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Development of Morphine Induced Tolerance and Withdrawal Symptoms is Attenuated by Lamotrigine and Magnesium Sulfate in Mice

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Abstract: The goal of this study was to evaluate the effects of lamotrigine and magnesium sulfate on morphine induced tolerance and withdrawal symptoms in mice. Different groups of mice were received morphine (30 mg kg⁻¹, s.c.) or morphine (30 mg kg⁻¹, s.c.)+lamotrigine (10, 20, 30 or 40 mg kg⁻¹, i.p.) or morphine (30 mg kg⁻¹, s.c.)+magnesium sulfate (20, 40 or 60 mg kg⁻¹, i.p.) or morphine (30 mg kg⁻¹, s.c.) + [lamotrigine (10 mg kg⁻¹, i.p.) + magnesium sulfate (20mg kg⁻¹, i.p.)] daily for 4 days. Tolerance was assessed using hot plate after administration of a test dose of morphine (9 mg kg⁻¹, i.p.) on fifth day. Withdrawal symptoms (Jumping and Rearing) were assessed by administration of naloxone (5 mg kg⁻¹, i.p.) 2 h after the last dose of morphine in fourth day. It was found that administration of lamotrigine or magnesium sulfate or their combination decreased the morphine induced tolerance and withdrawal symptoms. From these results it is concluded that lamotrigine and magnesium sulfate alone or in combination could prevent the development of morphine tolerance and withdrawal symptoms. Glutamate release inhibitory effect of lamotrigine and its possible mechanism and property of magnesium, blocking the N-Methyl-D-Aspartate (NMDA) receptor calcium channel, is probably its mechanism on preventing morphine induced tolerance and dependence.

Key words: Morphine tolerance, magnesium sulfate, lamotrigine, withdrawal symptoms

INTRODUCTION

Tolerance and dependency to the antinociceptive effect of morphine, the most widely used analgesic opioid, complicates the management of patients with chronic pain. Tolerance develops in patients receiving morphine for relief of cancer-related pain and requires increments of morphine doses. The development of tolerance to opioid antinociception is manifested as a shift to the right of the dose-response curve or as a decrease in the intensity of the response on repetitive administration of a constant dose. Having actions on various central nervous system functions both physiologically and pathologically, glutamatergic neurotransmission also plays a key role in modulating opiate dependence and tolerance (Trujillo, 2000, 2002; Mendez and Trujillo, 2008). During the past decades, many studies have focused on excitatory amino acid receptors to investigate the role which they play in the development of tolerance to the antinociceptive action of morphine (Trujillo, 2000, 2002; Mendez and Trujillo, 2008; Habibi-Asl and Hassanzadeh, 2004; Habibi-Asl *et al.*, 2005).

Chronic opioid treatment leads to activation of N-methyl-D-aspartate (NMDA) receptor and it can

mobilize the release of intracellular Ca²⁺ and activate PKC, leading to morphine-induced antinociception suppression (Fundytus and Coderre, 1996; Liu and Anand, 2000). Numerous studies in animals suggest that co-administration of N-methyl-D-aspartate (NMDA) receptor antagonists prevent the development of morphine induced tolerance and dependence (Trujillo, 2000, 2002; Mendez and Trujillo, 2008; Habibi-Asl and Hassanzadeh, 2004; Habibi-Asl *et al.*, 2005, 2008). Lamotrigine (LTG, 3,5-diamino-6-(2, 3-dichlorophenyl)-1, 2, 4-triazine) is an effective anticonvulsant in the treatment of generalized tonic-clonic and partial seizures, Bipolar Disorder (BD) and depression (Martinovic *et al.*, 2004; Hahn *et al.*, 2004). There are several hypotheses regarding the mechanism of action of lamotrigine: effects on voltage-gated Na⁺ channels (Kuo and Lu, 1997; Mcnamara, 2006), calcium channels (Lee *et al.*, 2008) and inhibition of glutamate release (Mcnamara, 2006; Lee *et al.*, 2008). Magnesium sulfate (MgSO₄) is a well-known NMDA receptor blocker and is widely used in patients with preeclampsia. Furthermore, it is presently being evaluated in the treatment of acute stroke (Thurnau *et al.*, 1987; Muir and Lees, 1995) also peripheral magnesium sulfate enters the brain and increases the

threshold for hippocampal seizures in rats (Hallak *et al.*, 1992). According to the above studies it could be suggested that magnesium may have a potential role in prevention of morphine tolerance and dependence. The aim of present study was to investigate the effects of magnesium sulfate and lamotrigine on development of morphine induced tolerance and dependence in mice.

