AĞRI 2012;24(2):49-55
doi: 10.5505/agri.2012.31032

The antinociceptive effects of systemic administration of tramadol, gabapentin and their combination on mice model of acute pain

Farelerde akut ağrıda sistemik uygulanan tramadol, gabapentin ve kombinasyonlarının antinosiseptif etkileri

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Summary

Objectives: The aim of the present study was to investigate the possible antinociceptive effects of systemic administration of tramadol and gabapentin either alone or in combination on acute pain models in mice.

Methods: After obtaining the approval of Animal Ethics Committee; 96 BALB/c albino male mice were divided into 12 groups: (I) control without injection, (II) control treated with saline, (III)-(IV) mice treated with tramadol 10 mg/kg or 30 mg/kg, (V)-(VIII) mice treated with gabapentin; 30, 100, 200, 300 mg/kg respectively. In order to determine possible interactions between tramadol gabapentin and; mice received four different combinations of tramadol + gabapentin (30+30, 30+100, 30+200 and 30+300 mg/kg) (Groups IX-XII respectively). Mice received 0.1 ml solution for every 10 g of their weight. The drug was injected into peritonea. Thirty minutes after the drug injection, tail-flick and hot-plate tests were conducted.

Results: Ten and 30 mg/kg tramadol produced dose dependent antinociceptive effect in tail-flick and hot plate tests. Gabapentin had no antinociceptive effect in the tail flick test except 300 mg/kg dose, and had dose dependent antinociceptive effect in hot-plate test. In both tests, various combinations of tramadol and gabapentin produced an antinociceptive effect that is greater than that produced by tramadol and gabapentin alone. But, just 30 mg/kg tramadol + 300 mg/kg gabapentin combination caused statistically significant increase in both tests ($p<0.05$).

Conclusion: When gabapentin and tramadol were used in combination, gabapentin had no additive antinociceptive effect except for 300 mg/kg in tail-flick and hot-plate tests. Tail-flick test showed that tramadol produced better antinociceptive effect than gabapentin.

Key Words: Drug interaction; gabapentin; hot-plate; mice; nociception; tail-flic; tramadol.

Özet

Amaç: *Tek başına veya birlikte sistemik olarak verilen tramadol ve gabapentinin farelerde akut ağrıda olası antinosiseptif etkilerini araştırmaktır.*

Gereç ve Yöntem: *Hayvan etik komitesinin onayı sonrası; 96 BALB/c albino dişi fare 12 gruba ayrıldı: (I) Enjeksiyon yapılmaksızın kontrol grubu, (II) salin uygulanan kontrol grubu, (III)-(IV) tramadol 10 mg/kg veya 30 mg/kg uygulanan gruplar, (V)-(VIII) gabapentinin sırasıyla 30, 100, 200, 300 mg/kg uygulandığı gruplar idi. Tramadol ve gabapentinin olası etkileşimlerinin araştırıldığı gruplarda farelere tramadol+gabapentinin dört farklı dozları uygulandı; (30+30, 30+100, 30+200 ve 30+300 mg/kg) (sırasıyla, Grup IX-XII). Farelerin her 10 gram ağırlığı için intraperitoneal olarak 0.1 mL ilaç uygulandı. Enjeksiyondan 30 dakika sonra tail-flick ve hot plate testleri gerçekleştirildi.*

Bulgular: *On ve 30 mg/kg tramadol tail-flick ve hot plate testlerinde doz bağımlı antinosiseptif etki oluşturdu. Gabapentin 300 mg/kg dışındaki dozlarda tail-flick testinde antinosiseptif etki oluşturmazken, hot plate testinde doz bağımlı antinosiseptif etki oluşturdu. Her iki testte de tramadol ve gabapentin birlikte kullanıldıklarında, tek başlarına kullanılmalarına oranla daha fazla antinosiseptif etki oluşturdu, fakat sadece 30 mg/kg tramadol + 300 mg/kg gabapentin birlikte kullanıldığında her iki testte de anlamlı antinosiseptif etki saptandı ($p<0.05$).*

Sonuç: *Gabapentin ve tramadol birlikte kullanıldıklarında, tail-flick ve hot-plate testlerinde gabapentin 300 mg/kg dozu dışında additif antinosiseptif etki oluşturmadı. Tail-flick testi sonuçlarına göre tramadol, gabapentinden daha iyi antinosiseptif etki oluşturdu.*

Anahtar sözcükler: İlaç etkileşimi; gabapentin; hot-plate; fare; nosisepsiyon; tail-flick; tramadol.

