

Nalbuphine ameliorates morphine/tramadol-induced dependence and tolerance to analgesia through locus coereulus (LC) norepinephrine.

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ABSTRACT

Chronic use of opioids as morphine and tramadol to control pain is associated with several side effects and tolerance to their analgesic effect and dependence. Some of the side effects of opioids can be ameliorated by naloxone, however this is associated with decreased analgesia. Nalbuphine was shown to ameliorate morphine and tramadol psychological dependence.

The current study aims to investigate the effect of co-administration of nalbuphine with morphine or tramadol on tolerance to analgesia and physical dependence and the possible involvement of norepinephrine in its effect.

Co-administration of nalbuphine with morphine or tramadol prevented tolerance to analgesia and physical dependence that was observed with each drug alone and this was associated with prevention of the elevation in norepinephrine in the locus coereulus (LC) following naloxone administration.

These results emphasize the possible use of nalbuphine in combination with morphine or tramadol to preserve their analgesic effect and to prevent the development of dependence to their effect.

Keywords: *nalbuphine, morphine, tramadol, tolerance to analgesia, dependence.*

Running title: *Nalbuphine against dependence and tolerance.*

INTRODUCTION

Chronic use of opioids to control moderate to severe pain can lead to dependence and tolerance (Jang, Kim et al. 2006). Most of the opioids used clinically are mu-opioid receptor (MOR) agonists (Nakamura, Narita et al. 2008).

The centrally acting analgesic tramadol acts through its weak MOR agonist affinity (Raffa, Friderichs et al. 1992) and nonopioid mechanism by norepinephrine / serotonin reuptake inhibition (Liu, Zhou et al. 1999, Nossaman, Ramadhyani et al. 2010). Long-term use of tramadol was associated with tolerance to analgesia, physical dependence and withdrawal symptoms (Tjaderborn, Jonsson et al. 2009, Lanier, Lofwall et al. 2010).

We have previously shown that co-administration of nalbuphine with tramadol blocked tramadol rewarding effect through blocking the increase in dopamine level in the nucleus accumbens induced by tramadol

accompanied by an increase rather than attenuation of the analgesic effect of tramadol (Abdel-Ghany, Nabil et al. 2015).

The opioid mixed agonist-antagonist nalbuphine acts as mu receptor antagonist and κ receptor agonist (Schmidt, Tam et al. 1985, Pick, Paul et al. 1992, Walker and Young 1993), therefore it can decrease the incidence of some opioid related side effects including respiratory depression, vomiting, and pruritus (Bailey, Clark et al. 1987, Davies and From 1988).

Opioid antagonists as naloxone can block the development of tolerance and dependence to morphine (Yano, Nishino et al. 1979) accompanied by withdrawal syndrome.

Norepinephrine is implicated in morphine reward (Olson, Heusner et al. 2006) and opiate-withdrawal (Delfs, Zhu et al. 2000). Locus coeruleus (LC), the main noradrenergic nucleus of the brain

(Mobasher, Sajedianfard et al. 2014) is implicated in the expression of morphine withdrawal syndrome (Fakhari, Azizi et al. 2017) as MOR agonists induce a reduction in norepinephrine level in LC which - upon repeated exposure - is associated with increased activity of LC neurons to compensate for the suppressive effect of opioids on norepinephrine resulting in normal level of norepinephrine amounts (Christie 2008). Therefore, opioid withdrawal is associated with elevation in norepinephrine level in the LC.

The present study was designed to investigate the effect of co-administration of nalbuphine with morphine or tramadol on tolerance to analgesia and dependence in mice which corresponds to physical dependence and the possible effect on norepinephrine level in the LC.

Materials and methods Chemicals

Tramadol hydrochloride was purchased from Mina Pharm Co., nalbuphine hydrochloride was purchased from Amoun pharmaceuticals Co., morphine was purchased from Misr pharmaceutical Co. and naloxone was purchased from Delpharm Tour (Egypt). All drugs were prepared in saline just before use.

Animals

Adult male balb/C mice weighing 20–30 g were purchased from Theodor Bilharz Research Institute, Cairo, Egypt. The mice were kept under standard environmental and nutritional conditions throughout the investigation. All experimental procedures were approved by the Ethical Committee for Animal Handling at Zagazig University (ECAHZU).