MATERIALS AND METHODS

Animals: Male albino mice (20-30 g) were studied. They were kept in a room at a controlled temperature (24±0.5°C) and maintained on a 12 h light/dark cycle (light on 08:00 h) with free access to food and water. All Experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1985) and were approved by the Research and Ethics Committee of Tabriz University of Medical Sciences. The study was conducted in Faculty of Pharmacy of Tabriz University (Medical Sciences) in Iran at period between January to October of 2008.

Drugs: Morphine sulfate (Darupakhsh-Iran), lamotrigine (Hetero drugs limited-India), magnesium sulfate (Pasteur Institute-Tehran, Iran) Naloxone Hydrochloride (Tolid daru-Iran). All drugs have been solved in normal saline (0.9%).

Assessment of nociception: Nociception was assessed using the hot-plate apparatus (55±0.5°C) (Eddy and Leimback, 1953). The hot-plate latency was recorded when the animal licked its hind paw. A cut-off time (40 sec) was imposed to prevent tissue damage. Hot-plate response latencies (s) are expressed as the percentage of Maximal Possible Effect (MPE%) using the equation below:

$$\text{MPE}(\%) = \frac{\text{Post drug latency(s)} - \text{Baseline latency(s)}}{\text{Cutt off value(s)} - \text{Baseline latency(s)}} \times 100$$

Induction of tolerance: In order to induce tolerance, groups of 9 mice were chosen randomly. Morphine (30 mg kg⁻¹) was administered subcutaneously (s.c.) in combination with either magnesium sulfate or lamotrigine or both magnesium sulfate and lamotrigine daily for 4 days. To evaluate the tolerance, the antinociceptive effect of a test dose of morphine (9 mg kg⁻¹, intraperitoneal=i.p.) was measured 24 h after the last dose of morphine in combination with magnesium sulfate or lamotrigine or both magnesium sulfate and lamotrigine (Habibi-Asl and Hassanzadeh, 2004; Habibi-Asl *et al.*, 2005, 2008).

Induction of dependence: Groups of 9 mice were chosen randomly. Mice were treated subcutaneously with morphine (30 mg kg⁻¹) in a combination with lamotrigine (i.p.) or magnesium sulfate (i.p.) or both lamotrigine and magnesium sulfate daily for 4 days. In order to evaluate the effects of different doses of magnesium sulfate and lamotrigine on dependence (Jumping and Rearing) a dose of naloxone (4 mg kg⁻¹, i.p.) was injected 2 h after the last dose of morphine on the 4th day.

Evaluation of the withdrawal symptoms: After naloxone injection, withdrawal symptoms (number of Jumping and Rearing) in 30 min were recorded

Statistical analysis: Data are expressed as Mean±SEM (Standard Error of Mean) for each time. The One-way Analysis of Variance (ANOVA) followed by Tukey was used to analysis the statistical significance for multiple comparisons. Analysis of variance is performed on data collected every 15 min. The p-value less than 0.05 was considered to be significant.

RESULTS

Development of morphine induced tolerance to analgesic effect: Animals received either saline (10 mL kg⁻¹, s.c.) or [morphine (30 mg kg⁻¹, s.c.)+saline (10 mL kg⁻¹, s.c.)] for 4 days. In each group antinociceptive response of a test dose of morphine (9 mg kg⁻¹, i.p.) was assessed 24 h after the last dose of morphine (30 mg kg⁻¹, s.c.). Animals that became tolerant to analgesic effects of morphine exhibited only a small antinociceptive response (Fig. 1).

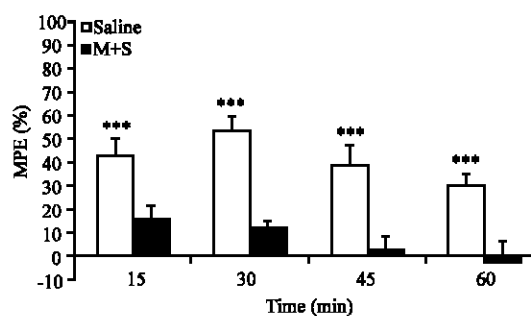


Fig. 1: Effects of morphine on tolerant and non tolerant mice. Animals received either saline (10 mL kg⁻¹, s.c.) or [morphine (30 mg kg⁻¹, s.c.)+saline (10 mL kg⁻¹, s.c.)] for 4 days. Antinociception of a test dose of morphine (9 mg kg⁻¹, i.p.) was tested 24 h after the last dose of morphine (30 mg kg⁻¹, s.c.) in tolerant and non tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). ***p<0.001 significantly different from tolerant control group. S: Saline, M: Morphine