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Submitted (*Başvuru tarihi)* 08.10.2010 Accepted after revision (*Düzeltme sonrası kabul tarihi)* 04.11.2011

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Introduction

Gabapentin (GBP) is an anticonvulsive drug and clinical studies have shown that GBP is effective on diabetical neuropathy, postherpetical neuralgia and reflex sympathetic dystrophy pains.[1-3]

In animal models, it was observed that GBP reduced nociception in mechanical or thermal hyperalgesia, peripheral nerve injury, incisional injury, inflammation injury, and injury related to formalin[4-6] While GBP that is applied systematically or intrathecally is not effective on acute thermal nociception, it is effective on the nociception related to substance P injection, pressure and formalin injection.[4,7]

GBP is a drug that shares a similar structure to that of GABA, although its mechanism of action cannot be explained solely by a direct gaba mimetic effect. [8-10]

It is believed that GBP shows its effect with selective inhibitory effect on voltage-gated calcium channels containing the alpha 2 delta-1 subunit.[11] This effect is derived from the up-regulation of spinal cord and dorsal root ganglion resulting from peripheral injury.[12] GBP generates antihyperalgesia by reducing the glutaminergical transmission to the spinal cord. In addition, GBP can inhibit central sensitization and thermal hyperalgesia that correlates with central sensitization. This effect stems from the direct postsynaptical Ca^{+2} influx of voltage dependent Ca^{+2} channels or the reduction of excitatory aminoacide which results from presynaptical Ca^{+2} influx.[13]

Tramadol is a centrally acting weak opioid analgesic drug that is used in the management of pain.[14] Experimental data suggest that tramadol exerts its analgesic effect through the activation of the central inhibitory monoaminergic pathway because its effect has been partially blocked by alpha-adrenoreceptor antagonists[15] as well as it works as an opioid.

The various interactions might be considered, additive, synergistic, or antagonistic. When two or more drugs are combined, these may produce independent effects (no relation) or effects may be equal to the sum of the effects of each (additive effect). Some pharmacologic agents may inhibit or reduce each other's effects (antagonism), or the effect observed may be more than the one excepted (synergy).[15]

The purpose of this study was to determine the antinociceptive effects of systemic administration of systemic tramadol, gabapentin and their combination on mice model of acute pain.

Material and Methods

Animals

Male Balb/c albino mice weighing 26-38 g were used. The animals were maintained in a temperature controlled (23±1°C) colony room under a 12 h day-night cycle, they were housed 12 per cage in plastic cages, and were given access to food and water ad libitum. The animals received a 1 week habituation period before the experimental procedures were initiated, during which time theywere handled daily. All experiments were performed in accordance with the guidelines for animal research from the National Institutes of Health (NIH publication No. 86-23, revised 1985). All experimental protocols were approved by the Animal Care and Use Committee of the Adnan Menderes University, and were carried according to Helsinki Declaration.

Experimental groups

The animals divided randomly into 12 groups.

Control g.: Mice were injected no drug and served as control group.

Group II: Mice were injected saline intraperitoneally (i.p.) and served as saline group.

Group III: Mice were injected 10 mg/kg tramadol (i.p.)

Group IV: Mice were injected 30 mg/kg tramadol (i.p.)

Group V: Mice were injected 30 mg/kg gabapentin (i.p.)

Group VI: Mice were injected 100 mg/kg gabapentin (i.p.)

Group VII: Mice were injected 200 mg/kg gabapentin (i.p.)

Group VIII: Mice were injected 300 mg/kg gabapentin (i.p.)

Group IX: Mice were injected 30 mg/kg tramadol

+ 30 mg/kg gabapentin (i.p.)

Group IX: Mice were injected 30 mg/kg tramadol + 100 mg/kg gabapentin (i.p.)

Group XI: Mice were injected 30 mg/kg tramadol + 200 mg/kg gabapentin (i.p.)

Group XII: Mice were injected 30 mg/kg tramadol + 300 mg/kg gabapentin (i.p.)

