



RESEARCH ARTICLE

Dose Related Analgesic, Motor and Reinforcing Effects of Nalbuphine in Rats

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ABSTRACT

Nalbuphine, a semi-synthetic opioid drug, is a kappa (κ) agonist/ mu (μ) partial agonist. It is clinically used for moderate to severe pain. It produces the analgesic effect largely by binding to kappa opioid receptors. The present study was designed to investigate locomotor sensitization as well reinforcing effects of different doses (5, 10 and 20 mg/kg) of nalbuphine in rats. Potential analgesic and hyperalgesic effects after single and repeated administration respectively were also monitored. Reinforcing effects were monitored in a conditioned place preference (CPP) paradigm and associated changes in motor activity were monitored during a drug conditioning phase. The hot plate test was used to monitor nociceptive response. The present study showed that low (5 mg/kg) and high (20 mg/kg) doses of nalbuphine were reinforcing, while the moderate dose (10 mg/kg) had no reinforcing effect in the CPP paradigm. All doses were analgesic after the first administration and on repeated administration hyperalgesia did not develop to any dose. Analgesic effects still occurred at moderate doses of nalbuphine. Sensitization-like effects were produced following moderate and high doses of nalbuphine. These findings suggested that a moderate dose of nalbuphine did not produce reinforcing effects and hyperalgesia so this dose can be used safely for treating pain.

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INTRODUCTION

Opioid drugs such as morphine are the gold standard for treating pain, however, these drugs are of little use for the treatment of chronic pain conditions such as arthritis, cancer, and low back pain (Witkin *et al.*, 2017). For example, morphine is used for a long duration produces tolerance, dependence, and hyperalgesia (Doyle *et al.*, 2020). Animal research of repeated administration of morphine has been shown to produce reinforcing effects in condition place preference (CPP) test, sensitization-like effects, and hyperalgesia (Haleem and Nawaz, 2017).

Morphine is an agonist at mu (μ) opioid receptor (Roeckel *et al.*, 2017). Pain-killing, as well as addictive effects of morphine, are produced because of the activation of mu-opioid receptors (Kim *et al.*, 2016). Studies show that kappa (κ) opioid receptor activation can reduce the addictive effects of morphine (Lee *et al.*, 1997; Wee and Koob, 2010). For instance, repeated

morphine treatment exhibits sensitization (Haleem and Nawaz, 2017). Moreover, sensitization is also produced in locomotor and condition the rewarding effect of μ -opioid agonist diacetylmorphine (Kvello *et al.*, 2020) and cocaine (Puig-Ramos *et al.*, 2008). Conversely, the kappa opioid receptor has been shown to block locomotor sensitization as well as condition rewarding effects of mu-opioid agonists (Glick *et al.*, 1995; Lee *et al.*, 1997; Tao *et al.*, 2006; Wee and Koob, 2010). Nalbuphine, a semi-synthetic opioid drug, having agonistic action for both κ and μ opioid receptors (Raghav *et al.*, 2018) has been shown to produce sensitization-like effects only at high dose, low and moderate doses of nalbuphine do not produce sensitization (Smith *et al.*, 2009a).

The current study was planned to evaluate locomotor sensitization as well reinforcing effect of lower, moderate, and higher doses of nalbuphine in rats. Potential analgesic and hyperalgesic effects after single and repeated treatment respectively were also investigated.

MATERIALS AND METHODS

Animals: Locally raised male Albino Wistar rats weighing 180-220 g and 8-12 weeks old were used in the present study. Rats were kept in an individual cage for 4 days with free access to rodent food and water before the experiment. The temperature of the room was set to $24\pm 2^\circ\text{C}$. All animal experiments were also carried out following a protocol accepted (ASP No: 2015-0016) by the institutional Ethics and Animal Care Committee.

Drug and doses: Nalbuphine ampoules of 20 mg/mL were purchased locally. The drug was administered intraperitoneally in dosages of 5-20 mg/kg. Saline (1 mL/kg) was administered to the control group. The drug was prepared in saline daily before the experiment.