Effect of administration of Lamotrigine on morphine induced tolerance and dependence: As it is shown in Fig. 2, lamotrigine injection (10, 20, 30 mg kg⁻¹, i.p.) 30 min before daily morphine administration, decreased tolerance to the analgesic effect of morphine significantly. Figure 5 and 6 have shown that administration of lamotrigine (10, 20, 30 mg kg⁻¹, i.p.) dose dependently decreased the withdrawal symptoms significantly.

Effect of administration of magnesium sulfate on morphine induced tolerance and dependence: Injection of magnesium sulfate (20, 40, 60 mg kg⁻¹, i.p.) 30 min before daily morphine administration decreased tolerance to the analgesic effect of morphine significantly (Fig. 3). Figure 5 and 6 have shown that administration of

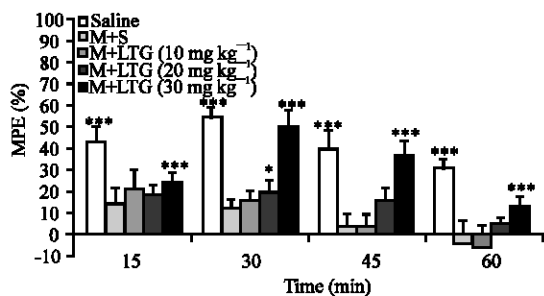


Fig. 2: Effects of different doses of lamotrigine (10, 20, 30 mg kg⁻¹, i.p.) on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). *p<0.05, ***p<0.001, significantly different from the control group (M+S). S: Saline, M: Morphine, LTG: Lamotrigine

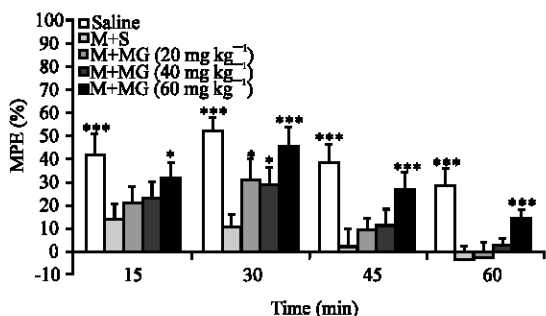


Fig. 3: Effects of different doses of magnesium (20, 40, 60 mg kg⁻¹, i.p.) on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). *p<0.05, ***p<0.001, significantly different from the control group (M+S). S: Saline, M: Morphine, MG: Magnesium

magnesium sulfate (20, 40, 60 mg kg⁻¹, i.p.) dose dependently decreased the withdrawal symptoms significantly.

Effect of administration of Lamotrigine and Magnesium sulfate on morphine induced tolerance and dependence: As it is shown in Fig. 4, co-administration of magnesium sulfate (20 mg kg⁻¹, i.p.) and lamotrigine (10 mg kg⁻¹, i.p.)

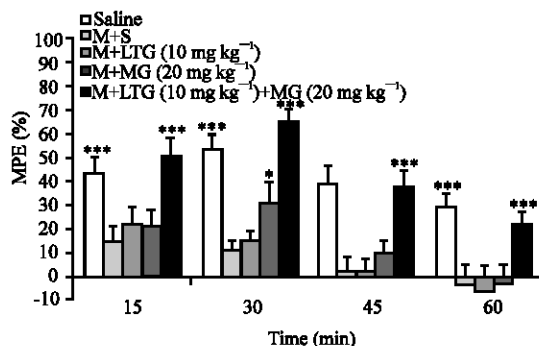


Fig. 4: Effects of lamotrigine (10 mg kg⁻¹, i.p.) or magnesium (20 mg kg⁻¹, i.p.) or [LTG (10 mg kg⁻¹, i.p.) + MG (20 mg kg⁻¹, i.p.)] on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). S: Saline, M: Morphine, MG: Magnesium, LTG: Lamotrigine.