Equipotent dose for mice is 12 times of human dose.[16,17] Tramadol dose is 1-2 mg/kg for human, so we used 10 and 30 mg/kg tramadol in mice treatments. Gabapentin was given maximally 3600 mg/day for human.[2,8] In spite of equipotent dose for mice is approximately 100 mg/kg. Because of antinociceptive effect of gabapentin on acute pain and interaction was investigated between tramadol and gabapentin, we tested 30, 100, 200, and 300 mg/kg doses of gabapentin.

Preparation of drugs and injection

Gabapentin (Neurontin 300 mg caps, Pfizer) and tramadol (Contramal amp, 100 mg/amp, Abdi Ibrahim) were diluted with saline (S). 300 mg Neurontin caps was diluted with saline, and mice received intraperitoneally 0.1 mL solution for every 10 g of their weight. For example Neurontin 300 mg cap was diluted with 30 ml saline and 0.3 ml solution was given intraperitoneally for 30 g of 100 mg/kg gabapentin treated mouse.

Tests

Tail-flick test was preferred as a measure of the response to thermal nociceptive up-regulations, and it is used in the determination of spinal reflex.[1] The hot-plate test was preferred in the determination of the effects of the central affectivity.

Tail-flick test (TFT)

The tail flick latency, defined by the time (in seconds) of withdrawal of the tail from a radiant heat source (bulb, 8 V/50 W), was measured via the usage of a semiautomated device (tail flick analgesiemeter; May Tic., Ankara). After the placement of the tails of the mice into the apparatus in accordance with the procedure, and activation of the apparatus at 55% power, the period required flicking of the tails of the mice was calculated as tail-flick period. Constant heat intensity was applied to the dorsum of the upper third of tails of the mice and when the mouse flicked its tail in response to the noxious thermal stimulus, both the heat source and the timer stopped automatically. A cut off time of 20 seconds (3-4 times more than the basal tail-flick period) was imposed to prevent any injury to the tail. The nociceptive threshold was observed before the study, and 30 minutes after the drug administration.

Hot-plate test (HPT)

The apparatus (May Tr., Ankara), was heated up to (56±0.3ºC) and prepared for the test. The researchers did not know to which group the mice belonged (O.E). When shoe-flick behavior (flicking and raising up foot, shaking- waving, licking foot) was observed, the chronometer of the apparatus was stopped. The latency to the first sign of hind paw licking, or the jump response to avoid heat nociception was taken as an index of nociceptive threshold. The nociceptive threshold was investigated at the beginning of study, and 30 minutes after the drug administration. A cut off time of 20 seconds was imposed to prevent any injury to the foot.

Statistical analysis

All results are expressed as mean (SEM). The tail-flick and hot-plate latencies, before and after the application of drugs, were determined by using the nonparametric Kruskal Wallis test for multiple samples. Kruskal Wallis post hoc test was used to determine statistical significance between the groups. $p<0.05$ was set as the level of statistical significance.

Results

1. Effects of i.p administered tramadol and gabapentin alone in tail-flick test

To test for possible analgesic action on acute nociceptive processing, drugs were administered to mice in the tail-flick test. In the tail-flick test there was no statistical difference between the control group and the saline treated group (4.37±0.70 and 5.78±2.01 s respectively). On the other hand 10 mg/kg and 30 mg/kg TRM treatment statistically increased

tail-flick latencies with dose-dependent fashion (9.16±2.71 and 13.03±4.12 s) ($p<0.05$). There were no significant changes observed in tail-flick test when mice treated with 30, 100 and 200 mg/kg doses of GBP (6.27±0.70, 6.50±0.91 and 6.81±1.12 s respectively). However, 300 mg/kg GBP treatment statistically increased tail-flick latency (11.48±4.30 s) ($p<0.05$).

2. Effects of i.p administered tramadol and gabapentin alone in hot-plate test

In the hot-plate test there was no statistical difference between the control group and the saline treated group (4.13±1.53 and 4.23±0.70 s respectively). However, 10 and 30 mg/kg TRM treatment statistically increased hot-plate latencies (9.91±2.31 and 11.41±1.54 s) ($p<0.05$). GBP treatment with 30, 100, 200 and 300 mg/kg doses caused statistically significant increase in hot-plate latencies (7.75±1.52, 7.87±2.20, 8.10±1.67 and 9.37±2.62 s respectively) ($p<0.05$). There were no significant changes observed between GBP groups.

