Comparative Evaluation of Tramadol and Tapentadol on Psychomotor Function in Healthy Volunteers

Vijay Khajuria, Shabnam Choudhary, Neelam Rani, Roshi, Sanjeev Gupta

Abstract
Centrally acting opioid analgesics are frequently used in clinical practice and these drugs are known to cause sedation. To compare the effect of two commonly used analgesics tramadol and tapentadol on critical flicker fusion frequency (CFFF) which is the most sensitive indicator of cortical arousal. The study was conducted in ten healthy volunteers. It was a single dose, open label, cross over study. Volunteers were familiarized with critical flicker fusion test apparatus till they attained plateau level in their values. Volunteers were given 50 mg single dose of either of test drug orally and then crossed over with ten days wash out period between each trial. In each arm, volunteers were followed up to six hours. Both tramadol and tapentadol decreased the CFFF significantly during entire study period (p<0.000) from their respective pre-drug values. On comparison no statistical difference was observed between two drugs on CFFF (p>0.05). Result of current study highlights the impairment of psychomotor performance (CFFF) with both drugs in a similar manner. These observations could be of immense clinical importance especially when prescribed to ambulatory patients, more so while executing complex tasks.

Key Words
Opioid Analgesics, Tramadol, Tapentadol, Critical Flicker Fusion Frequency, Psychomotor Performance

Introduction
Drugs affecting CNS are known to alter psychomotor function and cognition. Centrally acting opioids analgesics are often used in clinical practice for relief of post operative pain, chronic cancer pain and traumatic pain. Opioids cause significant impairment of psychomotor or cognitive function and would hamper performing of complex daily activities.

Since newer centrally acting analgesics are now prescribed widely for variety of indications like non-malignant, chronic low back pain or osteoarthritic knee pain and it becomes imperative that in addition to relieving pain, analgesic therapy must allow patients to maintain their independent and active state. Among these tramadol and tapentadol are commonly used analgesics.

Tramadol is a mu-opioid receptor agonist that also inhibits the reuptake of nor-epinephrine and serotonin. The non-medical use of prescription opioids, including tramadol, has increased in the U.S. over the last several years.

Oral tapentadol hydrochloride (HCl) is also a mu-opioid receptor agonist and monoamine-reuptake inhibitor approved by the Food and Drug Administration for treatment of moderate-to-severe acute pain in adults.

Though tramadol is known to cause sedation but only a few studies are available in literature regarding their effects on psychomotor functions and cognition. There is also a paucity of data on evaluation of tapentadol on psychomotor functions though a study has shown it not to interfere with driving ability. To best of our knowledge no study has comparatively evaluated the effect of tapentadol and tramadol on psychomotor functions.
Therefore, the present comparative study was conceived to evaluate the effects of tramadol and tapentadol on critical flicker fusion which is the most sensitive psychomotor functions test in evaluating cerebral cortical arousal with the objective that outcome of study would be useful in clinical practice to assess safety of these drugs while handling complex tasks.

**Material and Methods**

The present cross-over study was conducted in the Department of Pharmacology, Government Medical College, Jammu after prior approval of Institutional Ethics Committee. The volunteers were screened for inclusion and exclusion criteria.

Inclusion criteria included normal, non-smoker, non-alcoholic subjects without any history of intake of any CNS affecting drugs. Volunteers with co-morbid conditions, anxiety, depression, history of intake of psychotropic drugs, long term medication, and drugs interfering with psychomotor functions at least four weeks prior to commencing trial were excluded from the study.

Ten healthy volunteers with normal biochemical and pathological laboratory values were selected who fulfilled the eligibility criteria. The volunteers were asked to abstain from caffeinated drinks, cola drinks and chocolates during the trial period.

Volunteers were familiarized with the critical flicker fusion apparatus for several days until their task values reached a stable level to exclude the learning effect. Written informed consent was obtained from volunteers prior to their inclusion in the study.

The volunteers were both men and women in age group of 25-35 yrs with weight between 45-55 kg. Each volunteer was given either of the two test drugs (tramadol 50 mg, tapentadol 50 mg) orally and followed up to six hours, with a wash out period of ten days between the drug formulations followed by cross-over.

A semi-automatic Critical flicker fusion frequency apparatus was used under standardized conditions, and double-blind technique was employed. Volunteers were required to discriminate the flicker fusion in a set of four light emitting diodes. After a fixed period of one minute accommodation, the frequency either progressively increased or decreased until the volunteer reported change in his flicker perception (from flicker to fusion or vice versa). The volunteers were tested five times with increasing and five times with decreasing frequency and mean of these ten reading was calculated.

**Statistical Analysis**

Data obtained was expressed in mean ± standard error of mean. Change from baseline scores brought by test drugs was noted, and comparison was analyzed by paired "t" test. The p value less than 0.05 was considered significant.

**Results**

Both opioid agonist drugs led to impairment of critical flicker fusion frequency. Oral administration of tapentadol(50 mg) led to decline in CFFF from the baseline score taken prior to intake of test drug. The baseline value of 32.35 ± 0.856Hz decreased to 31.11±0.926 Hz at 1 hr (p=0.002), 30.73 ± 0.931Hz at 2 hr (p=0.0006), 30.55 ± 0.960 Hz at 3 hr (p=0.0002), 30.4 ± 0.938Hz at 4 hr (p=0.0002), 30.5 ± 0.931Hz at 5 hr (p=0.0002) and 30.35 ± 0.951 Hz 6 hr (p=0.0002).