Experimental protocol: Twenty four animals were randomly divided into 4 groups (n=6) as:

- i. Saline (1 mL/kg)
- ii. Nalbuphine (5 mg/kg)
- iii. Nalbuphine (10 mg/kg)
- iv. Nalbuphine (20 mg/kg)

Animals were injected accordingly with saline or nalbuphine at 9:30-11:30 h. The CPP paradigm was performed to evaluate the rewarding effect of repeated administration of nalbuphine planned for fourteen days as defined previously (Haleem and Nawaz, 2017). Saline was injected to animals on days 1, 3, 5, 7, 9, and 11, and then rats were kept in a non-drug compartment for 30 minutes. On other days, i.e. 2, 4, 6, 8, 10 and 12, rats of each group were injected with saline or nalbuphine (5 or 10 or 20 mg/kg) (as stated above for each group). Motor behavior was also observed daily during twelve days of conditioning. Horizontal and vertical crossings were determined for 10 minutes, five minutes post-drug administration. The hot plate test was used to monitor heat-induced nociception after 30 minutes of single injection of the drug at 12:00-12:30 hr and after 30 minutes of post-conditioning phase, 24 h post-treatment of the drug.

Apparatus for conditioned place preference: Three-compartment CPP apparatus (unbiased design) was used to monitor drug-induced reinforcement. The apparatus was made up of transparent plastic Perspex. Each compartment was divided by a sliding transparent door. The mid (shuttle) compartment ($14 \times 26 \times 26$ cm) did not have stripes. Each end (preference) compartment ($26 \times 26 \times 26$ cm) had different contexts; one partition had black horizontally oriented stripes on its walls and the other partition had vertically oriented black stripe.

The CPP test was conducted in three different stages: pre-conditioning, conditioning and post-conditioning. On the initial day (day 0) pre-conditioning phase was conducted without drug administration. The pre-conditioning phase ensured that the animals did not have a preference for any compartment. An animal was introduced in the CPP apparatus from the middle compartment and guillotine doors were raised. Each rat was allowed to access all three partitions for ten minutes and time passed in both end compartments was monitored.

On the next day of the pre-conditioning test, conditioning test was performed. Rats were randomly distributed into four groups as stated above. Over the next twelve days, (day 1-12) conditioning was done (one session each day) in which each animal was restricted to any of the horizontal or vertical stripes partition. On days 1, 3, 5, 7, 9, and 11 saline (at 9:30-11:30 h) was injected to animals and confined to the non-drug compartment for thirty minutes. On days 2, 4, 6, 8, 10, and 12, saline or nalbuphine (5 or 10 or 20 mg/kg) was injected. Immediately after injection rats were confined to the drug compartment for thirty minutes.

On day 13 post-conditioning phase was performed, in a drug-free state. As in the pre-conditioning test, the sliding doors were raised and animals had free access to all compartments for ten min. Time passed in the drug-coupled partition was recorded.

Motor sensitization effects of nalbuphine: Motor behavior was also monitored during conditioning sessions to evaluate tolerance or sensitization effects of drugs. Motor activity scored as no. of cage crossing 5 minutes post-drug administration for 10 min.

Hot plate test: For evaluating the analgesic effect of the drug an analgesiometer was used. The temperature of the hot plate and cut-off time were $52\pm 0.2^\circ\text{C}$ and 30 sec, respectively during the test.

Statistical analyses: Data were presented as Mean \pm S.D. Effects of nalbuphine on anti-nociception were examined by 1-way ANOVA. Values of pre- and post-conditioning time passed in drug-coupled sections and motor behavior of nalbuphine were evaluated via two-way ANOVA (Repeated measure design), nalbuphine used as between groups factor and days as within group factor. Posthoc analysis was done using Tukey's test and p values less or equal to 0.05 were considered significant.

RESULTS

Heat-induced nociception after a single administration: The dose-related effects of nalbuphine on anti-nociception were examined on hot plate apparatus 30 minutes post-administration (Fig. 1). One-way ANOVA revealed the effect of nalbuphine was significant on latency to first paw licking ($F=56.3$ df3,20 $P<0.01$) and no. of licks ($F=49.62$ df3,20 $P<0.01$). Post-hoc comparison exhibited enhanced latency time in paw lick at all dosages of nalbuphine as compared to saline group. Dose of 20 mg/kg showed more latency as compared to 5 and 10 mg/kg. Nalbuphine at all three doses exhibited a decrease in no. of licks than control group and this reduction was more at 20 mg/kg dose than at 5 and 10 mg/kg. Results suggested that nalbuphine produced dose-dependent anti-nociception effects after single administration.

