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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 11 (13): 1690-1695, 2008
ISSN 1028-8880

Evaluation the Effects of Dextromethorphan and Midazolam on Morphine Induced Tolerance and Dependence in Mice

Bohlul Habibi Asl, Kambiz Hassanzadeh, Esmail Khezri and Sadollah Mohammadi
Department of Pharmacology and Toxicology, School of Pharmacy,
Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: The main aim of this study was to evaluate the effects of dextromethorphan and midazolam and their combination on morphine tolerance and dependence in mice. In the present study, different groups of mice were rendered randomly and received morphine (50 mg kg^{-1}, s.c.), morphine (50 mg kg^{-1}, s.c.) + Dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.), morphine (50 mg kg^{-1}, s.c.) + midazolam (0.5, 1 and 2 mg kg^{-1}, i.p.), morphine (50 mg kg^{-1}, s.c.) + [Dextromethorphan (25 mg kg^{-1}, i.p.) + midazolam (0.5 mg kg^{-1}, i.p.)] once a day for four days. Tolerance was assessed by administration of morphine (9 mg kg^{-1}, i.p.) on fifth day. Withdrawal symptoms (markers for dependence) was assessed by administration of naloxone (4 mg kg^{-1}, i.p.) 2 h after co-administration of morphine with either Dextromethorphan or midazolam or their combination. Results showed that pretreatment with Dextromethorphan or midazolam decreased the degree of tolerance and withdrawal symptoms significantly. Additionally co-administration of Dextromethorphan and midazolam couldn't decreased the tolerance and dependence significantly. From these results it may concluded that Dextromethorphan and midazolam alone or in combination could prevent the development of morphine induced tolerance and dependence. These effects can be related to the N-Methyl-D-Aspartate (NMDA) receptor antagonist behavior of Dextromethorphan and GABA-receptor agonist property of midazolam.

Key words: Dextromethorphan, midazolam, morphine, tolerance, dependence

INTRODUCTION

Long-term exposure to opiates induces physical dependence and tolerance. The neurobiological mechanisms of these phenomena are not completely clear. On the other hand these drugs are widely used in clinical management of pain. Thus in patients who use opiates for example morphine in order to have analgesic effects, tolerance and dependence limit the therapeutic efficacy of opioids (Chan *et al*., 2002). It is generally believed that chronic opiate treatment induces neuroadaptations in intracellular signaling elements at multiple levels. Therefore, it is possible to modulate the development of opiate tolerance and dependence by regulating the intracellular neurotransmitters, ion channels and intracellular messenger pathways (Kozela and Popik, 2002; George, 2003; Eric and Aghajanian, 1997; Jaba *et al*., 2001; Liu and Anand, 2000). Chronic opioid treatment leads to protein kinase C (PKC) activation and translocation (George, 2003; Eric and Aghajanian, 1997; Jaba *et al*., 2001) which phosphorylates the NMDA receptor - gated Ca channel, resulting in potentiation of NMDA receptor activity (Kozela and Popik, 2002; Liu and Anand, 2000; Christensen *et al*., 1998; Rang *et al*., 2005). Opening of these channel leads to influx and increases intracellular Ca concentration, which produces several effects. NMDA receptor antagonists such as Dextromethorphan, ketamine and MK 801 have been shown in animal models and clinical trials to attenuate opioid tolerance and dependence (Chevlen, 2000; Huang *et al*., 2003; Bossard *et al*., 2002; Allen *et al*., 2002; Manning *et al*., 1996; Mao *et al*., 1996; Luger *et al*., 1995; Bartlett *et al*., 1994; Habibi Asl *et al*., 2005). On the other hand it is known that, γ-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the Central Nervous System (CNS). Several evidences have shown that GABAergic system plays an important role in the development of tolerance and dependence in morphine therapy (Habibi Asl *et al*., 2005; Tejwani *et al*., 1993; Sivam and Ho, 1985; Cao *et al*., 2002; Sheu *et al*., 1995; Sribanditmongkol *et al*., 1994; Tejwani *et al*., 1998; Rattan and Sribanditmongkol, 1994; Pepicelli *et al*., 2004).

