



ANTINOCICEPTIVE EFFECT OF GABAPENTIN IN NAIVE AND WITH NEUROPATHIC PAIN RATS

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ABSTRACT

PURPOSE: Neuropathic pain is dysfunction of the peripheral and central nervous system at different levels. Gabapentin is recently used as analgesic for neuropathic pain. **METHODS:** 72 male Wistar rats were used in 2 experimental series. In the first were 5 groups: saline; Metamizol 150 mg/kg; Gabapentin 30, 60 or 100 mg/kg. In the second were 4 groups: sham, saline, Diclofenac 25 mg/kg and Gabapentin 60 mg/kg. Neuropathic pain was induced by chronic constriction injury of the sciatic nerve. Seven days after ligature the antinociceptive effect was evaluated in two nociceptive tests. Criteria for hot-plate test were the reaction time in seconds on a heated surface, for analgesimeter -the paw reaction in cm. **RESULTS:** In 1st series Gabapentin in all doses increase the latency reaction in hot-plate test. In analgesimeter Gabapentin in a dose 60 mg/kg increased of pressure reaction. In rats with neuropathic pain the group treated with Gabapentin increased the latency reaction at 120 and 180 min in hot-plate test. In analgesimeter rats treated with Gabapentin did not change the latency of reaction. **CONCLUSIONS:** Our data show that Gabapentin produced inhibition on thermal-hyper analgesia in naïve and with neuropathic pain model, but had no effect on the mechanical-induced nociception.

Key words: experimental study, sciatic nerve injury, hot-plate test, analgesimeter

INTRODUCTION

Neuropathic pain is a direct consequence of injury or disease causing dysfunction of the peripheral and central nervous system at different levels (1). Based on the suspected pathophysiological mechanisms involved, different drugs have been used to treat neuropathic pain. Gabapentin is an anti-convulsive drug often used as analgesic for chronic pain that binds to the alpha-2-delta subunit of voltage-dependent calcium channels, whose number increases with central sensitization (2).

In this study we aimed to examine the antinociceptive properties of Gabapentin in naïve and rats with sciatic nerve constriction.

MATERIAL AND METHODS

There were used 72 male Wistar rats, divided in 2 experimental series. In the first series rats divided in 5 groups (n=8) were treated with: 1) saline 0.1 ml, i.p.; 2) Metamizol 150 mg/kg; 3) Gabapentin 30 mg/kg; 4) Gabapentin 60 mg/kg; 5) Gabapentin 100 mg/kg. In the second series animals were divided in 4 groups (n=8). Peripheral neuropathic pain was induced in rats by chronic constriction injury. Animals were anesthetized with intraperitoneal injection of Chloralhydrate (3,8% solution; 2,5 ml). After shaving the left back leg, the skin was incised and the proximal and distal parts of the biceps femoris muscle were separated to expose the sciatic nerve. Two loose ligatures were placed around the sciatic nerve to induce neuropathic pain. The muscle and skin were closed with

surgical sutures. The animals were allowed to recover from surgery for one week. Drug application started on the next day after operation: group I (shame); group II (control); group III-Diclofenac 25 mg/kg; group IV-Gabapentin 60 mg/kg. Seven days after ligation of the sciatic nerve, the antinociceptive effect was evaluated in hot-plate and Randall-Selitto tests (3). The hot-plate test evaluates the reaction time of rats in seconds with are dropped on a heated surface. The analgesic meter test exerts a force increased at constant rate and the paw reaction was measured in cm.

Statistical analysis

The obtained values were expressed as mean \pm SEM. The comparison between the groups

was made by Student's t-test of analysis of variance (one way ANOVA), in the INSTAT computer program. Tukey-Kramer Multiple Comparison Test was used to compare each parameter of the respective experimental group with the control group. A value of $P < 0.05$ was considered as statistically significant.

RESULTS

Series I

In the hot-plate analgesic test the average latency of the control was between 12 and 19 sec. The animals treated with Gabapentin in all doses increased the latency reaction on 60, 120 and 180 min ($p < 0.05$) as compared with the respective control group (**Figure 1**).

