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Gabapentin Increases Analgesic Effect of Chronic Use of Morphine while Decreases Withdrawal Signs

Manzumeh-Shamsi Meimandi, Mina-Mobasher
GholamReza-Sepehri and Ashrafganjooei Narges
Department of Physiology and Pharmacology, Kerman Neuroscience Research Center,
Kerman University of Medical Sciences, Iran

Abstract: This study was performed to evaluate the role of gabapentin co-administration in morphine antinociception and withdrawal effect. Four groups of male rats were examined for latency time using tail flick test; control, morphine (M), gabapentin (GB) and gabapentin-morphine (GB-M) treated groups. Rats received morphine (10 mg kg^{-1}, s.c.) or gabapentin (75 mg kg^{-1}, i.p.) or both of them twice a day for 9 days. Control rats received normal saline as schedule time. Latency time was recorded 3 times (5 min of interval) before drug injection and in 60, 65 and 70 min after drug injection in days 1, 3, 5, 7 and 9 by tail flick test. Percentage of Maximal Possible Effect (%MPE) as antinociceptive effect was calculated for all groups. On 9th day, rats were challenged for withdrawal signs by administration of naloxone (2 mg kg^{-1}, i.p.). Analysis of variance showed no significant difference of %MPE in control and GB groups while in M and GB-M groups the %MPE was changed significantly during the days of study. Gabapentin had no analgesic effect while morphine and gabapentin-morphine had significant analgesic effect compared to control. %MPE of GB-M treated rats was significantly higher than M in days 5, 7 and 9. Also this study showed that pre-treatment with gabapentin reduced most of the opioid withdrawal signs including jumping, weight loss and fore paw tremor. The mechanism(s) by which gabapentin enhances the analgesic effect of chronic use of morphine and attenuate opioid withdrawal signs remain to be establish.

Key words: Analgesia, morphine, withdrawal syndrome, gabapentin

INTRODUCTION

Opioid analgesics are the drug of choice for treatment of severe pain. In treating patients with persistent pain it is of particular interest whether the antinociceptive effect of an analgesic persists after repeated administration. But the use of opioids in chronic pain treatment has led to the development of tolerance and dependence which adds to other opioid side effects. These problems limit the opioid dose and result in inadequate analgesia. Therefore non-opioid analgesics are proposed to enhance analgesic effect and to attenuate side effects of opioids[1].

Gabapentin is a new anticonvulsant drug useful in treating other neurological or psychiatric conditions as spasticity, anxiety and pain[2]. Its analgesic efficacy has been demonstrated in neuropathic pain[3,4], in inflammatory pain[5] and in postoperative pain[6,7]. It is of interest to determine whether gabapentin affect morphine analgesia. In experimental models the co-administration of morphine and gabapentin had significant improvement on analgesic dorsal horn neuronal response in rat model of neuropathy[8]. In another study it was seen that gabapentin increased the antinociceptive effects of spinal morphine in the rat tail-flick test[9]. In a clinical study, in healthy human volunteers gabapentin increased the analgesic effect of morphine[10].

Because of good clinical tolerability of gabapentin and its synergistic effect with morphine in animal experimental model, this study attempt to address the following questions: 1) how gabapentin interact with analgesic effect of repeated administration of morphine? 2) Does gabapentine affect withdrawal syndrome as the consequence of morphine dependency? We therefore have performed an experimental animal study in which intact rats were treated with repeated doses of systemic morphine and gabapentin and tail-flick response and withdrawal signs were evaluated.

Corresponding Author: Manzumeh S. Meimandi, Kerman Neuroscience Research Center, Jomhoori Islami Blvd, P.O. Box 76175-113, Kerman, Iran
Tel: 98 341 2264021 Fax: 98 341 2111010 E-mail: manzume@yahoo.com

MATERIALS AND METHODS

Male NMRI rats (220-250 g) (Purchased from Kerman Neuroscience Research Center) were housed four in a cage in an animal room maintained at 21±2°C and a 12 h dark–light cycle. Food and water were available *ad libitum* except during experiment periods. The experiment was performed, following approval from the appropriate institutional animal subject committee.