Midazolam as a benzodiazepine-receptor agonist, has been widely used for induction and maintenances of

Corresponding Author: Kambiz Hassanzadeh, Department of Pharmacology and Toxicology, School of Pharmacy, Tabriz University of Medical Sciences, Zip Code: 51664-14766, Tabriz, Iran
Tel: 09144156941 Fax: 0411-4422448

anesthesia with opioids or inhaled anesthetic in clinics (Sivam and Ho, 1985; Rattan and Sribanditmongkol, 1994). This medication suppresses withdrawal responses by inhibition of the hyper sensitization of the spinal cord nervous (Luger *et al*., 1995).

Midazolam may occupy the benzodiazepine receptor on the benzodiazepine GABA-Cl channel complex and therefore facilitates the inhibitory action of GABA on neuronal transmission. Midazolam could prolong the antinociceptive effect of morphine by delaying in the chronic morphine-induced development of tolerance to antinociception in rats (Habibi Asl and Hassanzadeh, 2004; Tejwani *et al*., 1993; Cao *et al*., 2002). In the present investigation, the possible interaction of opiate tolerance and dependence, NMDA and GABA receptors was studied.

MATERIALS AND METHODS

Animals: Male albino mice (Razi Institute, Tehran, Iran) weighing 20-30 g were used. Animals were housed in standard polypropylene cages, 9 mice per cage.

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 and were approved by the Research and Ethics Committee of Tabriz University of Medical Sciences. Pain sensitivity was evaluated by hot-plate test.

Drugs: Morphine sulfate (Darupakhsh-Iran), Dextro-methorphan hydrochloride (Rotexmedica-Germany), Midazolam hydrochloride (Dormicum-Canada), Naloxone Hydrochloride (Tolid daru-Iran). Volume of injection was 250 μL for each mice.

Methods

Hot-plate test: Induction of tolerance: In order to induce tolerance, groups of 9 mice were chosen randomly. Mice were treated subcutaneously (s.c.) with morphine (50 mg kg^{-1}) in combination with either saline or dextro-methorphan or midazolam or both dextromethorphan and midazolam once a day for four days. To evaluate the degree of tolerance, the antinociceptive effect of a test dose of morphine (9 mg kg^{-1}, i.p.) was measured 24 h after the last dose of morphine in combination with saline or dextromethorphan or midazolam or both dextro-methorphan and midazolam. The cut-off point imposed was 45 sec (Porreca *et al*., 1984). In order to normalize the date to the baseline, hot-plate response latencies(s) are expressed as percentage of maximal possible effect (MPE%) using the equation:

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

At test day a baseline latency was determined, then morphine (9 mg kg^{-1}) was injected and post-drug latency recorded at 15, 30, 45 and 60 min after the injection of morphine and then the MPE% was evaluated for each quarter.

Induction of dependence: Groups of 9 mice were chosen randomly. Mice were treated subcutaneously (s.c.) with morphine (50 mg kg^{-1}) in a combination with saline or dextromethorphan or midazolam or both dextromethorphan and midazolam once a day for four days. To evaluate the effect of different doses of dextromethorphan and midazolam 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 syndrome: After naloxone injection, withdrawal symptoms (Jumping and Rearing) in 30 min were evaluated.

Statistical analysis: Data are expressed as Mean of MPE% ±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. ANOVA is performed on data collected every 15 min. p-value less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION

Development of tolerance to the morphine antinociception: Animals received morphine (50 mg 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 assayed 24 h after the last dose of morphine (50 mg kg^{-1}, s.c.). Animals that became tolerant exhibited only a small antinociceptive effect (Fig. 1).

Effect of pretreatment with dextromethorphan on morphine induced tolerance and dependence: As it is shown in Fig. 2, dextromethorphan injection (25, 50 and 75 mg kg^{-1}, i.p.) 30 min before daily morphine administration, decreased tolerance to the analgesic effect of morphine significantly. Figure 5 and 6 shows that pretreatment with dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.) dose dependently decreased the withdrawal symptoms significantly.

