contributory factor to fatal coronary disease.[5]

Pain

Pain is defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neurochemical processes in the peripheral and central nervous system.[6] Chronic pain is defined as pain that has been present for more than 6 months. Chronic pain is often accompanied by depression.[7] Although chronic pain is treated with many medications, such as tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anticonvulsants, and opioids, none has shown outstanding efficacy. Narcotics are usually avoided because of the risk of developing tolerance, dependence, and functional deterioration.[8] The release of transmitters, carrying the pain sensation from nerve endings, is regulated by intracellular calcium level, which also regulates the synthesis of prostaglandins.[9]

With the introduction of the newer generation of antidepressants and opioids drugs, some of these have been used in the treatment of pain associated with depression and their efficacy is still to be defined.

The objective of this study was to find out the drug which can be used in the treatment of pain associated with depression or as a sole agent.

Hence, this study may help psychiatrists and physicians to use these antidepressants and opioids in treating painful somatic symptoms or pain related disorders in both depressed and non-depressed patients.

Tapentadol

Tapentadol has got agonistic effect at the μ-opioid receptor which is responsible for analgesic effect and the inhibition of nor-epinephrine reuptake is responsible for antidepressant effect. Tapentadol has also been demonstrated to be sigma-2 receptor agonist, although whether or not sigma activity contributes to tapentadol analgesic effect is still a matter of contention and the function of the sigma-2 receptor has not yet been conclusively determined.

Mirtazapine

Mirtazapine enhances the release of nor-epinephrine by blocking a_2-adrenergic auto receptors as well as serotonin 5-hydroxytryptamine (5-HT2A) and 5-HT3 receptors and histamine H_1 receptors which is responsible for its antidepressant effects, whereas the antinociceptive effect of mirtazapine mainly involves μ- and κ3-opioid mechanisms.

METHODS

This study was conducted on healthy Swiss albino mice of either sex 3-4 months old and weighing around 25-30 g maintained at an ambient temperature of 25-35°C were procured from the disease free small animal house, NIMS Medical College and Hospital, Jaipur, Rajasthan, India. The animals had free access to food and water *ad libitum*, and were housed in an animal room with alternating light dark cycle of 12 hrs each. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experiments. Experiments were carried out between 9 a.m and 12 p.m. All the experiments were performed according to the CPCSEA after obtaining the approval of the Institutional Animal Ethical Committee.

Animals were divided into seven groups of six mice each.

1. Group I (control) was given normal saline (0.1 ml/10 g)
2. Groups II, III, IV (standard) was administered with mirtazapine (3, 5 and 7 mg/kg, i.p.) for 14 days
3. Groups V, VI, VII (test drug) were treated with three different doses (10, 20 and 40 mg/kg, i.p.) of tapentadol for 14 days.

Tapentadol and mirtazapine were dissolved in normal saline.

Model for testing antidepressant and analgesic activity

Forced swimming test (FST)

It is commonly used for the assessment of the antidepressant like properties of drugs. Mice were forced to swim individually in a glass jar (25 cm^3 × 12 cm^3 × 25 cm^3) containing fresh water of 15 cm height and maintained at 25°C (±3°C). In the first 2 mins, the animal was allowed to adjust to the new conditions, and then, the immobility time that alternated with conditions of enhanced motor activity was measured. Immobility time was measured with a stopwatch for the next 4 mins (Porsolt et al., 1977). Mice were removed from their cages and placed in individual glass cylinders containing water at 22-24°C at a depth of 14-16 cm so that they could not escape and could not touch the bottom. The animals were placed in the cylinders for observation in a 6 mins test swim. Two swimming sessions were conducted: an initial 15 mins pretest followed 24 hrs later by a 6 mins test). The duration of immobility was measured for a 4 mins period. The duration of immobility during the last 4 mins of the 6 mins test was measured. The mouse was considered as immobile when it stopped struggling and moved only to remain floating in the water, keeping its head above water. Shorter immobility time was an indicator of the stronger antidepressant effect of the tested substance (Urani et al., 2001).

Tail flick test

Analgesic activity was measured by the tail flick method, using the analgesiometer as described by D'Armour and Smith.[10] Radiant heat was directed to the proximal third of the tail through hot wire of analgesiometer and reaction time was noted when the mouse tried to pull the tail away. For each animal, the tail flick latency was obtained thrice before drug administration, and the mean was used as pre-drug latency. The tail flick latencies were measured at 0, 0.25, 0.5, 1, 1.5, 2 and 3 hrs after administration of vehicle or drug (s). For animals that did not respond within the cut-off time of 10 sec, the value of the cut-off time was considered as latency period for that animal.[11]

Statistical analysis

All results are expressed as mean ± standard error of mean (SEM). All the groups were analyzed using ANOVA, followed by Student's t-test. $p<0.05$ was considered significant.