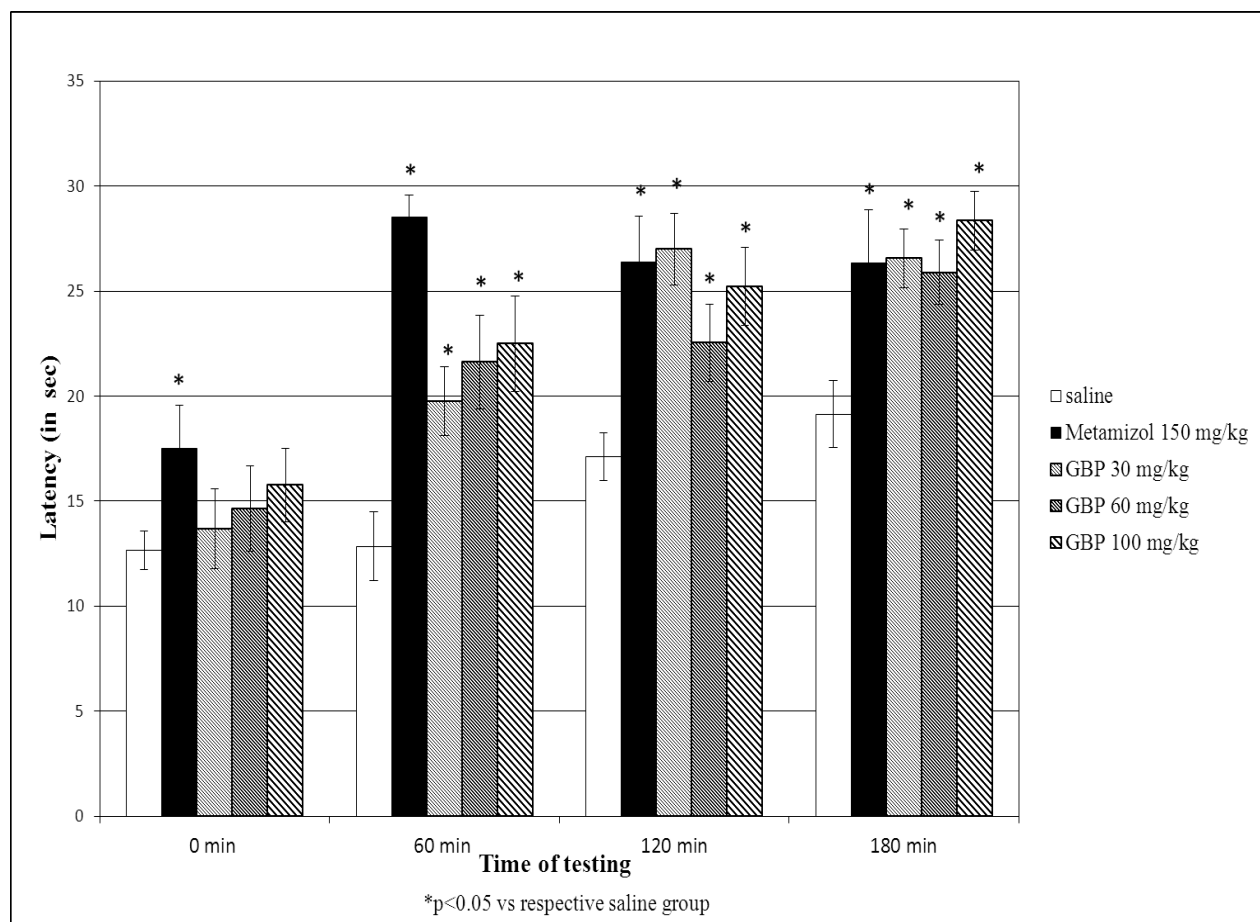


Figure1. Effects of Gabapentin (GBP) on hot-plate test

In the analgesy-meter test the control animals showed average pressure reaction between 7 and 12 cm. Rats treated with 60 mg/kg of Gabapentin showed a significant increase ($p < 0.05$) of pressure reaction on 120 min as compared with

the respective control group. The group treated with 100 mg/kg of Gabapentin showed an increase of pressure reaction on 0 min ($p < 0.05$) as compared with the respective controls (**Figure 2**).

