

A Study of the Analgesic Interaction between Intrathecal Morphine and Subcutaneous Nalbuphine in the Rat

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Nalbuphine reverses opioid-induced respiratory depression, but the effect on analgesia is unclear. The analgesic interaction between subcutaneous (sc) nalbuphine and intrathecal morphine in conscious, male, Sprague-Dawley rats implanted with chronic intrathecal catheters was investigated. Nalbuphine (10 mg/kg) injected 30 min after intrathecal morphine (4 µg) significantly antagonized the effect of morphine in the tail flick test. The antagonism was rapid in onset and persisted beyond the experimental period of 240 min. The magnitude and the duration of the effect were comparable to that observed with sc naloxone (1 mg/kg). In contrast to the results in the tail flick test, nalbuphine enhanced the effect of intrathecal morphine in the noninflamed paw pressure test. Nalbuphine (10 mg/kg) alone had no effect on the time course of tail flick latency but significantly increased paw pressure threshold during the 15-90 min interval after sc injection. Nalbuphine (0.5 mg/kg, sc) alone had no antinociceptive effect in either pain test and did not antagonize the antinociceptive effect of intrathecal morphine (4 µg) in the tail flick test. However, sc nalbuphine (0.5 mg/kg), injected 30 min after intrathecal morphine (1.5 µg), significantly enhanced the effect of morphine in the paw pressure test compared with intrathecal morphine + sc saline-treated rats. The results indicate a complex analgesic interaction between intrathecal morphine and sc nalbuphine. The net analgesic effect during the interaction was determined by the following: 1) the doses of morphine and nalbuphine; 2) the time after nalbuphine administration; and 3) the nature of the nociceptive stimulus. At lower doses, sc nalbuphine appeared to potentiate the effect of intrathecal morphine in the noninflamed paw pressure test. (Key words: Analgesia: measurement. Analgesics, intrathecal: morphine. Analgesics, subcutaneous: nalbuphine.)

EPIDURAL AND INTRATHECAL opioids produce profound, long-lasting analgesia by a localized action in the spinal cord^{1,2} that is not associated with sensory, sympathetic, or motor blockade.² Spinal opioids provide effective analgesia for many types of clinical pain,² but their use has been limited by potential delayed respiratory depression and the need for continuous surveillance of the patient for up to 12 h after spinal injection. Although the reported incidence of delayed respiratory depression following spinal opioids is low (0.09-0.9% following epidural morphine and 0.36-7.0% following intrathecal

morphine^{2,3}), the life-threatening nature of this adverse effect may preclude their routine use outside an intensive care or special monitoring unit.

Low doses of naloxone have been used to antagonize opioid-induced respiratory depression,^{4,5} but careful titration is required to prevent the reversal of analgesia and an increase in sympathetic tone.^{6,7} Adverse effects, such as hypertension, arrhythmias, and pulmonary edema, have been reported following naloxone antagonism of opioid-induced respiratory depression.⁸⁻¹⁰ In addition, naloxone has a short duration of action in humans and must be readministered at frequent intervals or be given by continuous infusion to prevent subsequent respiratory depression.

Nalbuphine, a partial agonist at μ -opiate receptors,^{11,12} also reverses opioid-induced respiratory depression^{13,14} by antagonizing the effect of μ -agonists (*e.g.*, morphine) in the respiratory center. Nalbuphine itself produces limited respiratory depression,^{15,16} and provides a margin of safety not shared by pure opioid agonists. It also has κ -agonist activity and produces significant analgesia.^{17,18} These pharmacologic characteristics suggest that nalbuphine could be useful in antagonizing opioid-induced respiratory depression while sparing or augmenting analgesia.

The effect of nalbuphine on opioid-induced analgesia is unclear. Some studies have reported no change in the level of pain after nalbuphine reversal of respiratory depression,^{13,19,20} whereas others have reported nausea, hypertension, tachycardia, arrhythmias, increased plasma catecholamine concentrations, and pain requiring additional analgesic therapy.^{14,21} The effect of nalbuphine on opioid analgesia during reversal of respiratory depression is an important question because preservation of analgesia and sedation represent theoretical advantages compared with pure antagonists, such as naloxone. In the present study, we investigated the analgesic interaction between sc nalbuphine and intrathecal morphine using two different nociceptive tests in rats, and compared these results with the effect of sc naloxone. Opioid-induced respiratory depression, its reversal by nalbuphine or naloxone, and plasma nalbuphine concentrations were not determined in this study.

