

Comparative animal study of the antinociceptive efficacy of lamotrigine and gabapentin for the management of pain

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Pain relief using drugs with high efficacy provides significant improvement in the patients' lives. Drugs like lamotrigine (LTG) and gabapentin (GBP) have the ability to overcome the symptoms of neuropathic pain. *Aim:* The present study offers a comparative analysis of LTG and GBP efficacy in a rat model of nociceptive pain after single administration. *Method:* Sixty-three Wistar-Bratislava rats randomized into 7 groups were included: a control group treated with saline solution and 6 groups treated with different doses of LTG and GBP. Nociceptive responses to thermal and mechanical stimulations were evaluated before and after drug administration, at different time intervals, using paw pressure and hot plate tests. The obtained data were statistically analyzed, with significance at p value < 0.05 . *Results:* LTG 100 mg/kg and 50 mg/kg presented a significant analgesic effect in both mechanical and thermal tests, 1 and 2 hours after administration. GBP 100 mg/kg increased latency time in hot plate test. The effect of both anticonvulsant drugs occurred rapidly after administration, but had a short duration. *Conclusions:* LTG and GBP had an analgesic effect in a single dose administration. The effect of LTG was more evident since it was observed in both tests. Their effect was dose dependent.

Keywords: pain, anticonvulsant, antinociception, gabapentin, lamotrigine

Pain is the most common physical symptom. Many patients experience more than one location of pain (33). A fifth of the European adult population is suffering from some kind of moderate or severe chronic pain (4). Chronic pain includes several types of syndromes – musculoskeletal pain, ischemic or visceral pain syndromes, neuropathic pain ranging from post herpetic neuralgia through diabetic neuropathy or phantom limb pain to trigeminal neuralgia, cluster headache and severe cancer pain (32, 33). Despite modern technology and the important advances in pharmacotherapy, pain management remains unsolved. Effective drugs with well-known mechanism and proven efficacy are still absent.

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Based on its etiology, chronic pain is classified as sensorial, neuropathic and mixed (18). Neuropathic pain is the most difficult to control, presenting multiple tasks to both basic researchers and clinicians (26). Neuropathic insults are frequently accompanied by severe and debilitating pain, which often becomes chronic, lacking responsiveness to basic analgesic treatment (1, 26, 33).

The existing pain treatment is currently based on three major classes of medications that are recognized as effective: paracetamol and nonsteroidal anti-inflammatory drugs, opiate and co-analgesic medication (26). Co-analgesic medications include several groups of drugs, like antidepressant and anti-seizure drugs. They all have certain well-defined benefits, but we are still away from that one drug that would effectively control and treat different manifestations of chronic pain (29).

Antiepileptic drugs act through a different mechanism in pain relief: potentiation of GABA transmission, reduction of glutamate transmission and blockade of different types of voltage-gated channels (21). The complexity of the underlying mechanisms is translated by the variable success to overcome pain (1, 33). One of the most used drugs is carbamazepine, but it has some limitations (absence of efficacy in some cases, drug–drug interactions, adverse effects, hypersensitivity) (19). Some anticonvulsants that seem to enhance GABA-ergic neurotransmission, e.g. gabapentin, tiagabine or pregabalin, are showed to be effective in managing debilitating pain by specifically targeting the spinal GABA-A receptors (11, 15, 24). Several forms of pain are based on the loss of inhibitory neurotransmission, normally performed by the GABA-ergic and glycinergic neurons (12).

Drugs like lamotrigine (LTG) and gabapentin (GBP) are used to provide adequate pain control. These drugs stabilize plasma membrane, preventing hyper-excitation, due to the lack of GABAergic inhibition and ectopic discharges in the peripheral nerve fibers (2). The antinociceptive effect of GBP is thought to be also due to its interaction with the α -2-delta subunit of the voltage dependent calcium channels (22).

LTG is an inhibitor of voltage-gated sodium and calcium channels (20). By stabilizing the neuronal membrane, LTG prevents the release of excitatory mediators, inhibiting the sustained neuronal firing (21, 22). In different pain models, LTG was shown to be the most potent drug due to its analgesic effects and mechanism of action (25, 28, 30).

The aim of this study is to compare the effect of gabapentin and lamotrigine in acute administration at different doses, in several animal models of acute nociceptive pain.