Oral Tramadol (50 mg) also caused decrease in CFFF in similar fashion like tapentadol. The baseline value of 32.35± 0.856Hz decreased to 31.3 ± 0.890Hz at 1 hr (p=0.001), 30.89 ± 0.940Hz at 2 hr (p=0.0002), 30.83 ± 0.858 Hz at 3hr (p=0.0002), 30.66 ± 0.877Hz at 4 hr (p=0.0002), 30.70 ± 0.898Hz at 5 hr (p=0.0002) and 30.63 ± 0.909 Hz 6 hr (p=0.0002)

On comparison, both the drugs showed similar magnitude of impairment of CFFF and there was no statistically significant difference among them (p>0.05), though numerically more impairment was noted with tapentadol. The results are shown in Table 1 & Fig 1.

**Discussion**

CNS depressants are known to cause impairment of psychomotor functions. (1) The impairment assumes clinical importance because of increase in accidental risks, handling of mechanical implements and carrying out daily routine work. Though central depressants impair cognitive functions but there is paucity of research work on elucidation of the effect of commonly used analgesics tramadol and tapentadol hydrochloride (HCl) on these functions. Consequently aim of the present was to compare and examine the effect of these drugs on psychomotor function with their common clinically used dose. Amongst the psychomotor function tests, the critical flicker fusion was selected. Critical flicker fusion (CFF) is the most reliable method for measuring the affects of CNS depressant drugs on cortical arousal. The effect on cerebral arousal varies greatly from one antidepressant to another and CFF is sensitive test for assessing the sedative effect of these drugs. (8)
In the present study, oral tramadol (50mg) administration significantly decreased the CFF values (p=0.00). Tramadol is commonly used to treat moderate to severe pain; its analgesic effects are mediated by a combination of mu-opioid agonist effects and nor epinephrine and serotonin reuptake. Full opioid agonists (e.g., morphine) have been shown to impair psychomotor and cognitive performance. (2) However, a few studies have evaluated the effect of tramadol on psychomotor functions but the results of these studies are equivocal. Most of these works carried out in opioid dependent or sporadic drug users failed to demonstrate the impairment of psychomotor performance with tramadol or morphine. (4,9,10) Miriam Z. Mintzer, et al 2010 (5) has also evaluated effects of repeated tramadol and morphine on psychomotor and cognitive performance in opioid-dependent volunteers. They have shown that performance was significantly worse in the morphine treated group than tramadol treated on psychomotor speed/coordination (circular lights task), psychomotor

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Baseline</th>
<th>1st hour</th>
<th>2nd hour</th>
<th>3rd hour</th>
<th>4th hour</th>
<th>5th hour</th>
<th>6th hour</th>
</tr>
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<tbody>
<tr>
<td>Tramadol (n=10)</td>
<td>32.35±0.856</td>
<td>31.3±0.890</td>
<td>30.89±0.940</td>
<td>30.83±0.858</td>
<td>30.66±0.877</td>
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<td>P=0.001</td>
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<tr>
<td>Tapentadol (n=10)</td>
<td>32.35±0.856</td>
<td>31.11±0.926</td>
<td>30.73±0.931</td>
<td>30.55±0.096</td>
<td>30.4±0.938</td>
<td>30.5±0.931</td>
<td>30.35±0.951</td>
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<td></td>
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<td>Intergroup P value</td>
<td>0.126</td>
<td>0.276</td>
<td>0.162</td>
<td>0.068</td>
<td>0.178</td>
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speed/pattern recognition (DSST). They suggested that tramadol is generally a safe medication with respect to cognitive and psychomotor functions in opioid dependence.

However, sedation and blurred vision has been reported with tramadol treated 22 percent patients to prevent psychomotor functions evaluation on Digit Symbol Substitution Test (DSST) compared to 32% with morphine. (11)

Tapentadol hydrochloride (HCl) is a centrally acting analgesic mu-opioid-receptor agonist and monoamine reuptake inhibitor (noradrenaline, serotonin) approved by the Food and Drug Administration for treatment of moderate-to-severe acute pain. However it has a potential to contribute to or precipitate serotonin syndrome and anticholinergic/5-HT3 antagonist effects and to induce physical/psychological dependence. (12)

In the current trial the oral administration of tapentadol lead to decline in CFF in a familiar fashion like tramadol. Review of literature revealed no report regarding effect of tapentadol on psychomotor functions(CFFF). Such an observation could be of clinical importance as strong centrally acting analgesics (e.g., opioids) are gaining acceptance in clinical practice for treatment of pain even in non-malignant, chronic pain. (13) These situations may require of long-term analgesic therapy and it becomes of utmost importance that patients remain independent and stay active (15). However, ?-opioid receptor agonist activity reported to adversely affect patients’ cognitive and psychomotor performance. (16,17) and current trial also demonstrated similar results.

Conclusions

The results of present study underscores the potential of tramadol and tapentadol to cause impairment of critical flicker fusion frequency which is an indicator of cortical arousal and important component of psychomotor performance. However impairment of psychomotor performance tests obtained in healthy volunteers must be carefully considered before these are interpolated in actual clinical situation. Current study suffers from limitation of being an acute study and not a placebo control trial. It is possible that results may be different with chronic usage of these drugs.

References