Groups of male rats were assessed for reaction time in tail flick test. The intensity of the radiant lamp was adjusted to provide base line levels of 4±0.5 sec. The cut-off point as a tail flick response sufficient to interrupt the tissue damage was 20 sec. The latency time was recorded three times (5 min of interval) before drug injection and in 60, 65 and 70 min after drug injection. Data were expressed in terms of percentage of Maximal Possible Effect (%MPE), defined as follows:

$$\%MPE = \frac{\text{Actual latency time (sec)-base line (sec)}}{\text{Cut-off time (sec)-base line (sec)}} \times 100$$

Morphine group (8 rats) received morphine sulfate (Temad-Iran) in normal saline solution in dosage of 10 mg kg^{-1} subcutaneously (s.c.) twice a day at 8:00 and 17:00 h for nine days sufficient for induction of dependency[11].

Gabapentin group (8 rats) received gabapentin (Park Davis Company) in dosage of 75 mg kg^{-1} in normal saline solution intraperitoneally (i.p.) twice a day at time schedule of morphine group.

Gabapentin-morphine group (8 rats) received gabapentin 75 mg kg^{-1} (i.p.) ten min before 10 mg kg^{-1} (s.c.) morphine as schedule time for nine days. Because morphine maximum effect was achieved after 60 min while that of gabapentin after 70 min post injection. Control group (8 rats) received normal saline as schedule time for the same nine days.

To determine the antinociceptive dose of gabapentin in tail flick assay, groups of rats were injected with four or five doses of gabapentin (i.p.) following between ED20 and ED90. The ED50 of gabapentin was calculated approximately from dose-response curve as 75 mg kg^{-1}.

On the 9th day, 2 h after the last dose of morphine each animal was weighed. Thereafter rats were challenged for withdrawal signs by the administration of naloxone (2 mg kg^{-1}, i.p.). At this dose level the naloxone consistently precipitated characteristics symptoms of morphine withdrawal. Immediately after naloxone injection each animal was placed in a cylindrical glass observation chamber (30×30×40 cm) and was observed for various withdrawal signs over a period of 20 min. The withdrawal signs were scored on a quantitative basis of jumping, writhing and forepaw tremor. Other withdrawal signs observed include diarrhea and weight loss. Diarrhea was measured on absorbent paper before naloxone and 20 min after its injection. The difference for each 100 g weight of animal is considered as diarrhea index. Weight loss was calculated as difference of weight before and 1 h after naloxone injection.

Statistical analysis: The data were expressed as Mean±SEM whenever appropriate Repeated Measure or Friedman test was used followed by paired t-test or the Wilcoxon on matched pairs or signed ranks test. The results were considered significant when $p<0.05$.

RESULTS

The effects of gabapentin on the antinociceptive effect of morphine: The results of this study showed that gabapentin (75 mg kg^{-1}, i.p.) had no significant analgesic effect, because %MPE of gabapentin treated rats was not significantly different from saline treated rats. Morphine (10 mg kg^{-1}, s.c.) caused significant analgesic effect, because %MPE of morphine treated rats were significantly higher than both control and gabapentin groups in all days of study. Moreover the %MPE of morphine treated rats was gradually decreased from the 3rd days of treatment and this decrease continued during the 9 days of study, in order that the %MPE in morphine group after 9 days of treatment was significantly decreased compared to the 1st day of morphine treatment (Fig. 1). In the 9th day the %MPE in gabapentin-morphine treated rats was also significantly higher than control and gabapentin treated rats.

The comparison between morphine with morphine-gabapentin treated animals in days 3, 5, 7 and 9 were as following: In the 1st and 3rd day no significant difference of %MPE was observed between morphine with morphine-gabapentin. In 5th, 7th and 9th days %MPE in morphine-gabapentin treated rats was significantly higher than morphine treated rats (Fig. 1).