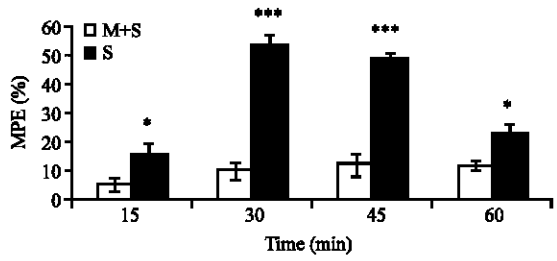

Fig. 1: Effects of morphine on tolerant and non tolerant mice. Animals received either saline (10 mL kg^{-1}, s.c.) or [morphine (50 mg kg^{-1}, s.c.) + saline (10 mL kg^{-1}, s.c.)] for 4 days. Antinociception of a test dose of morphine (9 mg kg^{-1}, i.p.) was tested 24 h after the last dose of morphine (50 mg kg^{-1}, s.c.) in tolerant and non tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). *p<0.05, ***p<0.001, significantly different from tolerant control group. S = Saline, M = Morphine

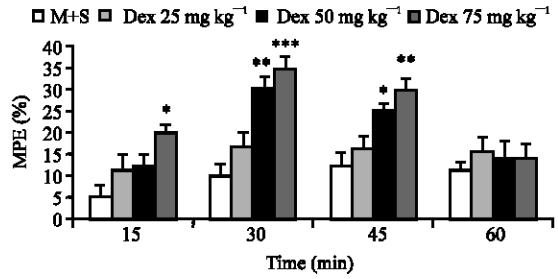

Fig. 2: Effects of different doses of dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.) on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). *p<0.05, **p<0.01, ***p<0.001, significantly different from the control group (M+S). S = Saline, M = Morphine, Dex = Dextromethorphan

Effect of pretreatment with midazolam on morphine induced tolerance and dependence: As it is shown in Fig. 3, injection of midazolam (0.5, 1 and 2 mg kg^{-1}, i.p.) 30 min before daily morphine administration decreased tolerance to the analgesic effect of morphine significantly with dose of 2 mg kg^{-1}. Figure 5 and 6 shows that pretreatment with midazolam (0.5, 1 and 2 mg kg^{-1}, i.p.) dose dependently decreased the withdrawal symptoms significantly.

Effect of co-administration of dextromethorphan and midazolam on morphine induced tolerance and dependence: As it is shown in Fig. 4, co-administration of dextromethorphan (25 mg kg^{-1}, i.p.) and midazolam

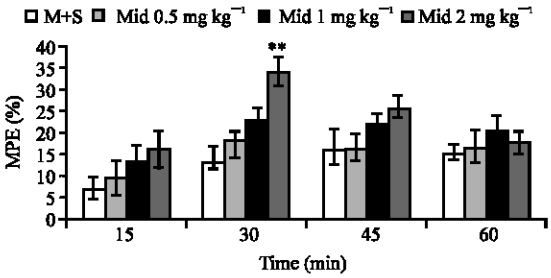

Fig. 3: Effects of different doses of midazolam (Mid 0.5, 1 and 2 mg kg^{-1}, i.p.) on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). **p<0.01, significantly different from the control group (M+S). S = Saline, M = Morphine, Mid = Midazolam

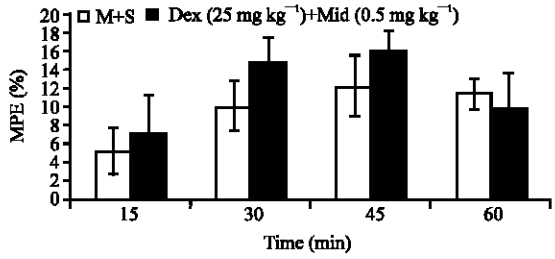

Fig. 4: Effects of [dextromethorphan (25 mg kg^{-1}, i.p.) + midazolam (0.5 mg kg^{-1}, i.p.)] on tolerance determined by hot-plate test in morphine-tolerant mice. Each bar represents mean of %MPE±SEM (n = 9 per group). S = Saline, M = Morphine, Mid = Midazolam, Dex = Dextromethorphan

