ABSTRACT

Background: Tramadol, an opioid group is one important central analgesic. Nimodipine is an L-type calcium channel blocker used generally in hypertension. Combining opioids with certain other drugs increases the analgesia. Nimodipine may be one such a drug.

Objective: To assess the adjuvant analgesic effect of nimodipine in tramadol-treated rats.

Methodology: Healthy 24 albino Wistar male rats of weight 150-200 gm were used. Animals were placed on the Hot-plate (temp: 55-56°C) and jumping was taken as hot-plate latency period. Cut off time 45 seconds taken to avoid thermal injury. The rats were placed on hot-plate and jumping latency was observed on day-1. On day-2 tramadol was given and after 60 minutes they were observed. After 5 days (wash out) nimodipine was given and observed in same manner. After another 5 days the combination of the drugs given and jumping latency was observed. Analysis: Mixed ANOVA was done after proper collection of data. Conclusion: Nimodipine potentiates the analgesic effects of tramadol.

KEYWORDS: Analgesic, Tramadol, Nimodipine, Hot-plate method.

INTRODUCTION

Pain is an ill-defined, disabling accompaniment of many medical conditions. It is often evoked by an external or internal noxious stimulus. Analgesics are the drugs which possess significant pain relieving properties by acting in the CNS or on peripheral pain receptors without significantly affecting consciousness. Combining opioids with certain other drugs increases the analgesia. Nimodipine may be one such a drug. There are lacunae of knowledge regarding this. So our main objective is to assess the adjuvant analgesic effect of nimodipine in tramadol-treated Wistar rats using Hot-plate method.
MATERIAL AND METHODS

This animal experiment was conducted in the Pharmacology Department of Government Medical College, India. Study duration was 8 weeks.

Animals

Wister albino rats (Rattus norvegicus Albinus), aged between 6-7 months weighing 150-200 gm (n=24) were obtained for present study from the appropriately maintained institutional animal house. The rats had free access to drinking water and rat food pellets. The light source in the animal room was regulated with 12 hr light period followed by 12 h dark schedule within a temperature of range of 22 ± 2°C at a relative humidity of 45 to 50%. All rats were acclimatized for at least 7 days before starting the study. All procedures involving animals were undertaking according to the Committee for the purpose of control and supervision on experiments on animals (CPCSEA) guidelines and the study was started after obtaining the approval from the concerned ethics committee (IAEC).

Study design

Animals were placed individually on the Hot-plate, which consists of electrically heated surface (Temp of the hotplate 55-56°C)\(^2\) and jumping was taken as hot-plate latency period. Cut off time 45 seconds\(^2\) taken to avoid thermal injury, following which the animal was removed from the hot-plate to prevent tissue damage. Jumping latency was observed before giving the saline/tramadol/nimodipine. The time period (jumping latency) of testing was 60 minutes\(^3\) after saline/tramadol/nimodipine administration. All drugs are given intraperitoneally. The rats were given physiological saline and after 60 minutes they were placed on hot-plate and jumping latency was observed on day-1. On day-2 tramadol (9mg/kg) was given and placed on hot-plate after 60 minutes. They were observed for jumping latency and times were recorded. Tramadol dose, calculated by extrapolation from maximum human dose (100 mg/day) came to 9mg/kg per rat per day. After 7 days (wash out) nimodipine (2 mg/kg intraperitoneally)\(^4\) was given and observed in same manner. After another 7 days (on day-16) the combinations of the drugs were given and jumping latency was observed after 60 minutes. A single brand and batch\(^5\) of nimodipine was chosen and purchased from local market and this was also true for tramadol.

The data for this study was subjected to standard statistical analysis using the IBM-SPSS ver. 20 data processing software for windows seven. For all tests, the p-value was considered to
be significant if it was less than 0.05 at a confidence level of 95%. Statistical analysis was done by mixed ANOVA followed by Bonferroni multiple comparison test.

RESULT AND ANALYSIS

TABLE 1. Pre and post jumping latency time.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pre* (mean±SD)</th>
<th>Post** (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4± 0.7</td>
<td>5.8± 1</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>4.8± 1</td>
<td>7± 0.5</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4.6± 1.6</td>
<td>13.8± 2.6</td>
</tr>
<tr>
<td>Nimodipine + Tramadol</td>
<td>5± 1.4</td>
<td>24.2± 5.4</td>
</tr>
</tbody>
</table>

*Jumping latency before giving the drug.
**Jumping latency after 60 minutes of giving the drug.

There was homogeneity of variances, as assessed by Levene’s test of homogeneity of variance (p > .05). There was homogeneity of covariances, as assessed by Box's test of equality of Covariance matrices (p = .048). There was a statistically significant interaction between the intervention and time on Hotplate latency, F (3, 95) = 119.58, p < .0005, partial eta squared = 0.957.

There was a statistically significant difference in hotplate latency between interventions at the post-point of the intervention, F (3, 16) = 130.47, p = .000, partial Eta Squared= 0.961.

Hotplate latency is significantly higher in tramadol (p=0.00) and nimodipine-tramadol combination group (p=0.00) when compared with control but not statistically significant in case of nimodipine group. Hotplate latency is significantly increased in both tramadol and nimodipine-tramadol combination group between pre and post intervention period.

DISCUSSION

Analgesics are mainly divided into two groups-1) narcotic/opioid and 2) non-narcotic/NSAID.[1] Nimodipine is short-acting dihydropyridine group of calcium channel (L-type) blocker which penetrates blood-brain barrier very efficiently due to high lipid-solubility.[3] It is generally used as anti-hypertensive. Though originally used as an anti-hypertensive agent, its current use is restricted to the treatment of acute subarachnoid haemorrhage.[4] L-type calcium channels have been reported to mediate the major part of membrane calcium currents in the small sized dorsal-root ganglion neurons.[5] Tramadol is an
atypical opioid which acts as a centrally acting analgesic. It has affinity for mu-receptor and also kappa and delta receptor. It also inhibits reuptake of NA & 5-HT, increases 5-HT release and thus activates monoaminergic spinal inhibition of pain.[3]

In 2008, Ray et al had showed in a study[4] that, Nimodipine is more effective than in attenuating Morphine tolerance on chronic co-administration in the rat tail-flick test. This shows similarity with our study where we use tramadol instead of Morphine. The result of our present study shows that nimodipine, which is an L-type calcium-channel blocker, which does not have any analgesic action by itself, but increases/potentiates the analgesic effect of tramadol by nimodipine. The mechanism responsible for the potentiation could be due to additional closure of L-type voltage-dependent calcium channels by nimodipine in neurons concerned with transmission of pain. This is besides closure of N- and P/Q-type voltage-dependent calcium channels by tramadol in the presynaptic nerve terminals.[4] Other studies have also showed the effect of L-CCBs on morphine-induced analgesia on chronic administration.[6,7]

CONCLUSION
Analgesic potential of nimodipine when combined with tramadol.

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REFERENCE