Materials and Methods

All experimental procedures received prior approval from the Animal Care Committee, Faculty of Medicine,

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Queen's University. Virus antibody-free, male, Sprague-Dawley rats (Charles River Inc., St. Constant, Canada) weighing 275–450 g were used. Rats were initially housed in group cages on a 12-h light-dark cycle (lights on 0700 h) with Purina® laboratory rat chow and tap water freely available.

Chronic intrathecal catheters were implanted under halothane anesthesia as previously described.²² Briefly, polyethylene catheters (PE-10) were filled with sterile saline (0.9%; Travenol Canada Inc., Mississauga, Canada) and inserted into the spinal subarachnoid space through a slit in the atlanto-occipital membrane so that the tip of the catheter terminated in the region of the lumbar enlargement. The rostral tip of the catheter was passed subcutaneously and externalized on the top of the head. A small volume of saline was injected to clear the catheter of any blood, and the externalized tip was sealed with a stainless steel plug. Animals were then housed individually and allowed to recover for a minimum of 4 days before the experiment. Only animals exhibiting normal motor function and having normal baseline responses in the tail flick (TF) and paw pressure (PP) tests were used in these experiments.

Drug solutions were prepared daily in sterile saline, and all doses of nalbuphine (Du Pont Pharmaceuticals, Du Pont Canada Inc. Mississauga, Canada) and morphine (BDH Pharmaceuticals, Toronto, Canada) are expressed as the hydrochloride and sulfate salts, respectively. Intrathecal morphine was injected in a volume of 10 μ l followed by 10 μ l of saline to flush the catheter. Rats were trained to voluntarily enter and remain inside a cloth restrainer during intrathecal injection.²³ Subcutaneous nalbuphine was always injected into a fold of skin between the scapula on the back of the animal using an injection volume of 0.1 ml/100 g body weight. Doses of intrathecal morphine were selected from dose–response curves previously determined in our laboratory. Nalbuphine doses were determined in preliminary dose–response experiments as part of this study. A threshold dose (0.5 mg/kg) and an antinociceptive dose (10 mg/kg) corresponding to a 30% maximum percent effect (MPE) in the PP test were selected. A 30% MPE was used so that there would be a wide range between antinociception and cutoff in the PP test thereby facilitating the observation of potentiation if it occurred.

The TF test²⁴ was used with a cutoff value of 10 s, and the PP test was a modification of the method of Randall and Selitto.²⁵ Pressure was applied to the dorsal surface of the noninflamed hind paw until a withdrawal response was observed; the cutoff pressure for this test was 300 mmHg.²² On the day prior to the experiment, rats were acclimatized to all procedures, and baseline responses in both pain tests were determined. Control responses were

also determined on the day of the experiment, immediately prior to drug injection. Experiments were started at the same time each morning to minimize the effects of diurnal variation, and the mean of three consecutive measurements was determined in each of the TF and PP tests at all experimental time points. There were no significant differences in the TF and PP baseline responses among the treatment groups in any of the experiments in this study. Data are presented as the absolute response latency in seconds (TF test) and PP threshold in mmHg (PP test).

In all experiments rats were randomly assigned to the different experimental groups, and the observer was blinded to the drug treatments. A washout period of at least 4 days was used between experiments. No residual drug effects in the PP or TF test were observed 4 days later; rats previously treated with drugs and then given saline did not differ from untreated rats or those previously treated with saline. Individual rats were not used in more than two experiments. Statistical analysis of the data at individual time points was conducted using randomized, one-way analysis of variance and Newman-Keuls test except for experiments with only two treatment groups where an unpaired Student's *t* test was used. Statistical analysis of the time course data within each treatment group was conducted using repeated-measures analysis of variance and Newman-Keuls test.