Reinforcing effects: Time passed in the drug-linked compartment was monitored during pre- and post-conditioning in animals administered with saline or nalbuphine (5, 10 and 20 mg/kg). ANOVA (two-way repeated measure design) revealed pronounced effect of

nalbuphine ($F=9.53$ $df_{3,20}$ $P<0.01$), repeated measures (days) ($F=16.03$ $df_{3,20}$ $P<0.01$) and nalbuphine \times repeated measures (days) interaction ($F=3.775$ $df_{3,20}$ $P<0.05$). Post-hoc analysis shown that time spent in drug-associated compartment during pre- and post-conditioning phase, was comparable in control and 10 mg/kg nalbuphine administered group. Rats administered with 5 and 20 mg/kg doses of nalbuphine spent more time during post- than pre-conditioning phase in drug-linked compartment. Post-conditioning time spent in the drug-associated compartment was more in nalbuphine (5 and 20 mg/kg) than control group (Fig. 2).

Motor behavior: Motor behavior on nalbuphine administration days was observed in control and nalbuphine injected animals. Data were examined by 2-way ANOVA showed pronounced effects of nalbuphine ($F=136.1$ $df_{3,20}$ $P<0.01$), repeated measures (days) ($F=109.55$ $df_{5,20}$ $P<0.01$) and interactions of repeated measures (days) \times nalbuphine ($F=32.71$ $df_{15,20}$ $P<0.01$). Post-hoc comparison exhibited that after single administration of nalbuphine (5 and 20 mg/kg but not 10 mg/kg) produced significant reduction ($P<0.01$) in motor activity on day-2, compared to same day saline-injected group (control). 2nd to 6th injection of nalbuphine (10

mg/kg) on days 4, 6, 8, 10 and 12 caused significant enhancement in motor activity compared to respective day saline-injected animals (Fig. 3). Nalbuphine (20 mg/kg) showed pronounced enhancement in motor behavior following 3rd to 6th administration compared to respective day saline-treated group, these outcomes suggested that tolerance in motor depressant effects was exhibited following 3rd drug injection.

Heat-induced nociception after repeated administration: Effects of nalbuphine (5, 10 and 20 mg/kg) after repeated treatment on alternate days on anti-nociception after 24 h of last drug injection were determined on day 13 (Fig. 4). One-way ANOVA revealed effect of nalbuphine was significant on latency to first lick ($F=14.22$ $df_{3,20}$ $P<0.01$) and no. of licks ($F=16.68$ $df_{3,20}$ $P<0.01$). Posthoc comparison exhibited enhanced latency in paw lick at 10 mg/kg dose of nalbuphine as compared to control and nalbuphine (5 and 20 mg/kg) groups. The number of licks decreased at 10 and 20 mg/kg dosages of nalbuphine than saline injected group and reduction was more at 10 mg/kg than to 5 mg/kg dose. Results suggest that after repeated administration on alternate days moderate doses were more effective to produce anti-nociceptive effects.

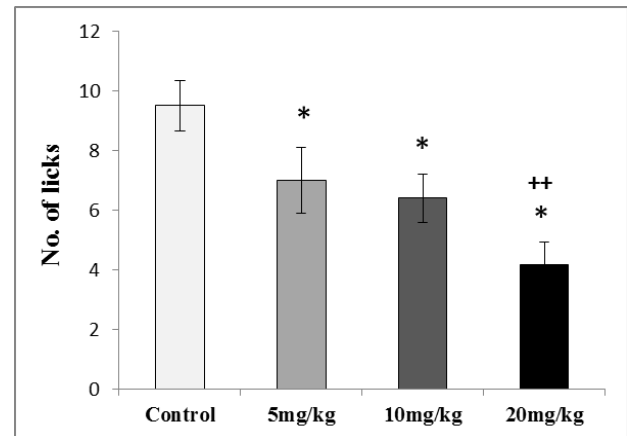
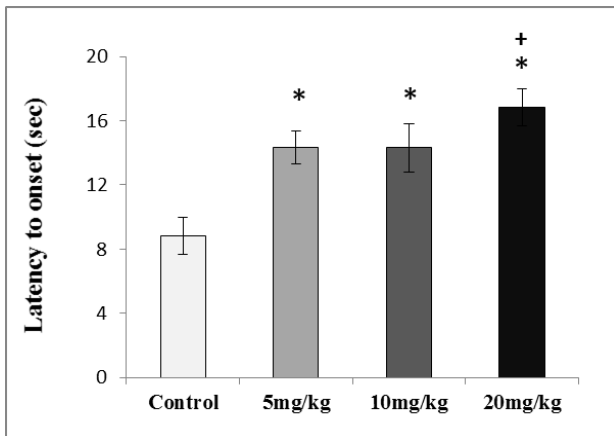