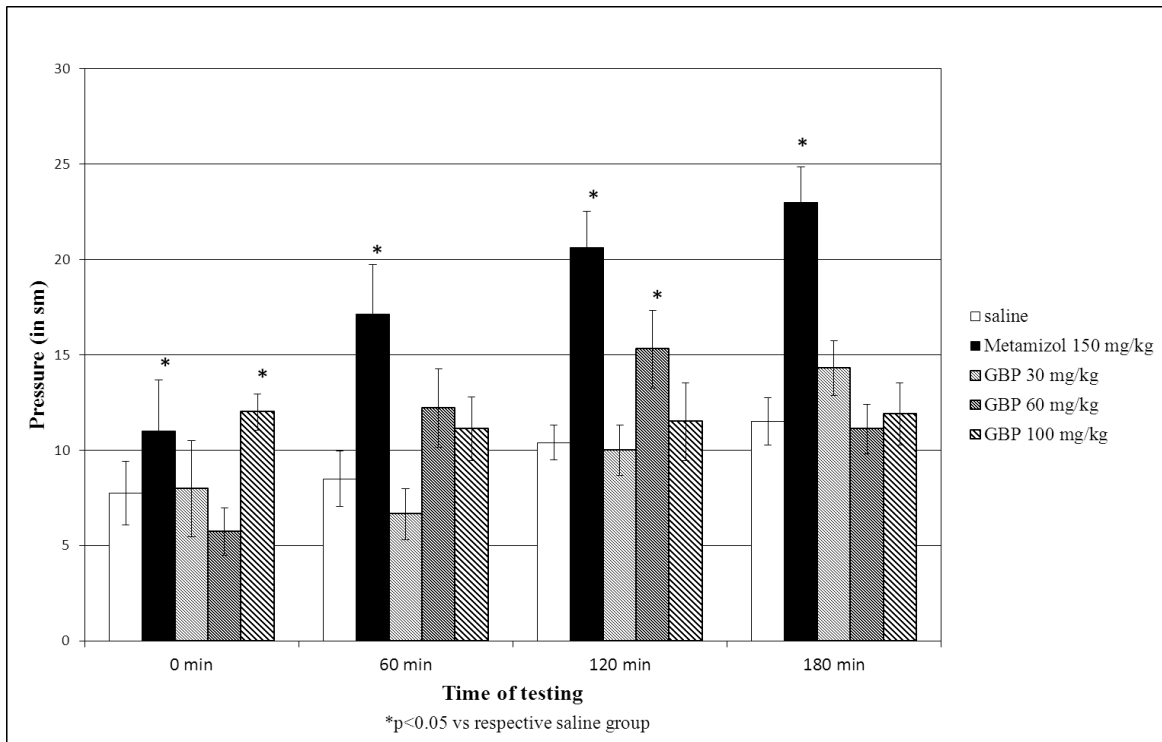


Figure 2. Effects of Gabapentin (GBP) on Randall-Selitto test

Series II

In hot-plate test the saline group increased the latency at 0 and 60 min compared with

respective sham control. Gabapentin treated rats increased the latency at 120 and 180 min ($p < 0.05$) compared with respective saline control (**Figure 3**).