Materials and Methods

Animals

A number of 63 adult white male Wistar-Bratislava rats, weighing 60–120 g, were obtained from the Animal Facility and Research Unit of “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania. The rats were housed five in a cage and were kept under standard 12-hour circadian rhythm in constant temperature ($21 \pm 1^\circ\text{C}$) and humidity ($55\% \pm 5\%$) conditions, with free access to food (standard animal chow) and water. Prior to the experiment, the animals were fasted for 12 hours with *ad libitum* access to water.

Drugs

Lamotrigine and gabapentin (Sigma Chemical St. Louis, MO, USA) were dissolved in saline solution. Drugs were injected intraperitoneally (i.p.) in a total volume of 0.2 ml/100 g as a single dose. All solutions were freshly prepared before each experimental series. The prepared

stock solution was used to obtain different doses of the mentioned drugs that were used in the experiment: 1 mg/kg, 10 mg/kg and 100 mg/kg for GBP and 10 mg/kg, 50 mg/kg and 100 mg/kg for LTG.

Measurement of nociceptive response

Hot plate test: An evaluation of central and peripheral pain mechanisms can be assessed using the hyperalgesic response on the hot plate test (HPT) (Ugo Basile, Milan, Italy), a model for acute nociception. Together with the tail flick test, they are standard tests that determine if a drug has antinociceptive effects. Animals were individually exposed to noxious heat stimulation by being placed on a metal plate (50 ± 0.1 °C). The first sign of jumping or paw licking was recorded as the latency of the nociceptive withdrawal response. Basal latency was set 24 hours prior to drug administration. In order to prevent tissue damage, a 60 s cut-off time was set.

Paw pressure test: Mechanical nociceptive threshold of the left rear paw was assessed using the mechanical analgesic test (MAT) with the plantar mechanical analgesimeter (Ugo Basile, Milan, Italy) by applying linearly increasing mechanical force to the rat's paw until the retraction of the paw or a squeak (vocalization) was recorded. Basal latency was defined as the force determining the rat to withdraw its paw and it was set 24 hours prior to the tests. The cut-off pressure was set at 500 g.

Experimental groups

The animals were randomized into seven groups, each consisting of 9 animals. One group, the control one, was injected with saline solution 0.2 ml/100 g. The other 6 groups were experimental groups. The animals from group 1 to 3 were injected with LTG 10 mg/kg, 50 mg/kg and 100 mg/kg, while groups 4 to 6 were injected with GBP 1 mg/kg, 10 mg/kg and 100 mg/kg. The drugs were given by intraperitoneal injection in a constant volume of 0.2 ml/100 g. The assessment of the nociceptive responses to noxious mechanical and heat stimuli was performed before injection (baseline) and 1, 2, 4 and 24 hours after drug administration, for both tests mentioned above.

The experiments were carried out in accordance with the European Union guidelines and the institutional guidelines of the University of Medicine and Pharmacy, Cluj-Napoca, Romania. The protocol was approved by the Ethical Committee of the University of Medicine and Pharmacy Cluj-Napoca, Romania.

Statistical analysis

The statistical analysis was performed using SPSS version 19. The obtained results are expressed as mean \pm SEM (standard error of mean). Differences between time points and drugs or doses were assessed with a variation of ANOVA for repeated measures. The results at each time point were compared using the one-way ANOVA, with post hoc Tukey test, or Student *t*-test, whenever appropriate. Significance was taken at a *p* value of < 0.05 .

Results

In the present study, the animal groups were homogeneous, without statistically different results in terms of animal weight in the 7 groups. The homogeneity is also indicated by the lack of differences between the basal values of the 7 groups studied for both hot plate and paw pressure tests.

ANOVA for repeated measures showed that nociceptive threshold in mechanical test varied significantly between time points and the difference was related to LTG doses ($p < 0.001$). One-way ANOVA performed 1 hour after drug administration revealed statistically significant differences ($p < 0.001$) in the case of the mechanical test. The group treated with 50 mg/kg LTG presented a significantly increased nociceptive threshold compared to the control group ($p = 0.005$), showing a certain analgesic effect. The antinociceptive effect of LTG is also suggested by the other tested doses, being noticed especially for LTG 100 mg/kg. However, in spite of its presence, the analgesia produced did not reach the level of statistical significance when performing the mechanical test. In the case of GBP, no significant analgesic effect was observed for the tested doses when performing the analgesiometric method one hour following drug administration.