Fig. 1: Effects of different dosages of nalbuphine on heat-induced nociception. Values represented as Mean \pm SD (n=6) 30 min after the first administration of nalbuphine. Significant difference by Tukey's comparison: * $P<0.01$ from saline injected group; + $P<0.05$, ++ $P<0.01$ from 5 mg/kg nalbuphine injected group.

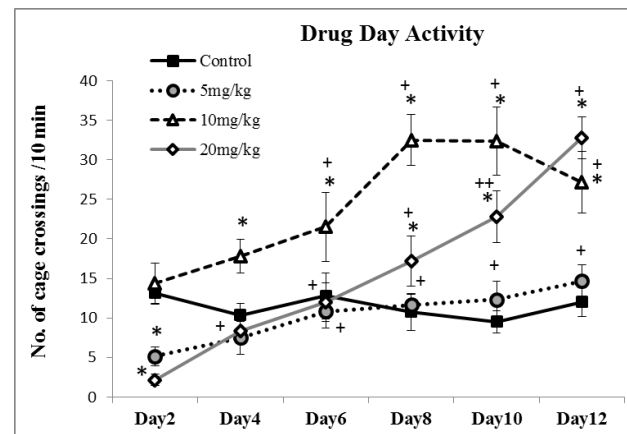
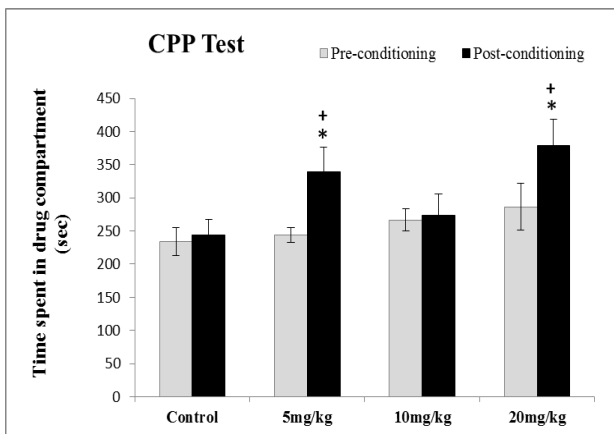


Fig. 2: Effects of different doses of nalbuphine on pre- and post-conditioning data of time spent in the drug-linked compartment. Data represented as Mean \pm SD (n=6). Significant difference using Tukey's test: * $P<0.01$ from relative pre-conditioning data; + $P<0.01$ from saline injected rats using 2-way ANOVA.

Fig. 3: Effect of all dosages of nalbuphine injection on motor behavior on drug administration day. Values represented as Means \pm S.D (n=6). Significant different by Tukey's analysis: * $P<0.01$ from the relevant day control group, + $P<0.05$, ++ $P<0.01$ from data of day-2 of similar administration animals following two-way ANOVA repeated measure.