Results

The effects of intrathecal morphine (4 μ g) on the time course of TF latency and PP threshold in three separate groups of rats are shown in figures 1 and 2, respectively. Intrathecal morphine significantly increased TF latency and PP threshold at 15 and 30 min in all groups compared with their respective baseline values. The maximum responses were 8.7 ± 1.4 , 9.2 ± 1.2 , and 9.3 ± 0.8 s (mean \pm SD) in the TF test and 201 ± 52 , 210 ± 52 , and 237 ± 79 mmHg in the PP test. There were no significant differences between the three groups at 15 or 30 min in either test.

Immediately after analgesia testing at 30 min, each experimental group received an sc injection of either saline, naloxone (1.0 mg/kg), or nalbuphine (10 mg/kg), and TF and PP testing resumed at 45 min. In the TF test, naloxone and nalbuphine completely antagonized the effect of morphine compared with the effect of morphine in saline-treated rats (fig. 1); response latencies were decreased to baseline. The antagonism was also rapid in onset. At 45 min TF latency in the naloxone- and nalbuphine-treated groups was 2.0 ± 0.6 and 2.7 ± 0.8 s, respectively, and there was no recovery of morphine-induced antinociception thereafter.

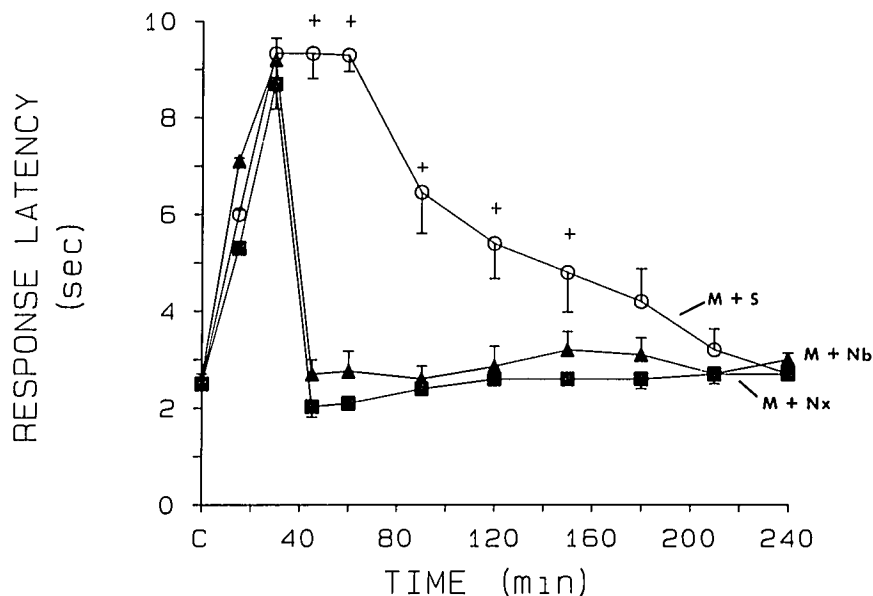


FIG. 1. The effect of intrathecal morphine (M; 4 μ g) injected immediately after baseline testing (C), followed 30 min later by sc nalbuphine (Nb; 10 mg/kg), naloxone (Nx; 1 mg/kg), or saline (S) on the time course of tail flick latency. Data are presented as the mean \pm SEM of seven rats, and all points were significantly different from their respective baseline value except 180, 210, and 240 min in the M + S group and 45–240 min in the M + Nx and M + Nb groups. *Significant difference from both the M + Nx and M + Nb groups at the individual time points.

The effect of naloxone on morphine-induced antinociception in the PP test (fig. 2) was similar in onset and magnitude to that observed in the TF test. PP threshold was significantly less in rats treated with morphine + naloxone compared with morphine + saline treatment from 45 to 150 min. In contrast, nalbuphine enhanced morphine-induced antinociception in the PP test. The threshold for paw withdrawal was consistently greater than the morphine + saline group from 90 to 240 min, with significant differences observed at 180, 210, and 240 min (fig. 2).

The effect of sc nalbuphine alone (0.5 and 10 mg/kg) on the time course of TF latency and PP threshold are

shown in figures 3 and 4, respectively. In the TF test, nalbuphine (10 mg/kg) had no significant antinociceptive effect and there was no evidence of hyperalgesia after nalbuphine treatment. In the PP test, nalbuphine (10 mg/kg) significantly increased PP threshold from 15–90 min compared with baseline (78 ± 8.2 mmHg, mean \pm SD). The maximum increase in PP threshold (148 ± 65 mmHg) was observed 30 min after injection, whereas sc saline had no effect on PP threshold throughout the experiment.