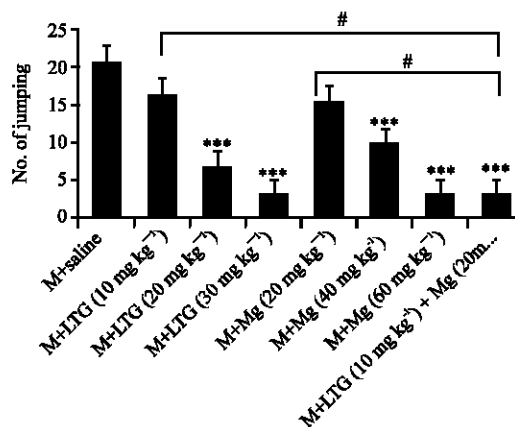


Fig. 5: Effects of different doses of Lamotrigine (10, 20, 30 mg kg⁻¹, i.p.) and magnesium sulfate (20, 40 or 60 mg kg⁻¹, i.p.) and [Lamotrigine (10 mg kg⁻¹, i.p.) + magnesium sulfate (20 mg kg⁻¹, i.p.)] on jumping induced by naloxane (4 mg kg⁻¹, i.p.) in morphine-dependent mice. Each group had at least 9 mice. Results are expressed as Mean±SEM. ***p<0.001, significantly is different from control group. #p<0.001. M: Morphine, Mg: Magnesium, LTG: Lamotrigine

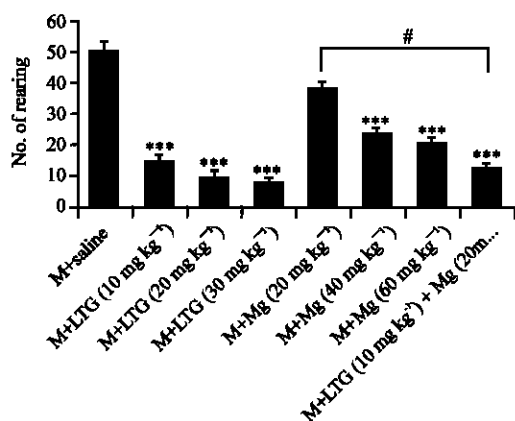


Fig. 6. Effects of different doses of Lamotrigine (10, 20, 30 mg kg⁻¹, i.p.) and magnesium sulfate (20, 40 or 60 mg kg⁻¹, i.p.) and [Lamotrigine (10 mg kg⁻¹, i.p.) + magnesium sulfate (20 mg kg⁻¹, i.p.)] on Rearing induced by naloxone (4 mg kg⁻¹, i.p.) in morphine-dependent mice. Each group had at least 9 mice. Results are expressed as Mean±SEM. ***p<0.001, significantly is different from control group. #p<0.001. M: Morphine, Mg: Magnesium, LTG

30 min before daily morphine administration decreased tolerance phenomenon but it was not significant and Fig. 5 and 6 showed that this combination decreased withdrawal symptoms significantly.

Naloxone-induced withdrawal: Animals received morphine (30 mg kg⁻¹, s.c.) daily for 4 days. In order to induce withdrawal symptoms, naloxone (4mg kg⁻¹, i.p.) injected. As it is shown in (Fig. 5, 6) Naloxone induced withdrawal signs (Jumping and Rearing) in control group which received morphine and saline in comparison with saline.

DISCUSSION

Evidences from before studies suggest that N-methyl-D-aspartate glutamate receptors (NMDARs) are involved in the plasticity that arises from long-term administration of morphine (Trujillo, 2002; Mao, 1999). This opiate related activation of NMDA- receptors may initiate subsequent intracellular changes such as production of Nitric Oxide (NO) and/or the activation of protein kinase C (PKC). Both NO and PKC have been shown to be critical for development of morphine tolerance (Liu and Anand, 2000).

After this discovery, numerous studies have demonstrated that a variety of NMDA receptor antagonists have the ability to inhibit the development of opiate tolerance and dependence (Mendez and Trujillo, 2008; Habibi-Asl and Hassanzadeh, 2004; Habibi-Asl *et al.*, 2005, 2008).

Lamotrigine (LTG) is a comparatively novel antiepileptic agent used primarily in the treatment of generalized and partial seizures (Bazil, 2002; Kwan *et al.*, 2001).

The action of LTG has been reported as a blockade of voltage-gated Na⁺ channels and reducing neuronal depolarization in dissociated hi.p.pocampal neurons (Kuo and Lu, 1997). Furthermore, LTG has been found to inhibit excitatory postsynaptic currents (EPSC) or potential (EPSP) by blocking voltage-gated sodium (Leach *et al.*, 1986) or calcium channels (Wang *et al.*, 1996). Previous studies have observed that LTG inhibits glutamate release and attenuates neuronal excitability on presynaptic sites. It has been suggested that LTG's inhibition of voltage-activated sodium channels stabilizes the presynaptic neuronal membrane, thus preventing the release of excitatory neurotransmitters and inhibits sustained repetitive neuronal firing (Lee *et al.*, 2008; Leach *et al.*, 1986).