Evaluation of tolerance to analgesic effect

Animals were treated with morphine (50 mg/kg S.C.), tramadol (50 mg/kg S.C.), nalbuphine (5 mg/kg S.C.), morphine plus nalbuphine or tramadol plus nalbuphine twice daily for 15 consecutive days. The dose of tramadol, morphine was selected based on previous studies that investigated tolerance and dependence (Abdel-Zaher, Abdel-Rahman et al. 2011, Habibi-Asl, Vaez et al. 2014), while the ratio of

nalbuphine coadministered was based on our previous study on tramadol (Abdel-Ghany, Nabil et al. 2015).

The analgesic effect was determined 60 min after the first injection on the first day, and the last injection on the last day using the hot plate model in order to assess tolerance to analgesia (Gholami, Saboory et al. 2015).

The time (in seconds) from placing the mouse on the hotplate (55 oC, (XH-2002 premiere slide warmer; Daigger, Vernon Hills, IL) to paw licking or jumping was referred to as the latency time which was compared between different groups. The cut-off time was set at 30 seconds to avoid tissue injury (Abdel-Ghany, Nabil et al. 2015).

Induction and evaluation of withdrawal syndrome

Two hours, after the last injection on the last day, each mouse was treated with the opioid antagonist naloxone (5 mg/kg S.C.), and immediately placed in a transparent acryl cylinder (20 cm in diameter, 35 cm in height) to observe/record withdrawal manifestations (jumping, rearing, teeth chattering and paw tremor) for 30 min. (Abdel-Zaher, Abdel-Rahman et al. 2011, Zhang, Wu et al. 2016) that was manually evaluated by co-workers blind to the treatment protocol.

Quantification of norepinephrine:

After recording the withdrawal manifestations for each animal, animals were sacrificed by decapitation, the whole brain was isolated and the area of locus coeruleus (LC) was dissected (Paxinos and Franklin 2001) and norepinephrine level was quantified using ELISA kit, manufactured by Abnova, according to the manufacturer's instructions.

Statistical analysis

Data are expressed as mean \pm standard error of mean. Statistical analysis was performed using one way analysis of variance (ANOVA) to compare multiple groups followed by Tukey's post-hoc test using Graph pad Prism software version 5.

For all analysis, the level of statistical significance was set at $P < 0.05$.

Results

Analgesic effect and tolerance to analgesia induced by administration of morphine (50 mg/kg s.c.), tramadol (50 mg/kg s.c.) alone or combined with nalbuphine (5 mg/kg s.c.):

Figure (1) shows that single administration of morphine produced an analgesic effect compared to control animals represented by the increase in latency time in the hot plate test (16.3 vs 3.1 sec) which was increased upon nalbuphine co-administration (21.3 vs 16.3 sec) on day 1.

Repeated administration of morphine for 15 days led to tolerance to its analgesic effect as evidenced by the partial decrease of the latency period compared with that observed after the first treatment with morphine (12.3 vs 16.3 sec), however, the effect was still significant compared to control animals (3.2 sec) indicating reversal

of the tolerance to analgesia following its repeated administration.

Single administration of tramadol produced an analgesic effect in the hot plate test (6.8 vs 3.1 sec). Nalbuphine co-administration with tramadol was associated with a significant increase in the latency period compared to tramadol alone (9.7 vs 6.8 sec) on day 1.

Repeated administration of tramadol for 15 days was associated with a significant decrease in the latency time compared with tramadol single treatment (4.2 vs 6.8 sec). While, co-administration of nalbuphine with tramadol for 15 days was associated with a significant increase in the analgesic effect compared to repeated administration of tramadol alone for 15 days (9 vs 4.2 sec) indicating reversal of the tolerance to analgesia following its repeated administration.

Treatment of mice with nalbuphine alone was associated with an analgesic effect (6.2 vs 3.1 and 5.8 vs 3.2 sec) after single administration and repeated administrations respectively.