The effects of gabapentin on morphine withdrawal sign: Systemic naloxone as an opioid antagonist (2 mg kg^{-1}, i.p.) induced some behavioral indicative of opioid withdrawal in different groups, such as weight loss, writhing, jumping, diarrhea and fore paw tremor. All these signs were observed in morphine treated group to demonstrate the development of dependency. Statistically, some withdrawal signs such as jumping, diarrhea and fore paw tremor in morphine group were significantly different from normal saline group (Fig. 2).

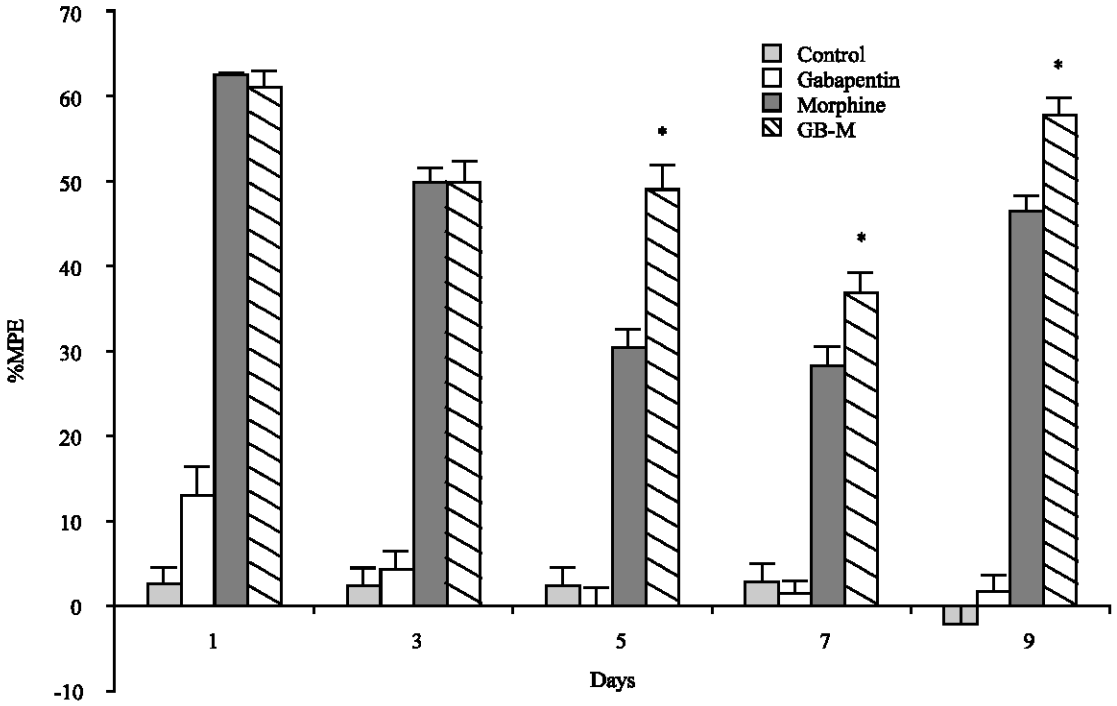

Fig. 1: The Maximal Possible Effect (%MPE) during the days 1, 3, 5, 7 and 9 after drug injection in four groups of rats: Control, Gabapentin (75 mg kg^{-1}, i.p.), Morphine (10 mg kg^{-1}, s.c.) and Morphine-gabapentin treated rats as described in materials and methods. Data are expressed as mean±SEM of at least 8 rats.*Significantly different from morphine group $p<0.05$

In gabapentin group which received repeated doses of 75 mg kg^{-1}, i.p. as schedule time, naloxone injection (2 mg kg^{-1}, i.p.) induced significant weight gain compared to normal saline group. Other opioid withdrawal signs were not observed in gabapentin treated rats (Fig. 2).

In gabapentin-morphine group, writhing, jumping and diarrhea were observed but only writhing and diarrhea was significantly different compared to normal saline group (Fig. 2).