Two hours after drugs administration, one-way ANOVA revealed significant statistical difference in the case of the analgesimeter test. The statistically significant results, confirmed by the post hoc Tukey test, were observed for LTG 100 mg/kg ($p < 0.007$) and 50 mg/kg ($p < 0.001$) compared to the control group in MAT. The third group injected with 10 mg/kg did not reveal any significant increase in nociceptive threshold. The comparison between LTG doses indicated the same statistical significance as the smallest dose of it for both LTG 100 mg/kg ($p = 0.003$) and LTG 50 mg/kg ($p = 0.014$). At the two hours time point, GBP-induced analgesia did not reach the statistical significance at either dose, compared to the control group when performing MAT.

Four hours following drug administration, the highest LTG dose (100 mg/kg) maintained the statistically significant effect ($p < 0.001$) compared to control when performing MAT. In case of the lower LTG doses (50 mg/kg and 10 mg/kg), the statistically significant effect compared to the control group is not present during MAT, but even the lowest dose (10 mg/kg) induced a reduction of pain threshold (Fig. 1).

ANOVA for repeated measures for hot plate test indicated an increase in latency time for LTG 100 mg/kg and LTG 50 mg/kg at 1 hour time point, compared to basal values ($p = 0.01$, $p = 0.02$). For GBP, only the highest dose (100 mg/kg) induced a significant increase in latency time compared to baseline values ($p = 0.005$) and to other GBP doses. LTG 100 mg/kg ($p = 0.02$) and 50 mg/kg ($p = 0.02$), and GBP 100 mg/kg ($p = 0.0001$) induced an increase in latency time compared to the control group.

In HPT, there was a significant increase in latency time for all LTG doses (100 mg/kg, $p = 0.001$; 50 mg/kg, $p = 0.0008$, respectively, 10 mg/kg, $p = 0.05$) and for PGB 100 mg/kg ($p = 0.0006$), compared to the control group at 2 hours time point.

The lowest dose of LTG (10 mg/kg) presented a statistically significant effect compared to control group ($p < 0.001$) during HPT at 4 hours time point. LTG 100 mg/kg ($p < 0.001$) and 50 mg/kg ($p = 0.02$) induced a significant reduction in latency time in 4 hours time point compared to basal values and to the control group. GBP had a statistically significant effect compared to the control when used in higher doses (100 mg/kg and 10 mg/kg). However this effect was not present in case of lower doses during the second test (Fig. 2).

None of the administered drugs and none of the selected doses presented any statistically significant analgesic effects 24 hours after drug administration.

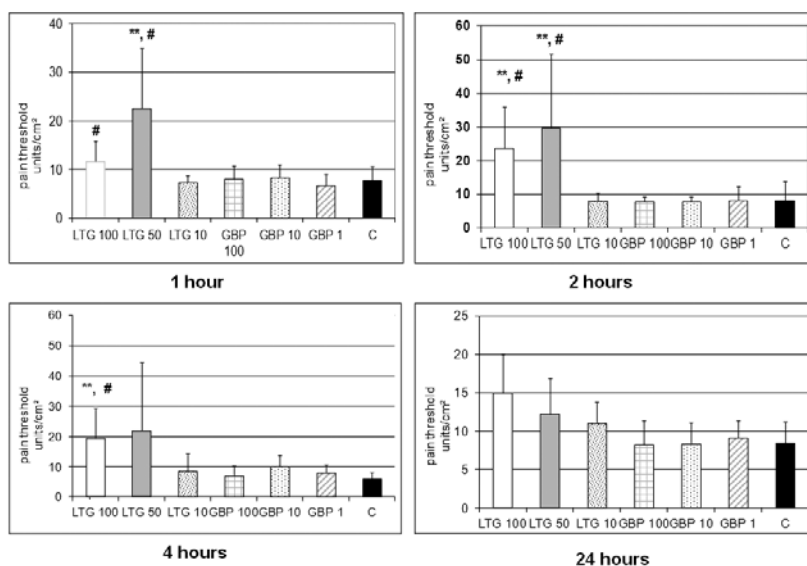


Fig. 1. Effect of lamotrigine (LTG) and pregabalin (PGB) in mechanical test (MAT).