3. Effects of combined of tramadol and gabapentin tail-flick and hot-plate test

Dose-dependent antinociceptive effects of the drug combinations a tail-flick and hot-plate tests were shown in Fig.1 and Fig. 2. In both tail-flick and hot-plate tests, various combinations of TRM and GBP produced an antinociceptive effect that is greater than that produced by TRM and GBP alone. On the other hand, only 30 mg/kg TRM + 300 mg/kg GBP combination caused statistically significant increase in both tests ($p<0.05$). Other combinations of TRM+GBP were not significant for alone doses of TRM or GBP.

Discussion

It was concluded that TRM is more effective than gabapentin on acute thermal pain in tail-flick test. GBP was not effective on nociception in acute thermal pain, and combination of gabapentin with tramadol has no positive contribution to the antinociception.

The antinociceptive effect mechanism of GBP is believed that GBP shows its effect by means of GABA, NMDA, adenosine receiver and L-arginine nitric oxide or Ca^{+2} channels. Despite the fact that gabapentine increases the synthesis and oscillation of GABA[18] intrathecal (i.t.) application of the receptor antagonists of GABAA and GABAB cannot turn back the effect of GBP.[18,19] While there is no proof that GBP is directly linked to the spinal NMDA receptor; D-serine, a NMDA receptor agonist, can turn back the antinoniceptive effect of GBP.[20] All these findings make one think that GBP generates its effect through NMDA receptors.[21] Bryans et al. [18] speculated that GBP shows its effect with the Ca^{+2} channels in consequence of the connection of voltage sensitive Ca^{+2} channels to the $\alpha_2\delta_1$ subunit. The calcium re-uptake inhibitor is minimally effective on the effect of GBP.[19] Furthermore, the

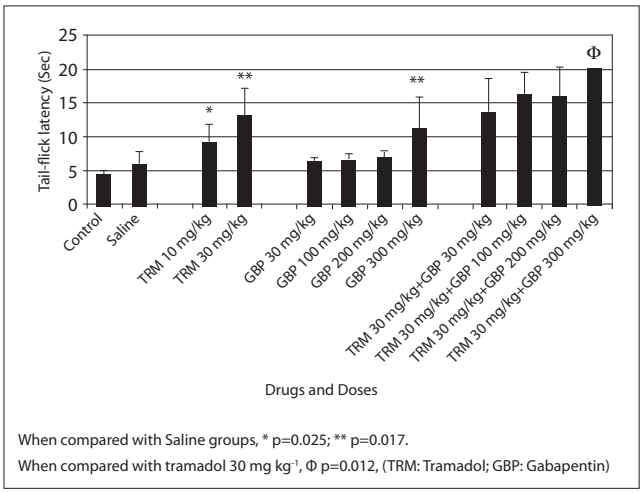

Fig 1. Effect of tramadol, gabapentin, and tramadol + gabapentin on tail-flick test.

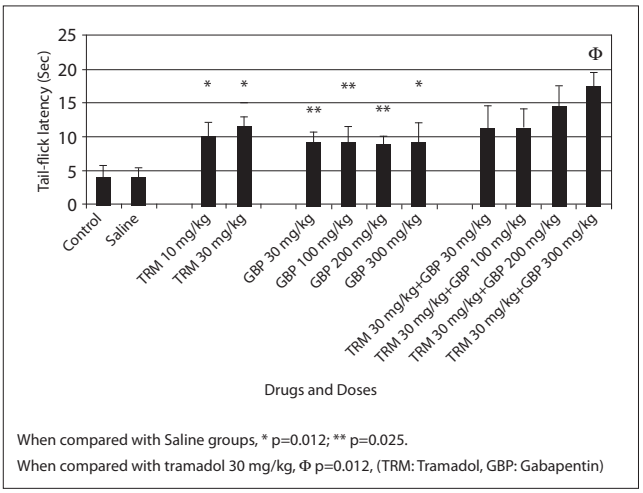

Fig 2. Effect of tramadol, gabapentin, and tramadol + gabapentin on hot-plate test.

antinociceptive effect of GBP is more powerful in i.t. application than it is in its systematical application[6]; therefore, it is thought that the area on which GBP has major effect is the spinal cord.[5,19] While GBP is given systematically and intrathecally reduces the hyperalgesia in the animals with pain related to tissue trauma,[6,7,20] it is not definitely effective on acute pain.[7,20,22]