To investigate the possibility of potentiation, the analgesic interaction between an inactive dose of sc nalbuphine (0.5 mg/kg) and a lower dose of intrathecal morphine (1.5 μ g) in the PP test was determined. This dose

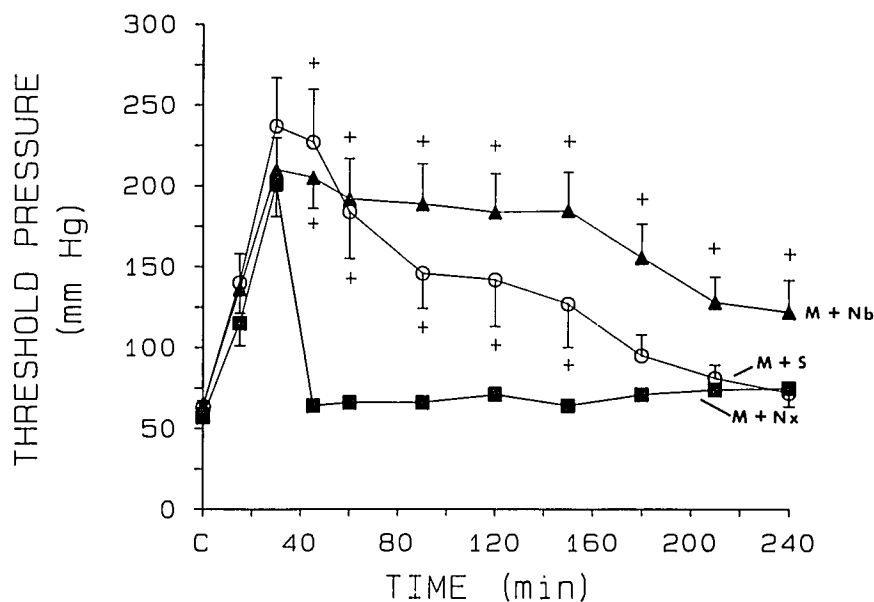
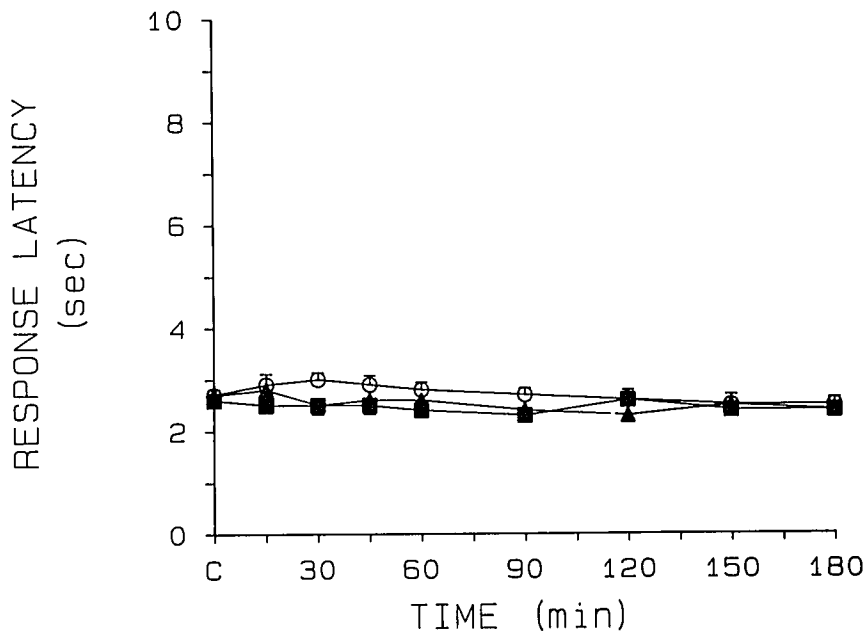


FIG. 2. The effect of intrathecal morphine (M; 4 μ g) injected immediately after baseline testing (C), followed 30 min later by sc nalbuphine (Nb; 10 mg/kg), naloxone (Nx; 1 mg/kg), or saline (S) on the time course of paw pressure threshold in the noninflamed hind paw. Data are presented as the mean \pm SEM of seven rats, and all points were significantly different from their respective baseline value except for 150–240 min in the M + S group and 45–240 min in the M + Nx group. *Significant difference from the M + Nx group at the individual time points.