Legend: Columns represent the pain threshold (mean±SEM) at 1 hour (upper left), 2 h (upper right), 4 h (lower left) and 24 h (lower right). LTG = lamotrigine, GBP = gabapentin, LTG 100 = LTG 100 mg/kg, LTG 50 = LTG 50 mg/kg, LTG 10 = LTG 10 mg/kg, GBP 100 = GBP 100 mg/kg, GBP 10 = GBP 10 mg/kg, GBP 1 = GBP 1 mg/kg.

** $p < 0.05$ comparison vs control, # $p < 0.05$ comparison vs LTG 10

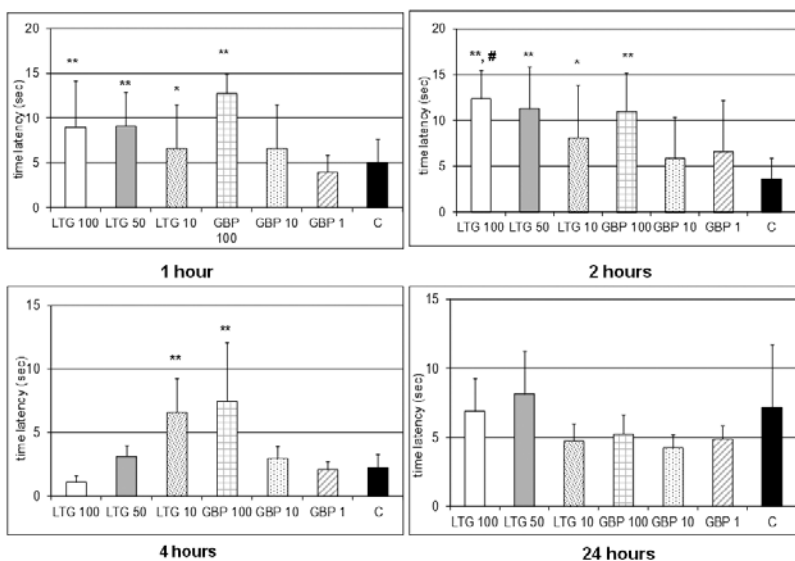


Fig. 2. Effect of lamotrigine (LTG) and pregabalin (PGB) in hot plate test (HPT).

Legend: Columns represent the pain threshold (mean±SEM) at 1 hour (upper left), 2 h (upper right), 4 h (lower left) and 24 h (lower right). LTG = lamotrigine, GBP = gabapentin, LTG 100 = LTG 100 mg/kg, LTG 50 = LTG 50 mg/kg, LTG 10 = LTG 10 mg/kg, GBP 100 = GBP 100 mg/kg, GBP 10 = GBP 10 mg/kg, GBP 1 = GBP 1 mg/kg.

** $p < 0.05$ comparison vs control, # $p < 0.05$ comparison vs LTG 10

Discussion

The present study demonstrates the antinociceptive effect of lamotrigine and gabapentin, two anticonvulsant drugs commonly used for treatment of neuropathic pain to reveal their efficacy in acute nociceptive pain tests. We used the thermal analgesic test, the hot plate test and the mechanical analgesic test. These tests are simple and easy to reproduce and are frequently used for the investigation of the analgesic properties of different drugs.

The obtained results show an important analgesic effect of LTG 100 mg/kg and 50 mg/kg that does not reach the statistically significant threshold when used in lower doses (10 mg/kg). The analgesic effect of GBP is only present in high doses (100 mg/kg). The results are consistent with LTG, being used in both tests. The analgesic effect of LTG and GBP occurs immediately after drug administration and lasts at least four hours when using the highest investigated doses.

Ever since the first reports on the analgesic effect of carbamazepine in trigeminal neuralgia indicated by Blom (3), the use of anticonvulsant drugs in pain management has increased (2). Basic and clinical studies show an even better efficacy of these drugs in control and final stage therapy for several clinical conditions characterized by chronic pain (1, 2, 18, 30). AEDs act by modifying the muscle or nerve excitability threshold, by controlling the ectopic firing and the chaotic neuronal discharge. Blocking voltage-gated Na and Ca channels, promoting GABA-A mediated inhibition, they counteract pain by inhibiting several electrophysiological changes that would make the cells fire from ectopic sites spontaneously and at inappropriately high frequencies (2, 22, 29). They have an important role in promoting the inhibition of abnormal neuronal activity and pain relief.