Furthermore, before studies indicated that lamotrigine is a neuroprotective agent and one of these researches showed that, the drug does appear to have protective efficacy parallel to that of MK-801 (a NMDA receptor antagonist) in the prevention of excitatory amino acid injury to neurons (Willmore, 2005).

Present results showed that morphine (30 mg kg⁻¹, i.p.) induced tolerance and dependence. LTG (20, 30 mg kg⁻¹, i.p.) could attenuate morphine tolerance and increased the analgesic effect of morphine significantly but LTG (10 mg kg⁻¹, i.p.) couldn't affect morphine tolerance. These results support the previous studies which indicated the mechanism of action for lamotrigine in reducing the glutamate release (Lee *et al.*, 2008).

It has also been reported that combined and continuous administration of morphine and 5-HT1A receptor agonists inhibit the development of tolerance to morphine analgesia in trigeminal neuropathic pain (Deseure *et al.*, 2004) on the other hand before results suggest that postsynaptic 5-HT1A receptors might be involved in the activity of lamotrigine and its activity strongly is potentiated with 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), a standard 5-HT1A receptor selective agonist (Kaptanoglu *et al.*, 2003) so it might be one of the possible mechanism for effect of lamotrigine on morphine induced tolerance and dependence. Mg²⁺ and Ca²⁺ have opposite effects in these physiological roles such as vascular tone. Magnesium also antagonizes Ca²⁺ at the N-methyl-D-aspartate subtype of glutamate receptor site and decreases calcium influx into cells and suggests that magnesium may have a role in the treatment of spinal cord injury in human (Bourin *et al.*, 2005).

It is demonstrated that at resting membrane potentials, NMDA receptors are blocked by magnesium ions and this prevents them from being activated by glutamic acid (Doble, 1999).

Long term administration of opiate leads to removing the magnesium (Mg) blockade in the Calcium channel and opening the Calcium channel of NMDA receptors and increasing in intracellular Ca. Magnesium (Mg)-deficient rats develop a mechanical hyperalgesia which is reversed by a N-Methyl-D-Aspartate (NMDA) receptor antagonist (Begon, 2001).

Present results in this study showed that administration of magnesium sulfate (20, 40 or 60 mg kg⁻¹, i.p.) could attenuate the tolerance to analgesic effect of morphine and the dose (60 mg kg⁻¹, i.p.) was the most effective and it seems that this effect of magnesium is dose dependently but it needs more studies by other doses. These results, in agreement with our previous study, indicate that magnesium is a useful drug for preventing morphine tolerance (Habibi-Asl *et al.*, 2005).

Before studies indicated that systemic administration of morphine and magnesium sulfate attenuated pain-related behavior in mononeuropathic rats and magnesium influences on morphine induced Pharmacodependence in rats (Nechifor *et al.*, 2004; Ulugol *et al.*, 2002). Therefore, our results confirmed the finding of previous studies on magnesium about its mechanism of action. Also, it helps us understanding the mechanism of opioid tolerance. In another part of this study we examined the effect of lamotrigine and magnesium sulfate on morphine withdrawal symptoms. Results showed that LTG (10, 20, 30 mg kg⁻¹, i.p.) and magnesium sulfate (20, 40 or 60 mg kg⁻¹, i.p.) decreased the withdrawal symptoms, both jumping and rearing significantly and the possible mechanisms for these effects are the same as were explained for tolerance for each one. Last part of our study has shown that co-administration of magnesium sulfate (20 mg kg⁻¹, i.p.) and LTG (10 mg kg⁻¹, i.p.) attenuated morphine tolerance and withdrawal symptoms significantly in comparison with magnesium or lamotrigine alone. This result suggests a probable synergistic effect for those drugs but more studies with different doses are recommended.

In conclusion, results have shown that lamotrigine and magnesium sulfate alone or in combination inhibited the development of morphine tolerance and dependence. Fortunately, there is a possible synergistic effect between two drugs, thus combination of the lowest doses could have a significant effect. In order to clarify the mechanisms by which lamotrigine and magnesium sulfate affect morphine induced tolerance and withdrawal symptoms, further studies are needed.

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