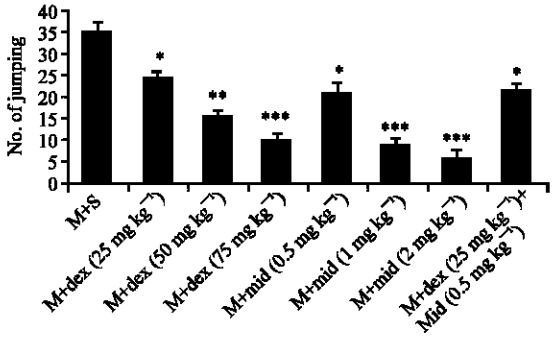

Fig. 5: Effects of different doses of dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.) and midazolam(0.5, 1 and 2 mg kg^{-1}, i.p.) and [dextromethorphan (25 mg kg^{-1}, i.p.)+ midazolam (0.5 mg kg^{-1}, i.p.)] on jumping induced by naloxone (4 mg kg^{-1}, i.p.) in morphine-dependent mice (n = 9 per group). Results are expressed as Mean±SEM. * p<0.05 ** p<0.01, ***p<0.001, significantly different from the morphine control group

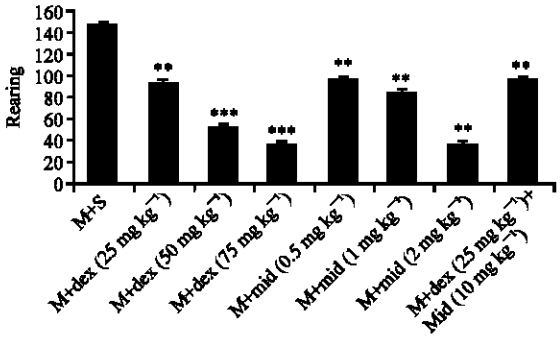

Fig. 6: Effects of different doses of dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.), midazolam (0.5, 1 and 2 mg kg^{-1}, i.p.) and [dextromethorphan (25 mg kg^{-1}, i.p.) + midazolam (0.5 mg kg^{-1}, i.p.)] on Rearing induced by naloxone (4 mg kg^{-1}, i.p.) in morphine-dependent mice (n = 9 per group). Results are expressed as Mean ± SEM. ** $p<0.01$, ***$p<0.001$, significantly different from the morphine control group

(0.5 mg kg^{-1}, i.p.) 30 min before daily morphine administration decreased tolerance phenomenon but it was not significant and Fig. 5 and 6 shows that this combination decreased withdrawal symptoms significantly.

Naloxone-induced withdrawal: Animals were rendered dependent to morphine by administration of morphine (50 mg kg^{-1}, s.c.) once a day for four days. The dose of 4 mg kg^{-1}, i.p. of naloxone was injected for induction of withdrawal symptoms. Naloxone induced withdrawal signs: Jumping and Rearing (Fig. 5, 6).

The principle aim of this study was to evaluate the effects of dextromethorphan (as a non competitive NMDA receptor antagonist) and midazolam (as a benzodiazepine receptor agonist) on development of morphine tolerance and dependence in mice. It has been proposed that repeated administration of opiate may activate the NMDA-receptor through G protein associated with opioid receptor and/or intracellular mechanisms (Chan *et al*., 2002; George, 2003; Eric and Aghajamian, 1997; Jaba *et al*., 2001; Liu and Anand, 2000; Rang *et al*., 2005).

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) (Eric and Aghajamian, 1997; Liu and Anand, 2000). Both NO and PKC have been shown to be critical for development of morphine tolerance (Eric and Aghajanian, 1997; Liu and Anand, 2000). This results in present study show that the NMDA- receptor antagonist, dextromethorphan (25, 50 and 75 mg kg^{-1}, i.p.) could attenuate development of morphine tolerance dose dependently. Before studies have shown dextromethorphan could potentiate the antinociceptive effects of the μ-opioid receptor agonist morphine under some conditions (Christensen *et al*., 1998; Allen *et al*., 2002) so behavioral effect of dextromethorphan in this study may be mediated, in part, by its antinociceptive effect but according to the figures, it is not the whole story and attenuation the morphine tolerance is the major mechanism in this results. As it is shown in Fig. 1-4, maximum analgesic effect of morphine represents at 30 and 45 min after morphine administration and pretreatment with dextromethorphan increased the latency time of morphine induced analgesia in these times.