Data regarding the efficacy of these drugs in acute models of nociceptive pain are inconsistent in the literature. Most studies are related to chronic neuropathic pain (2, 9). Both investigated anticonvulsants decreased the hot plate response, but the effect is more pronounced for LTG, as it is noticed at different doses. The previous studies mentioned different results for LTG, with low efficacy in acute nociceptive pain (15, 21). Antinociceptive effect of LTG in models of acute pain evoked by PGE₂ (16) or capsaicin (14) were reported. Lee et al. (16) observed that pre-treatment with LTG suppressed mechanical and thermal hyperalgesia in an acute model of inflammatory pain. Post-treatment with LTG had an effect only on mechanical nociception. Joshi et al. (14) observed an attenuation of mechanical hyperalgesia in capsaicin model of pain, but they used lower doses compared to the present study. All these studies described antinociceptive effects under hyperalgesic conditions (14, 16). Results presented in this paper provide, however, clear evidence that particularly LTG but also GBP diminish nociception also under physiological conditions.

The antinociceptive effect of LTG is probably a consequence of sodium channel blocking effect. It has already been proven that sodium channels are essential for action potential initiation and propagation and further neuronal conduction, in both normal and pathological pain (8, 23). In the case of neuropathic pain, there is an over-expression of sodium channel subtypes (such as NaV1) in the dorsal ganglia of the spinal cord (17, 23). Recent findings mention the LTG modulation of the GABA system in damaged neuronal networks involved in neuropathic pain (6). We consider that the antinociceptive effect of LTG is a consequence of the inhibition of several sodium channel subtypes and the release of excitatory mediators that prevent mechanical allodynia and thermal hyperalgesia, similar to neuropathic and inflammatory pain models.

On the other hand, GBP had no effect on the model of acute pain used in our study during the mechanical test. This observation is similar to others that indicated the lack of GBP effect in different types of measurements of normal transient nociceptive signaling (11, 15, 21). It is known that GBP has no effect on normal fiber activity, but inhibits the discharge activity associated with nerve injury, lesions that are present in neuropathic pain (11, 20). However, GBP and pregabalin, have been reported to be efficient in certain types of cancer-related pain (10) or experimental nociception (13, 24). Previous studies noticed that GBP reduced thermal and mechanical responses in different types of hyperalgesia (chemical or inflammatory pain) (7, 11, 13, 21), suggesting that GBP is rather an antihyperalgesic drug than an antinociceptive drug.

Experimental studies using GBP in models of acute pain hypothesized the existence of different mechanism involved at spinal level, that could explain the effect of high doses of GBP in preventing noxious thermal responses: inhibition of excitatory mediators like glutamate (34), inhibition of NMDA and AMPA-mediated responses (27) or activation of GABA_{B1a-B2} heterodimer in the superficial laminae of the spinal cord (31). In the case of neuropathic pain other laminae of spinal cord are involved, with different type of GABA dimers in modulation of pain.

Different mechanism may explain the results in nociception under physiological condition. Christensen et al. (5) remarked that gabapentin alleviated the mechanical allodynia in a model of neuropathic pain, but only in repeated administration, not after a single dose of drug. Compared to gabapentin, lamotrigine had not influenced the mechanical allodynia in this type of model, either in single or repeated administration. The antinociceptive effect of GBP 100 mg/kg during the hot plate test and lamotrigine effect during both tests probably involves different mechanisms that need further investigation.

This study shows clear evidence that LTG or GBP are not long-acting drugs. The effect of GBP is maintained longer than LTG, also being present at the 4-hour time interval during the hot plate test. Either a multiple administration schedule or drug combinations are needed for a continuous effect, which is in accordance with Christensen's study (5).

Despite the absence of conclusive and concrete results, the efficacy of AEDs in nociceptive pain is fairly encouraging. Further studies and much more research are needed to fully understand the importance and necessity of AEDs in pain treatment. The elevated threshold for the propagation of neuronal impulses and the abnormal neuronal discharge, which are depressed by AEDs (10, 20), conceal their therapeutic efficiency in nociception and neuropathic pain. In the past years, the treatment of these pain states has been fundamentally reconsidered, since a promising novel treatment method was promoted involving the use of AEDs.

In conclusion, this study demonstrates the effect of different doses of GBP and LTG in nociceptive pain. The analgesic effect of LTG in acute pain in rats is more constant than that of GBP. In both cases, the analgesic effect is dose-dependent. However, further studies are required to explain the mechanisms responsible for this difference in efficacy.

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