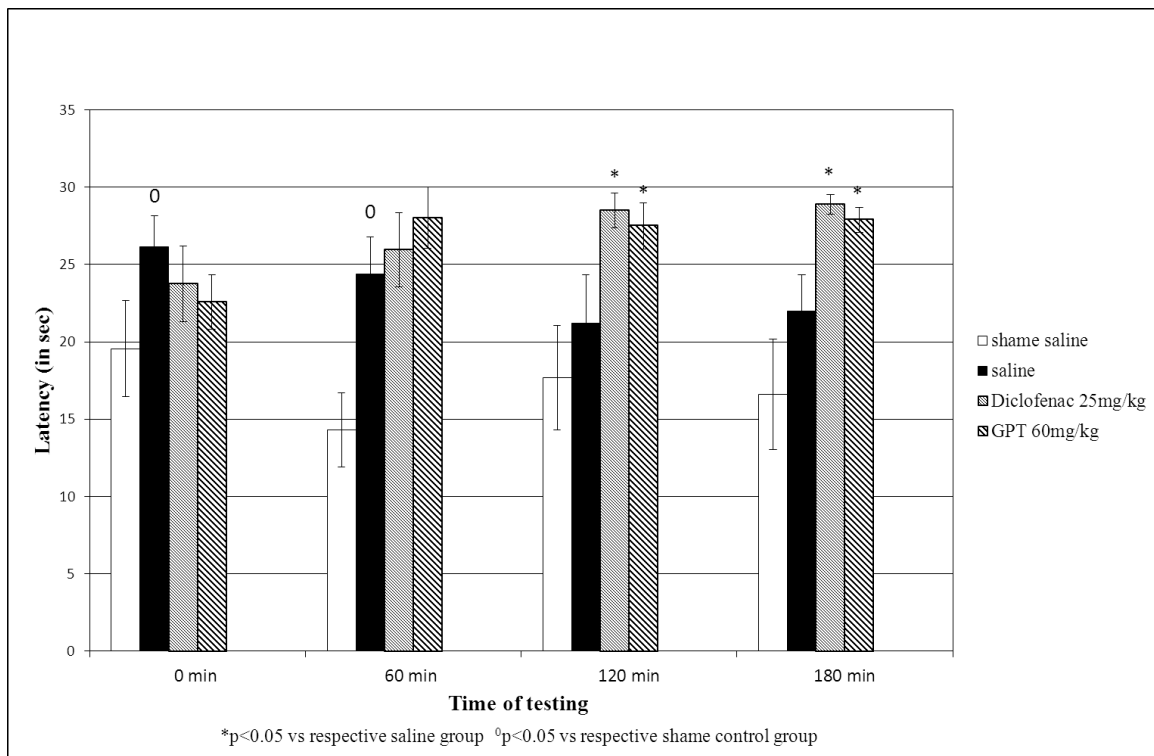


Figure 3. Effects of Gabapentin and Diclofenac on hot plate test in rats with neuropathic pain

In analgesy-meter test the controls and rats treated with gabapentin did not changed the

latency of reaction (**Figure 4**).