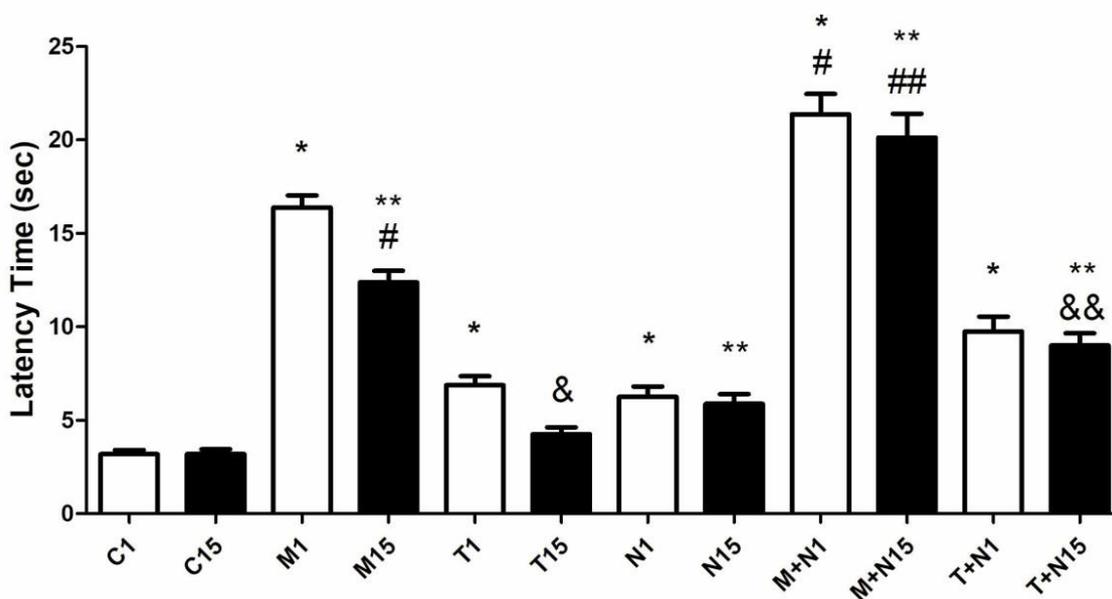


Fig 1: Analgesic effect and tolerance to analgesia induced by administration of morphine (50 mg/kg s.c.), tramadol (50 mg/kg s.c.) alone or combined with nalbuphine (5 mg/kg s.c.). Data are expressed as mean \pm S.E.M. n=8.

* significantly different from control day 1, ** significantly different from control day 15, # significantly different from morphine day 1, ## significantly different from morphine day 15, & significantly different from tramadol day 1, && significantly different from tramadol day 15 at $p < 0.05$ using ANOVA followed by Tukey's post hoc test.

Effect of nalbuphine on naloxone precipitated withdrawal manifestations in morphine and tramadol-dependent mice

In mice treated with morphine or tramadol for 15 days, i.p. injection of 5 mg/kg naloxone 2 h after the last dose, induced withdrawal manifestations including jumping and rearing.

Withdrawal manifestations were observed in morphine-treated mice (32.3 vs 6.6) for jumping (fig 2a) and (98.3 vs. 19.2) for rearing (fig. 2b). Nalbuphine co-administration with morphine significantly reduced rearing manifestations (81.3 vs 98.3).

Tramadol treated mice developed similar withdrawal manifestations (20.7 vs 6.6) for jumping and (80 vs 19.2) for rearing. Nalbuphine co-administration with tramadol significantly reduced rearing manifestations (67.8 vs 80).

Also, in mice treated with nalbuphine, naloxone administration induced weaker withdrawal manifestations (12.1 vs 6.6) for jumping, and (61.3 vs 19.2) for rearing.

Evaluation of norepinephrine level in Locus Coeruleus (LC) after naloxone injection:

Chronic administration of morphine twice daily for 15 days significantly increased the level of norepinephrine in LC after naloxone injection in comparison to control animals (7.9 vs 2.1 nmol/g), which was significantly decreased upon nalbuphine co-administration (5.9 vs 7.9 nmol/g).

Also, chronic treatment of tramadol significantly increased the level of norepinephrine in the LC after naloxone injection in comparison to control animals (5.9 vs 2.1 nmol/g), which was significantly decreased upon nalbuphine co-administration (3.8 vs 5.9 nmol/g).