Earlier studies (Chan *et al*., 2002; Chevlen, 2000; Allen *et al*., 2002; Manning *et al*., 1996; Mao *et al*., 1996) showed that administration of dextromethorphan attenuated intracellular Ca influx both in NMDA-receptor gated channel as well as in voltage-gated Ca channel. Some studies showed a significant increase in dopamine metabolites following morphine administration was demonstrated in the nucleus accumbens (NAc) (Huang *et al*., 2003; Johnson and North, 1992). Morphine induced increase in Ca influx could be attenuated by co-administration of morphine with dextromethorphan. Further more Neurochemical analysis revealed that the effect of dextromethorphan could be through its action on the dopaminergic mesolimbic pathway, which could be activated by morphine and attributed to the cause of rewarding (Huang *et al*., 2003; Johnson and North, 1992). Dopaminergic mesolimbic pathway has a critical role in drug dependence and our results seem to suggest that possible mechanism for dextroetorphan on withdrawal signs is its effect on dopaminergic pathway (Jumping and Rearing).

Other studies have shown that there is an interaction between GABA and opioid system and GABA ergic system has a role in opioid tolerance and dependence (Luger *et al*., 1995; Bartlett *et al*., 1994; Tejwani *et al*., 1993; Sivam and Ho, 1985; Cao *et al*., 2002; Sheu *et al*., 1995; Sribanditmongkol *et al*., 1994; Tejwani *et al*., 1998; Rattan and Sribanditmongkol, 1994; Tejwani *et al*., 1998; Sinkkonen *et al*., 2004; Shoji *et al*., 1999). Both $GABA_A$-and $GABA_B$-mediated synaptic potentials in dopamine cells of the Ventral Tegmental Area (VTA) were inhibited presynaptically by opioids (Eric and Aghajanian, 1997; Johnson and North, 1992). The $GABA_A$-mediated synaptic potential is thought to arise from inter neurons that are hyperpolarized by opioids (Huang *et al*., 2003; Johnson and North, 1992; Shoji *et al*., 1999). The inhibition of spontaneous activity recorded from inter neurons correlated with the inhibition

of tetrodotoxin-sensitive GABA-mediated IPSPs recorded in dopamine cells (Johnson and North, 1992). It was concluded that cells that were hyperpolarized by μ-opioid receptors in the VTA were GABA interneurons (Johnson and North, 1992). Furthermore, before Studies have demonstrated that selective GABA(A) receptor antagonist such as bicuculline enhanced cGMP production, revealing that the cortical NOS/sGC system is tonically inhibited by endogenous GABA (Pepicelli *et al*., 2004). Thus production of NO is decreased in attendance of midazolam as an GABA (A) agonist and as it was mentioned before NO have been shown to be critical for development of morphine tolerance. Present results showed midazolam (2 mg kg^{-1}) decreased the morphine tolerance and its low doses couldn't attenuate significantly so, it is recommended to evaluate the effect of higher doses than 2 mg kg^{-1} only or in combination with other drugs. Furthermore, previous studies showed that administration of midazolam can increase or decrease morphine-induced antinociception, depending upon relative concentration of these drugs by modulating spinal opioid receptors and it also can inhibit morphine-induced tolerance and dependence in rat (Johnson and North, 1992).

It had been demonstrated that concomitant administration of diazepam to morphine results in inhibition of the development of morphine tolerance and dependence. Some mechanisms are proposed by Sheu *et al.* (1995), Sribanditmongkol *et al.* (1994) and Tejwani *et al.* (1998) but more studies are needed.

Earlier studies showed the reduction the subunits of GABA (A) receptors in attendance of NMDA antagonist (Sinkkonen *et al*., 2004) thus it is suggested that using NMDA antagonists may result in anxiety on the other hand studies have shown that NMDA-receptor antagonists such as dextromethorphan or phencyclidine have some psychotic adverse effects. According to the above informations we used a combination of dexthromethorphan and midazolam at the lowest doses.

The present study confirms that the combination of low doses of dextromethorphan and midazolam intraperitonealy was not effective in preventing morphine antinociceptive tolerance. When, morphine had been co-administered with this combination, the development of morphine dependence was exacerbated and it is seemed that this combination therapy could decrease some adverse effects of NMDA antagonists.

In conclusion, pretreatment with dextromethophan and midazolam, inhibited the development of tolerance to morphine induced antinociceptive effect and dependence, while combination of dextromethophan and midazolam at low doses couldn't decrease the development of morphine tolerance.

However, since the exact interaction between opioids and neurotransmitters in the development of morphine antinociceptive tolerance and dependence has still not been fully understood, further studies are necessary.

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