The comparison between morphine and gabapentin-morphine group demonstrated that gabapentin apparently attenuate some withdrawal signs such as jumping, while enhanced significantly writhing. Gabapentin also decreased significantly weight loss and forepaw tremor (Fig. 2).

DISCUSSION

Gabapentin, which is a new anticonvulsant drug, is also effective in relief of different model of experimental and clinical pain sensation[12]. Especially its analgesic efficacy has been demonstrated in neuropathic pain[3,4,13] in inflammatory[5,14] and postoperative pain[6,7]. But its efficacy in treatment of acute pain is not established yet[15]. The result of this study showed that although gabapentin (75 mg kg^{-1}, i.p.) had no analgesic effect in tail flick test as acute model of pain, but its co administration with morphine increased both antinociceptive effect of morphine and prevented the decrement in the antinociceptive effect of morphine during the nine days of study, i.e. gabapentin co-administration with morphine prevented the development of tolerance to morphine antinociception as compared to controls (Fig. 1). In accordance, it was seen that in rat model of neuropathy gabapentin co-administration with morphine had significant improvement on dorsal horn neuronal response[8]. Also in healthy volunteers gabapentin showed no analgesic effect alone but it increased the analgesic effect of morphine[10].

This is in agreement with Shimoyama report that sub analgesic intrathecal injection of gabapentin enhanced morphine analgesia probably through μ opioid receptors and this effect persist for three days[9]. Also in neuropathic and postoperative pain, gabapentin demonstrate a synergistic analgesic effect with morphine[7,8]. These results have important implication in severe pain treatment whenever continuous administration of opioid is required. Since gabapentin has demonstrated low side effects and a good pharmacokinetic profile[12,13,15,16], it may well be safe to co-administer opioid with gabapentin in order to benefit from the synergy of pain relief in chronic pain

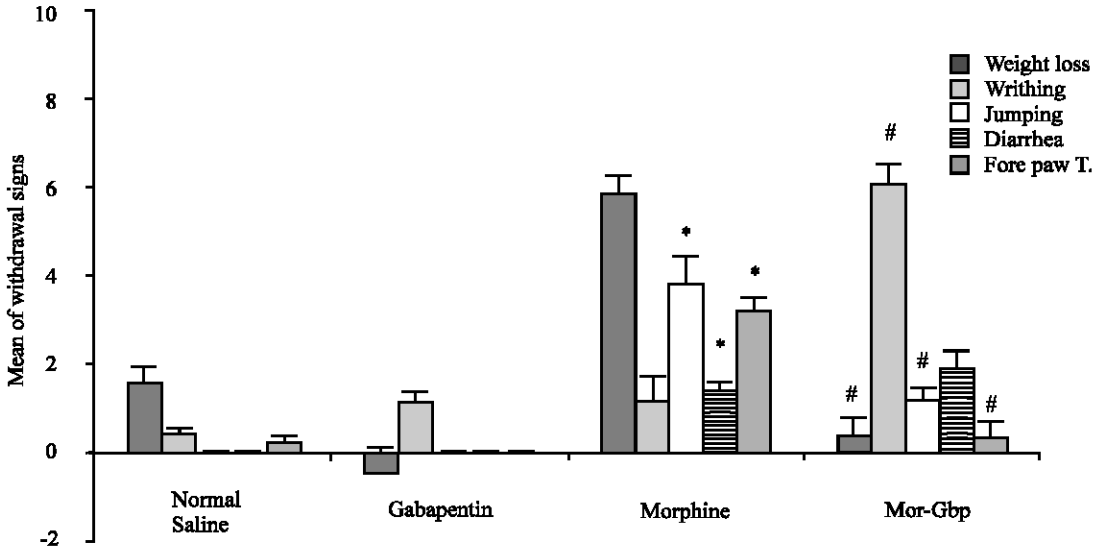

Fig. 2: Withdrawal signs precipitated after naloxone injection (2 mg kg^{-1}, i.p) in four groups of rats; control, gabapentin (75 mg kg^{-1}, i.p.), morphine (10 mg kg^{-1}, s.c.) and morphine- gabapentin (same dosage) twice a day for nine days of repeated injection as described in material and methods. Weight loss, Jumping, Diarrhea and forepaw tremor was significantly observed in morphine group as withdrawal syndrome compared to saline (*). In gabapentin group none of withdrawal signs were observed. In gabapentin-morphine group weight loss, jumping and Diarrhea were decreased while writhing was increased compared to morphine group (#). Data are expressed as mean±SEM of at least eight rats