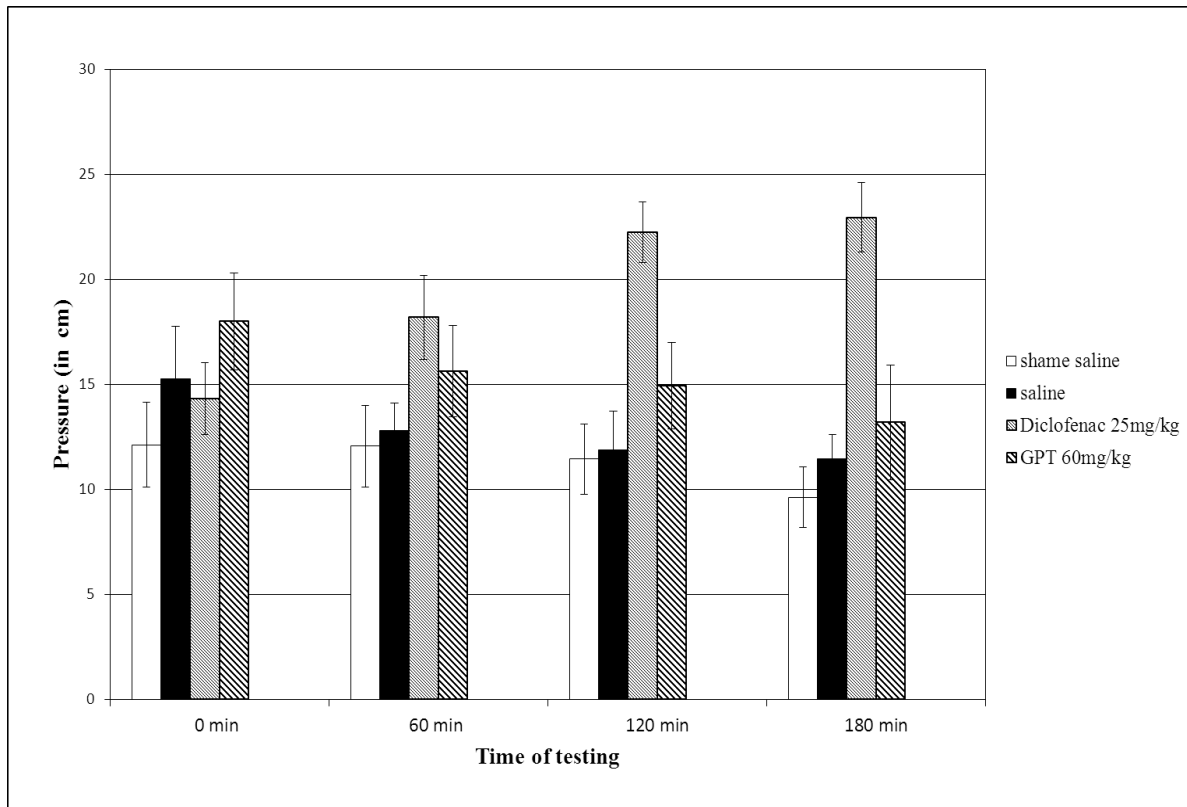


Figure 4. Effects of Gabapentin and Diclofenac on Randall-Selitto test in rats with neuropathic pain

DISCUSSION

In the experiments of the Series I, gabapentin in all doses exhibited antinociceptive effect on thermal hyperalgesia assessed with the hot-plate test. Further, 60 mg/kg gabapentin showed analgesic effect because it increases the latency of reaction at 120 min in the Randall-Selitto paw pressure test. Our experiments of the Series II confirmed the analgesic effect of gabapentin using the thermal test following sciatic nerve injury, further supporting the beneficial gabapentin role on neuropathic pain. Camara et al (2013) using the same model also demonstrate antihyperalgesic effect of gabapentin on the same doses (1). On the contrary, Gabapentin showed no preventive effect on the development of neuropathic mechanical hypersensitivity. This observation may be attributable to the divergent types of afferent fibers involved in the transmission of mechanical versus thermal stimuli, i. e., myelinated (A- β and A- δ) fibers for mechanical stimuli and unmyelinated C fibers for noxious heat. Second, the low doses of

gabapentin used in these experiments may have been insufficient to exert analgesic effects on both sensory modalities. Another explanation for the discrepancy between treatment effects on mechanical and thermal sensitivity could be due to the mechanism of action gabapentin in the different nerve fibers. The action of gabapentin on the $\alpha 2\delta$ subunit of voltage-dependent calcium channels is thought to include a decreased release of neurotransmitters in the synapse and the redistribution of calcium channels from plasma membrane to the cytosol (4). Gabapentin's spinal and supraspinal actions are thought to include increasing the flow of N-methyl-D-aspartate in GABAergic interneurons and activating the ATP-sensitive K^+ channel currents that contribute to neuronal hyperpolarization (5).

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REFERENCES

1. Camara, C.C., Ramos, H.F., Alan P. da Silva, Oral gabapentin treatment accentuates nerve and peripheral inflammatory responses following experimental nerve constriction in Wistar rats. *Neuroscience Letters*, 556: 93-98, 2013.
2. Kilic, F.S., Sirmagul, B., Yildirim, E., Antinociceptive effects of gabapentin and its mechanism of action in experimental animal studies. *Indian J Med Res*, 135: 630-635, 2012.
3. Randall L.O., Selitto J. J., A method for measurement of analgesic activity on inflammed tissue. *Arch. Int. Pharmacodyn.*, 61: 409-419, 1957.
4. Hahm,T.S., Ahn, H.J., Bae, C.D., Kim, H.S., Protective effects of gabapentin on allodynia and alpha 2 delta 1-subunit of voltage-dependent calcium channel in spinal nerve-ligated rats. *J.Korean Med. Sci.*, 24: 146-151, 2009.
5. Cheng JK, Chiou LC., Mechanisms of the antinociceptive action of gabapentin. *J Pharmacol Sci.*, 100:471-486, 2006.