RESULTS

Effect of test drugs on immobility period in FST for antidepressant activity

Mean duration of immobility was significantly reduced by mirtazapine in a dose and duration dependent manner as compared to control ($p<0.05$) as shown in Figures 1-3 respectively. Similarly, the duration of immobility observed in mice presented with all the doses of tapentadol was also reduced ($p<0.05$). Decrease in immobility due to tapentadol (20 and 40 mg/kg) was found to be significant ($p<0.05$) when we compared to mirtazapine at dose of (3 mg/kg) as shown in following Figures 1-3 antidepressant effect of tapentadol was found to be effective with increasing doses.

The SEM for Group I (control) is 10.98, Group II (tapentadol 10 mg/kg) is 8.33, Group III (tapentadol 20 mg/kg) is 7.57, Group IV (tapentadol 40 mg/kg) is 6.06, Group V (mirtazapine 3 mg/kg) is 6.81, Group VI (mirtazapine 5 mg/kg) is 6.06, Group VII (mirtazapine 7 mg/kg) is 5.30 and in total 7.30.

The SEM for Group I (control) is 10.22, Group II (tapentadol 10 mg/kg) is 7.95, Group III (tapentadol 20 mg/kg) is 7.19, Group IV (tapentadol 40 mg/kg) is 5.68, Group V (mirtazapine 3 mg/kg) is 6.43, Group VI (mirtazapine 5 mg/kg) is 5.68, Group VII (mirtazapine 7 mg/kg) is 4.54 and in total 6.81.

The SEM for Group I (control) is 9.46, Group II (tapentadol 10 mg/kg) is 7.19, Group III (tapentadol 20 mg/kg) is 6.43, Group IV (tapentadol 40 mg/kg) is 5.30, Group V (mirtazapine 3 mg/kg) is 5.68, Group VI (mirtazapine 5 mg/kg) is 4.92, Group VII (mirtazapine 7 mg/kg) is 4.16 and in total 6.16.

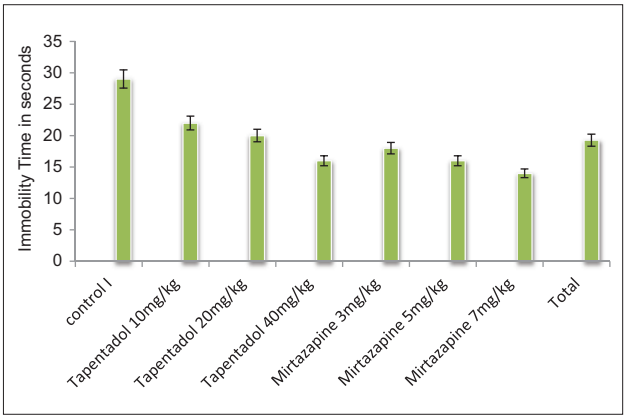

Figure 1: Forced swim test on day 1.

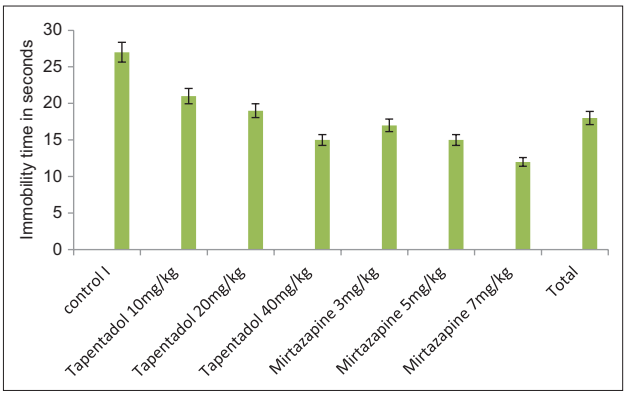

Figure 2: Forced swim test on day 7.