Field and colleagues[6] emphasized that in the animal models upon which postoperative pain is studied, GBP prevented allodinia and hyperalgesia development, and in rats with acute herpetical pain, systematic or intrathechal GBP reduced both allodinia and hyperalgesia depending on the dosage. It was stressed that in animal models GBP reduced nerve injury, inflammation and hypersensitivity that stems from postoperative pain.[6,20,22]

After the i.t. usage of GBP or following its pre-emptive disposition postoperative pain reduces and the requirement of postoperative opioid decreases.[23,24] When GBP is applied systematically, foot-flick and foot-lick are prevented after 2.5% of formalin hence it is believed that GBP shows its effect systematically and it is effective on allodinia and hyperalgesia rather than nociception.[25] It is demonstrated that GBP is not effective on transient pain models (tail-flick), but only on the models with peripheral tissue injury or nerve legions that result in hyperalgesia or allodinia.[5,6]

Shimoyama et al.[7] when applying i.p. GBP to rats observed meaningful pressurizing in foot-flick after 10 minutes (phase 2) in formalin test and emphasized that this effect takes place with the central sensitization. They mentioned that GBP is not effective on the acute pain depending on surgical injury. As we demonstrated in our study, GBP not having any effects on μ receptor, and not being effective on the tail-flick test explains nociception. GBP is effective on the hot-plate test due to its central effect.

GBP and morphine combination with subanesthesic dose increases the antinoniceptive effect in tail-flick test. This test is an opioid sensitive test by which the analgesic effects of opioids are researched. Since the antinoniceptive effect decreases or increases depending on the spinal morphine dosage, and since opioid antagonists (nalokson) reduce with the effect, it is thought that antinoniception is formed with μ receptor.[26]

It is known that TRM is an opioid analogue affects through μ receptors on acute pain.[27] We concluded that TRM has an antinoniceptive effect on acute thermal pain in the tail-fick test.

Antihyperalgesic drugs like GBP can assume roles in postoperative pain, and their combination with other antinoniceptive medicine can generate synergistic effect.[28] The essential purpose of combining different analgesics is to provide synergistic and additive analgesia by using low and secure dosages of each drug.[22] Due to the variety of the mechanisms that generate pain, usage of opioid and nonopioid analgesic in addition to centrally or peripherally effective drugs, decreases the side effect and the opioid requirement.[29]

We planned our study, in addition to studying the additive/synergistic effect of using the TRM effective on both the central and μ receptors together with GBP, perceiving the lack of studies in which these are used together, based on our literature review.

It was shown that GBP increases the analgesic effect of morphine in volunteers,[23,28] and in the patients with neuropathic cancer pain. When added into the morphine it provided longer analgesia than morphine received alone.[29] Turan et al.[28] mentioned that GBP that is used preoperatively reduces pain scores in the early postoperative period and the postoperative morpine consumption diminishes.

The tonic phase of formalin shows central sensitivity. GBP, by affecting the dorsal horn directly and indirectly, blockades the activation and pressurizes central sensitivity. Spinal GBP and morphine combination, effective on dorsal horn, pressurizes the presynaptical μ receptors.[30] The i.t. usage of GBP in clinic has not been possible in recent times. We can think that i.t. usage of GBP in combination with TRM and other analgesics can be more effective on thermal and acute pain treatment in the future.

In our study we did not observe the additive/synergistical effect of TRM supplied with GBP. We think

that our usage of both drugs in a systematic way (i.p.) instead of i.t., μ receptors less than morphine, and also usage of the acute thermal pain model, resulted in the inability to determine the additive effect formation.

Hurley et al.[31] on a systematic review showed that perioperative oral GBP is a useful adjunct for the management of postoperative pain that provides analgesia through a different mechanism than opioids and other analgesic agents and would make a reasonable addition to a multimodal analgesic treatment plan.

In summary, it was observed that TRM is antinociceptively effective on the acute thermal pain; GBP is not effective on the acute pain, although it generates antihyperalgesia with the central effect. When GBP and TRM are used together in the acute attacks of neuropathic pain will not generate additive and synergistic effect in regular doses.

Acknowledgement

This study was supported by Research Fund Center of Adnan Menderes University.

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