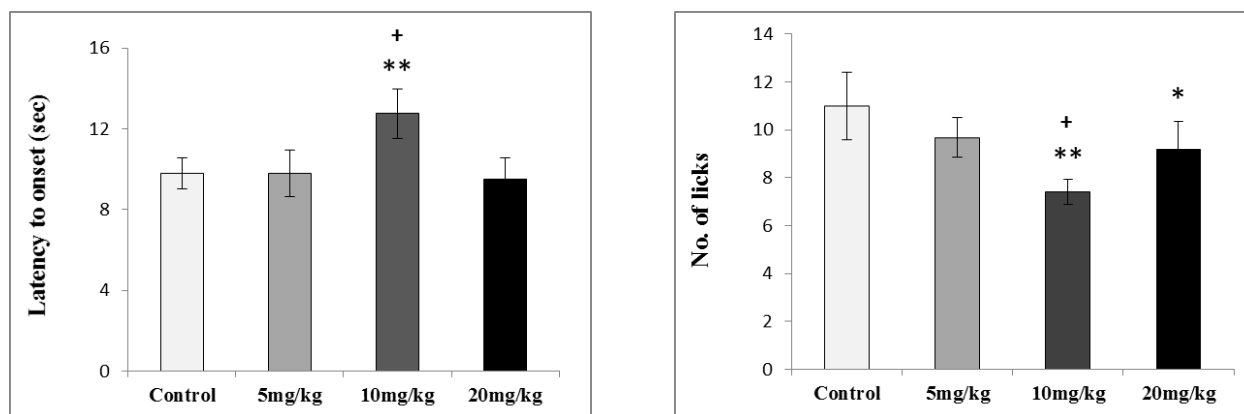


Fig. 4: Effects of different dosages of nalbuphine on heat-induced nociception. Values represented as Mean \pm SD (n=6) 24 h of last drug injection after repeated treatment on alternate days. Significant difference via Tukey's comparison: *P<0.05, **P<0.01 from saline injected rats; ++P<0.01 from 5 mg/kg nalbuphine administered group.

DISCUSSION

The current study aimed to elucidate dose-dependent potential reinforcing, sensitization like and antinociceptive/hyperalgesic effects of nalbuphine. The results revealed that administration of lower (5 mg/kg) and higher (20 mg/kg) doses of nalbuphine to animals produced reinforcing effect, while moderate dose (10 mg/kg) had no rewarding effect in the CPP test. All doses were analgesic after the first administration and on repeated administration hyperalgesia did not develop to any dose; analgesic effects still occurred at moderate doses of nalbuphine. Sensitization-like effects were produced following moderate and high doses of nalbuphine.

The results tend to show that in moderate doses nalbuphine is not reinforcing and produces long-lasting analgesia which may be due to its activity towards both μ as well as kappa opioids receptors.

Previous studies showed that qualitatively μ and κ -opioids produced different effects in place-conditioning test, μ -opioids produced place-preference (Smith *et al.*, 2005; Haleem and Nawaz, 2017) and kappa-opioids produced place-aversion (del Rosario Capriles and Cancela, 2002). Kappa opioids had been shown to block condition rewarding effects of mu-opioid agonists (Lee *et al.*, 1997; Shippenberg *et al.*, 2001; Tao *et al.*, 2006). Mu opioids reinforcing effects were associated with increased levels of dopamine in nucleus accumbens. Kappa opioids inhibit mu-opioids-induced CPP by inhibiting levels of dopamine in nucleus accumbens (Tao *et al.*, 2006).

Studies showed that mixed mu-kappa agonists such as nalbuphine, butorphanol produced either inconsistent or reduced reinforcing actions (Smith *et al.*, 2005; Kaski *et al.*, 2019). Nalbuphine had partial activity for mu and full activity for kappa receptors, but it had limited efficacy for mu receptors (Traynor *et al.*, 2002).

Auto-radiographic-based studies showed that the binding affinity of nalbuphine for μ -opioid receptors was comparable to morphine, while its affinity for kappa-opioid receptors was lesser (De Souza *et al.*, 1988; Raghav *et al.*, 2018). The overall effects produced by nalbuphine depend on which receptor was activated.

Our study also revealed inconsistent effects of nalbuphine. Nalbuphine dosages of 5 and 20 mg/kg but

not 10 mg/kg dose exhibited place-preference. Reinforcing effects caused by low dose may be due to activation of mu receptor. But as the dose increased it also activate the kappa receptor, which opposed the reinforcing effect. At 10 mg/kg dose, nalbuphine bound equally to kappa and μ receptors so reinforcing effects not occurred.

Nalbuphine had a low affinity at high doses towards kappa-receptors, as reported previously (De Souza *et al.*, 1988; Traynor *et al.*, 2002). These findings suggest the role of mu-opioid receptors in inducing CPP at higher doses.