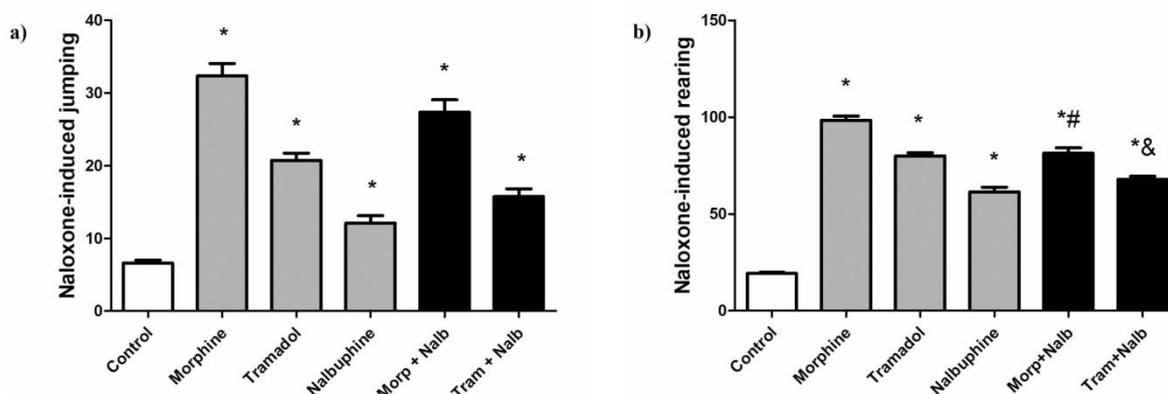


Fig 2: Effect of nalbuphine on naloxone precipitated withdrawal manifestations in morphine and tramadol-dependent mice. Data are expressed as mean \pm S.E.M. n=8. * significantly different from corresponding control group, # significantly different from corresponding morphine alone group, & significantly different from corresponding tramadol alone group at $p < 0.05$ using ANOVA followed by Tukey's post hoc test.

Discussion

Repeated treatment with μ opioid receptor agonists as morphine to control pain is associated with dependence and tolerance to analgesia (Jang, Kim et al. 2006). κ receptor agonists provide acceptable analgesia and do not induce morphine-like physical dependence (Millan 1990) nor respiratory depression (Zeng, Lu et al. 2015).

Nalbuphine is a μ antagonist and κ agonist (Schmidt, Tam et al. 1985) that was

previously shown to attenuate the development of tolerance and dependence to morphine (Dabrowska-Wojciak and Piotrowski 2008), however, the exact mechanism of this effect was not shown.

We have previously shown that co-administration of nalbuphine with tramadol blocked the development of its psychological dependence through dopamine (Abdel-Ghany, Nabil et al. 2015). However, its effect on tramadol physical dependence is not clear yet.

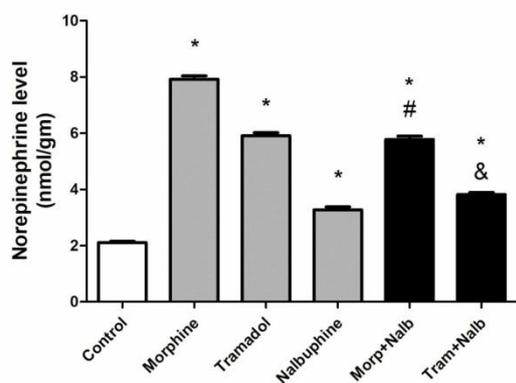


Fig 3: Evaluation of norepinephrine level in LC after naloxone injection. Data are expressed as mean \pm S.E.M. n=8. * significantly different from control, # significantly different from morphine alone, & significantly different from tramadol alone at $p < 0.05$ using ANOVA followed by Tukey's post hoc test.

In the current study, we attempted to investigate the effect of repeated nalbuphine co-administration with morphine or tramadol on the development of tolerance to analgesia and physical dependence and the possible involvement of brain norepinephrine in this effect.

In the present study, single administration of morphine, tramadol, nalbuphine induced analgesic effect as evidenced by the increase in the latency time in the hot plate test. The analgesic effect of tramadol, nalbuphine (Abdel-Ghany, Nabil et al. 2015) or morphine (Orabueze, Adesegun et al. 2016) was previously shown. Interestingly, co-administration of nalbuphine with morphine or tramadol produced higher analgesic effect than either drug alone on day 1.

However, repeated administration of morphine for 15 days was associated with tolerance to its analgesic activity as evidenced by the significant decrease in the latency time observed at day 15 of morphine administration compared to its effect on day 1. The development of tolerance following repeated morphine administration was previously reported (Fotio, Palese et al. 2020).

Similar effects were observed following repeated administration of tramadol for 15 days as evidenced by the decrease in the latency time compared to its

effect on day 1 as was previously shown (Abdel-Zaher, Abdel-Rahman et al. 2011).

Induction of tolerance to analgesia following repeated administration of MOR agonists was previously reported (Tjaderborn, Jonsson et al. 2009, Lanier, Lofwall et al. 2010).

Repeated administration of nalbuphine alone or for 15 days was associated with nearly similar analgesic action as that observed on day 1 confirming that nalbuphine itself has limited liability to tolerance (Schmidt, Tam et al. 1985).