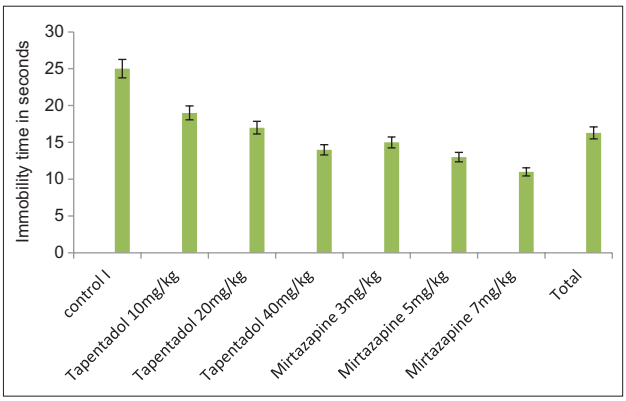

Figure 3: Forced swim test on day 14.

Effect of test drugs on tail flick latency for analgesic activity

Mirtazapine (3 mg/kg) showed no significant increase in tail flick latency period as compared to the corresponding 0 mins values in mice on tail flick analgesiometer but mirtazapine (5 and 7 mg/kg) produced significant increase in tail flick latency at all-time intervals ($p<0.05$) as shown in Figures 4-6 while tapentadol showed significant increase in tail flick latency at all the doses (10, 20, 40 mg/kg) and at all the time intervals ($p<0.05$) and was found to be effective. These drugs produced a dose-dependent antinociception.

The SEM for Group I (control) is 4.92, Group II (tapentadol 10 mg/kg) is 8.33, Group III (tapentadol 20 mg/kg) is 9.09, Group IV (tapentadol 40 mg/kg) is 10.98, Group V (mirtazapine 3 mg/kg) is 4.92, Group VI (mirtazapine 5 mg/kg) is 7.57, Group VII (mirtazapine 7 mg/kg) is 8.71 and in total 7.79.

The SEM for Group I (control) is 5.68, Group II (Tapentadol 10 mg/kg) is 9.46, Group III (tapentadol 20 mg/kg) is 10.22, Group IV (tapentadol 40 mg/kg) is 11.74, Group V (mirtazapine 3 mg/kg) is 5.68, Group VI (mirtazapine 5 mg/kg) is 7.95, Group VII (mirtazapine 7 mg/kg) is 8.71 and in total 8.49.

The SEM for Group I (control) is 6.06, Group II (tapentadol 10 mg/kg) is 10.60, Group III (tapentadol 20 mg/kg) is 11.74, Group IV (tapentadol 40 mg/kg) is 12.5, Group V (mirtazapine 3 mg/kg) is 5.68, Group VI (mirtazapine 5 mg/kg) is 8.71, Group VII (mirtazapine 7 mg/kg) is 9.09 and in total 9.19.

DISCUSSION

In this study, antidepressant and analgesic activity of tapentadol was evaluated in the FST and tail flick test respectively. Tapentadol and mirtazapine produced significant antidepressant and analgesic activity in a dose-dependent manner as compared to control. In our study, we found less antidepressant activity of tapentadol at a dose of 10 mg/kg but it was still significant as compared to control animals. Similar finding were observed from the same group of drugs in earlier study.[12] In our study, the antidepressant activity of tapentadol at a dose of 20 mg/kg and 40 mg/kg was comparable to the antidepressant drug which was very much similar to the findings of Tayal et al.[13] The analgesic activity of tapentadol was significant at all the doses as compared to control animal which was similar to the previously done studies.

There is large body of evidence to suggest that the analgesic action of tapentadol is mainly related to central monoaminergic mechanism and opioids receptor pathway. *In-vitro* studies have shown that tapentadol effectively inhibit reuptake of monoamines. It has also been established that tapentadol inhibits the reuptake of serotonin in the raphe nucleus. Anti-depressants mainly act by inhibiting nor-epinephrine and serotonin reuptake and tapentadol by virtue of its property of blocking monoaminergic reuptake also act as antidepressants.

Similarly mirtazapine at the dose of 3 mg/kg showed no antinoceptive effect which was different from the study done by (Abdalla and Kalthom, 2012) who showed the antinociceptive effect at the dose of 1.25 mg/kg. In our study, mirtazapine showed better antinociceptive effect at the dose of 5 and 7 mg/kg which is supported by the findings of Bomholt et al.[14] and Muth-Selbach et al.[15] Brannon and Stone[16] who reported analgesic effect of mirtazapine for chronic back pain. These results suggest

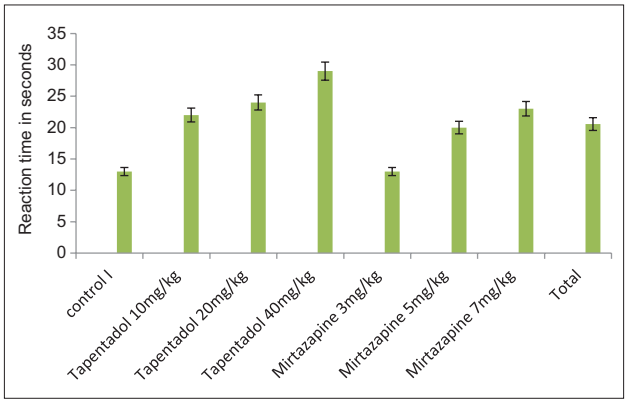

Figure 4: Tail flick on day 1.