treatment that has been shown to occur without danger of enhancement of morphine tolerance and dependence liability.

In this study gabapentin (75 mg kg^{-1}, i.p.) was ineffective as analgesic in tail flick test in rats (Fig. 1). Other authors showed that gabapentin didn't change pain threshold sensation[5,10,17]. However, in sciatic nerve constriction model of neuropathic pain, gabapentin dose-dependently increased the response time in cold allodynia like behavior[4] probably via spinal site of action[18]. Also in formalin and carrageenan inflammatory pain model gabapentin given either systemically or intrathecally inhibited only late phase of nociceptive response[5,14], which reflects inflammatory condition involving a state of central sensitization[9,14]. It seems that gabapentin has a selective effect on spinal cord neuronal response to noxious (Aδ and C fibers) versus innocuous (Aβ fiber) peripheral stimulation[12]. So these findings suggest that gabapentin reduces pain transmission via sensitized nervous system whenever a nerve injury occurs and reduces pathologic pain while leaving other protective nociceptive mechanisms. Furthermore antinociceptive effect of gabapentin depends on stimulus integration and kind of pain assessment[4].

The result of the last part of this study showed that pretreatment with gabapentin reduces some of the opioid withdrawal signs, including jumping, weight loss and fore paw tremor, while increases writhing behavior following naloxone administration. In agreement, other authors sustain those gabapentin-like compounds, which have no intrinsic rewarding properties, may block the development of Conditioned Place Preference (CPP) of morphine[19]. Although the pharmacological action of gabapentin is not completely described yet, the mechanism(s) by which gabapentin prevents opioid withdrawal signs and by which increases opioid analgesia founds explanation in the following hypothesis; first, gabapentin enhance opioid peptide release in amygdala[20], where is proposed for some of withdrawal signs, as Jumping [21,22]. This is in accordance with present finding which we observed a significant reduction of jumping withdrawal sign in gabapentin-morphine group compared to morphine group. Second, gabapentin binds with high affinity to a $\alpha_2\gamma$ subunit of voltage- sensitive Ca^{+2} channels (the same binding site that associated with morphine effect) in the brain cell membrane[23,24], in dorsal horn[13] and in dorsal root ganglia which are involved especially in pain perception. Third, it was shown that gabapentin increases the rate of release of GABA in brain through increasing of its concentration and synthesis[23]. Although many authors excluded any agonistic activity of gabapentin on GABA receptors[23,25] but it was shown that morphine

co-administration gabapentin didn't change serum concentration[10]. It may explain why we found an enhancement of antinociception in gabapentin-morphine group compared to morphine group from 3rd day of study. In the present study gabapentin didn't change reduced jumping behavior probably through activation of GABA-ergic system and more probably because of its selective agonistic activity on GABA (B) receptors demonstrated by Lanneau *et al.*[26].

Other mechanisms, like synergic effect of gabapentin on "non-NMDA antagonist" or "AMPA antagonist" and also its ability to reverse the effect of substance P in a dose dependent manner may be involved in agreement with the result of this study[27-29]. But the precise mechanism(s) is not determined yet and should be investigated in future.

In conclusion, the result of this study showed that gabapentin increased the analgesic effect of chronic use of morphine and also attenuates some of opioid withdrawal signs, including jumping. However the precise mechanism(s) should be established, we proposed gabapentin as co-analgesic with opioids in long term treatment of severe pain.

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