Reinforcing effects of abused drugs are also associated with behavioral sensitization (Koob and Volkow, 2016). Opioids such as morphine initially produced the motor depressant effect which was disappeared on repeated administration (Vanderschuren *et al.*, 1999; Smith *et al.*, 2009a), activity enhanced after long-term treatment (Trujillo, 2002; Smith *et al.*, 2009a).

While spiradoline (a kappa agonist) reduced locomotor movement dose-dependently (Smith *et al.*, 2009a). Previous studies had also shown that kappa agonists inhibit cocaine (Puig-Ramos *et al.*, 2008) and morphine (Smith *et al.*, 2009b) induced behavioral sensitization.

Studies showed that repeated administration of high dose (30 mg/kg), but not low (3 mg/kg) or moderate doses (10 mg/kg) of mixed mu and kappa agonists (Butorphanol, nalbuphine, and nalorphine) exhibited sensitization in locomotor behavior. Pre-treatment with kappa agonists produced a progressive enhancement in locomotor behavior at lower and moderate dosages of mixed mu and kappa agonists (Smith *et al.*, 2009a), suggesting that kappa agonistic activity was responsible for opposing the increase in motor activity. At higher doses (30 mg/kg) single administration of mixed mu and kappa agonists caused a little decrease in motor behavior followed by an increase in motor activity (Smith *et al.*, 2009a). Nalbuphine had a lower affinity at high doses towards kappa-receptors, as reported previously (De Souza *et al.*, 1988; Traynor *et al.*, 2002). These findings suggest a role of mu-opioid receptors for inducing sensitization at the higher dose.

In the present study, activity was also observed during the conditioning time of the CPP paradigm. Our

results illustrated that nalbuphine at lower (5 mg/kg) and high (20 mg/kg) dosages but not moderate (10 mg/kg) dose exhibited a motor depressant effect on single administration. Consistent with previous studies, higher doses of nalbuphine caused tolerance in motor-depressant effect followed by sensitization after repetitive drug treatment. Sensitization-like effects were also observed at the moderate dose of nalbuphine (10 mg/kg). According to previous studies at higher doses, nalbuphine affinity towards kappa receptor decreased so it may be possible that at high doses mu receptor was activated producing sensitization effects.

Nalbuphine analgesic properties are predominantly mediated through agonist activity at the kappa-opioid receptor when compared to morphine (Davis *et al.*, 2018b). Evidence suggested that μ and κ agonists produced anti-nociception via the separate mechanism. Mu-receptor is coupled to potassium ion channels, while κ -receptors are connected to a voltage-sensitive calcium ion channel (Schultz and Gross, 2001).

Parenteral administration of low dose (10-15 mg) of nalbuphine exhibited anti-nociception comparable to equivalent doses of morphine (Davis *et al.*, 2018a). However, high dosages of more than 0.4 mg/kg caused ceiling effects to anti-nociceptive effects (Lee *et al.*, 1997; Chen *et al.*, 2020).

Nalbuphine exhibited dose-related analgesia in mice (10–100 mg/kg) and rats (0.5–10 mg/kg) (Pick *et al.*, 1992; Khasar *et al.*, 2003). Tolerance in analgesic effects of nalbuphine was not observed after repeated administration (Barakat *et al.*, 2020) instead co-use of nalbuphine with morphine or tramadol prevented tolerance to analgesia and physical dependence (Barakat *et al.*, 2020).

Present data revealed that nalbuphine after a single injection exhibited analgesia at all doses (5, 10 & 20 mg/kg). While on alternative days repetitively administered nalbuphine at 10 and 20 mg/kg but not on 5 mg/kg dose showed analgesic effects, in a drug withdrawal state. Moderate doses of nalbuphine revealed more analgesia than higher doses. Our findings showed that hyperalgesic effects were not produced after long-term administration of moderate and high doses of nalbuphine, instead, moderate doses of nalbuphine exhibited long-lasting analgesic effects.

Conclusions: We conclude that repeated administration with a moderate dose of nalbuphine did not cause hyperalgesia and reinforcing effects, suggesting that this dose can be used safely for treating pain.

Authors contribution: SN: study conception and design, performed all experiments, collection and/or assembly of data, data analysis and interpretation, wrote the whole manuscript, final approval of the manuscript; TS: helped in experimenting; SG: helped in study conception; DJH: experimental design, supervised this research, data analysis and helped in manuscript writing.

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