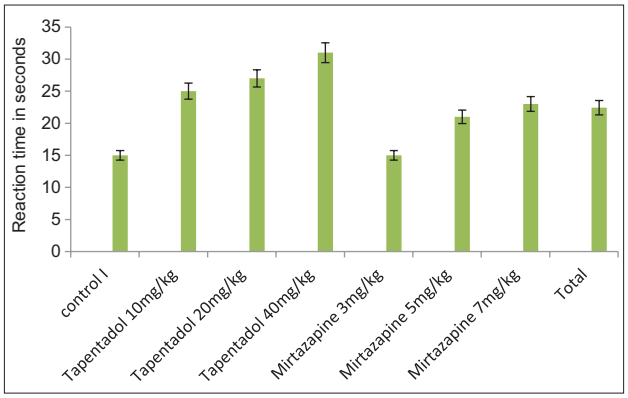

Figure 5: Tail flick on day 7.

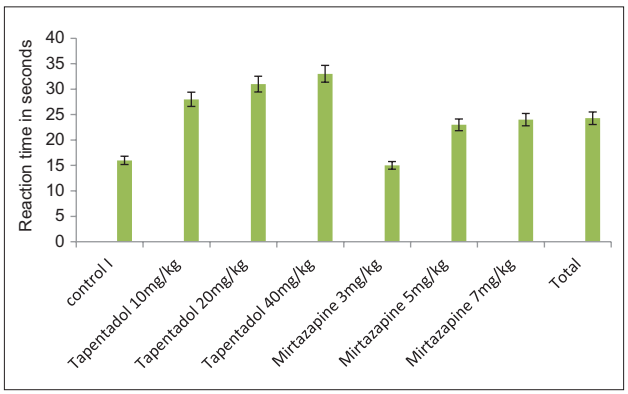

Figure 6: Tail flick on day 14.

that the antinociceptive activity of this antidepressant drugs could involve opioid mechanisms. These observations are in agreement with the findings of Singh et al.[17] and Anjaneyulu and Chopra.[18] As the analgesic activity of tapentadol is mediated through μ receptors, it is likely that mirtazapine act through opioid pathways involving the μ opioid receptors. Apart from that there is ample evidence to suggest that descending pain inhibitory pathways involve monoamines such as noradrenaline (NA) and 5-HT, serotonin. Spinal inhibition of pain, brought about by inhibiting NA and 5-HT reuptake, is one of the major mechanisms of action of opioid analgesics and mirtazapine by virtue of its property of blocking monoaminergic reuptake is responsible for its antinociceptive activity.

Apart from that, mirtazapine blocks selectively 5-HT2 and 5-HT3 type receptors, and increases noradrenergic and serotonergic neurotransmission via a blockade of the central α2-auto- and hetero-adrenoreceptors and thus shows antidepressant and antinociceptive action.

Mirtazapine is not considered to have a risk of many of the side effects often associated with other antidepressants like the selective serotonin reuptake inhibitors, and may actually improve certain ones when taken in conjunction with them. These adverse effects include decreased appetite, weight loss, insomnia, nausea and vomiting, diarrhea, urinary retention, increased body temperature, excessive sweating, pupil dilation and sexual dysfunction.

The antidepressant activity of mirtazapine is very well-known as it increases the level of monoamines in different way which is responsible for its antidepressant actions and it was significant at all the doses as compared to control animal which is also supported by the findings of earlier studies. During the study mirtazapine showed some mild adverse effects peripheral edema while we did not observe any sort of adverse effect with tapentadol.

CONCLUSION

The result of this study indicates analgesic activity of tapentadol at all the doses and mild antidepressant property (10 mg/kg) and moderate at (20, 40 mg/kg) while mirtazapine have no analgesic activity at (3 mg/kg) and significant at (5, 7 mg/kg), but showed antidepressant effect at all the doses. Hence, we concluded that tapentadol as superior drug in case of pain associated with depression than mirtazapine because of its suitable profile of action. However, further studies are required to substantiate these findings especially in clinical set up.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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