Repeated co-administration of nalbuphine with morphine or tramadol for 15 days was associated with an analgesic action nearly similar to that observed at day 1 of the corresponding combination showing that nalbuphine could effectively prevent the development of tolerance to morphine or tramadol as previously shown for morphine (Lee, Wang et al. 1997) which might be attributed to dual effects on μ and κ receptors acting as κ agonist (Yamamoto, Ohno et al. 1988) and the μ antagonist (DeLander, Portoghese et al. 1984).

Concerning physical dependence, naloxone-precipitated withdrawal manifestations including rearing and jumping were observed in mice treated with morphine, tramadol, nalbuphine or morphine/tramadol + nalbuphine. This confirms the previous reports showing the incidence of dependence with morphine (Lee, Wang et al. 1997), tramadol (Sprague, Leifheit et al. 2002), while nalbuphine has less potential to develop dependence (Schmidt, Tam et al. 1985).

Concerning jumping, all groups showed significantly higher number of jumping events compared to control group. Co-administration of nalbuphine with morphine or tramadol caused mild reduction that did not reach a significant level. However, in case of rearing, all groups were significantly higher compared to control group and co-administration of nalbuphine with morphine or tramadol caused a significant reduction in the number of rearing events compared to either drug alone

indicating a partial amelioration in withdrawal symptoms.

Brain norepinephrine was reported to play an important role in drug reward (Olson, Heusner et al. 2006) and withdrawal (Aston-Jones, Delfs et al. 1999) in the ventral bed nucleus of the stria terminalis (vBNST) (Fox, Rodeberg et al. 2017) and in the locus coeruleus (LC) (Schwarz and Luo 2015)

In the current study, administration of naloxone after the last dose of repeated administration of morphine or tramadol was associated a significant elevation in norepinephrine in the LC.

Similar elevation in norepinephrine level following administration of naloxone after chronic morphine administration in LC (Zachariou, Liu et al. 2008) and vBNST that coincided with specific withdrawal symptoms (Fox, Rodeberg et al. 2017) was shown. Administration of nalbuphine postoperatively was associated a reduction in norepinephrine level (Gong, Zhang et al. 2018).

On the other hand, administration of naloxone after the last dose of repeated

administration of each combination was associated reduced LC norepinephrine which might explain the effect of nalbuphine in reducing the dependence to morphine or tramadol observed in this study.

Our results also suggest that nalbuphine could effectively reduce the development of withdrawal manifestations induced by morphine or tramadol (which is linked with the development of physical dependence in humans) without attenuating their analgesic effect.

Author contribution:

MA and WB designed the research, MN performed the animal experiments, MN and WB analyzed the data and wrote the manuscript, MA revised the manuscript.

Conflict of interest:

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Also the authors confirm that all data were generated in-house and that no paper mill was used

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النالبوفين يحسن الاعتماد وفقدان التأثير المستحدث بالمورفين و الترامادول من خلال النورابينيافرين في اللوكس كوريلبيوس

رشا حسن عبد العني – محمود نبيل – محمد عبد العال - وليد بركات *
قسم علم الأدوية والسموم – كلية الصيدلة – جامعة الزقازيق

إن الاستخدام المزمّن للأفيونات مثل المورفين للتحكم في الألم يصاحبه العديد من التأثيرات الجانبية مثل فقدان التأثير المسكن للآلم والاعتماد. يمكن تحسين بعض هذه الآثار الجانبية باستخدام النلوكسون ولكن ذلك يقلل من التأثير المسكن للآلم. ثبت أن النالبوفين يحسن من الاعتماد النفسي على المورفين و الترامادول. تهدف الدراسة الحالية إلى بحث تأثير استخدام النالبوفين مع المورفين أو الترامادول على فقدان تأثيرهما والاعتماد الجسدي عليهما والدور المحتمل للنورابينيافرين في ذلك استخدام النالبوفين مع المورفين أو الترامادول أدى إلى منع فقدان التأثير والاعتماد الجسدي الذي لوحظ مع كلا منهما بمفرده وكان ذلك مصحوبا بمنع الارتفاع في مستوى النورابينيافرين في اللوكس كوريلبيوس بعد استخدام النالوكسون. تشير هذه النتائج إلى إمكانية استخدام النالبوفين مع المورفين أو الترامادول للحفاظ على تأثيرهم المسكن للآلم ومنع الاعتماد عليهما.