FIG. 3. The time course of tail flick latency following the sc injection of nalbuphine (10 mg/kg), nalbuphine (0.5 mg/kg), or saline (see fig. 4 legend for symbols). Drugs were injected immediately after baseline testing (C). Data represent the mean \pm SEM of nine rats for the low-dose nalbuphine group and ten rats for the high-dose nalbuphine and saline groups. There were no significant differences in tail flick latency from their respective baseline values in any of the groups.



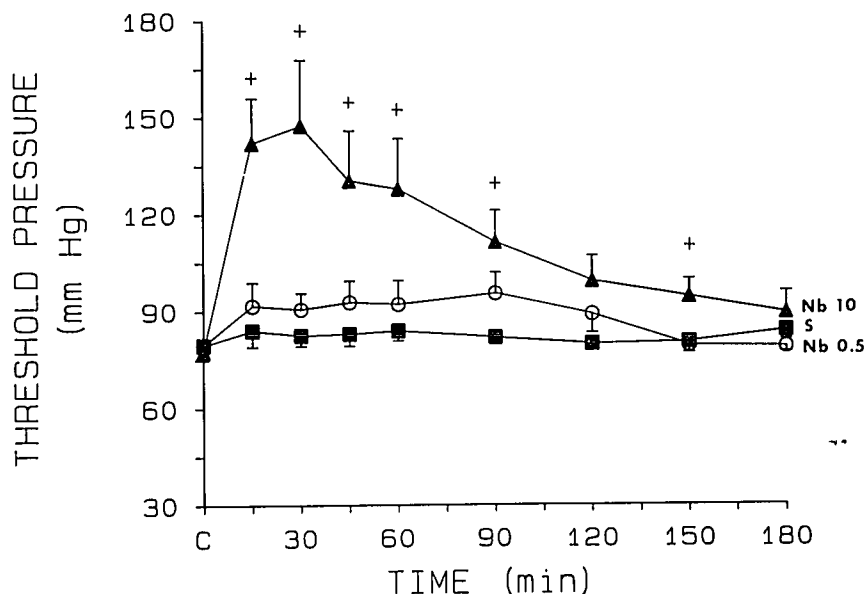
of sc nalbuphine did not antagonize intrathecal morphine (4 μ g) in the TF test (fig. 5) and had no effect on morphine (4 μ g) in the PP test (data not shown). As shown in figure 6, intrathecal morphine (1.5 μ g) significantly increased PP threshold at 15 and 30 min in the two experimental groups, and both groups had identical threshold values (154 and 156 mmHg) at 30 min immediately prior to nalbuphine or saline treatment. Fifteen minutes after the sc injection of nalbuphine (0.5 mg/kg), PP threshold increased to 187 mmHg, and the response values remained consistently higher than the saline-treated group throughout the experiment. Significant differences from

saline treatment were observed at 90, 120, 150, and 180 min.

Discussion

The analgesic interaction between systemic nalbuphine and spinal morphine is a major consideration in the clinical use of partial opioid agonists for antagonizing opioid-induced respiratory depression. To investigate this interaction, the combination of intrathecal morphine and sc nalbuphine was tested in rats implanted with chronic intrathecal catheters using two different nociceptive tests. This preparation was selected for several reasons. First,

FIG. 4. The time course of paw pressure threshold in the noninflamed hind paw following the sc injection of nalbuphine (10 mg/kg; Nb 10), nalbuphine (0.5 mg/kg; Nb 0.5), or saline (S). Drugs were injected immediately after baseline testing (C). Data represent the mean \pm SEM of nine rats for the low-dose nalbuphine group and ten rats for the high-dose nalbuphine and saline groups. All points in the 10-mg/kg nalbuphine group were significantly different from baseline except 120, 150, and 180 min. *Significant difference from both the Nb 0.5 and S groups except at 90 min, which was significantly different from S only.



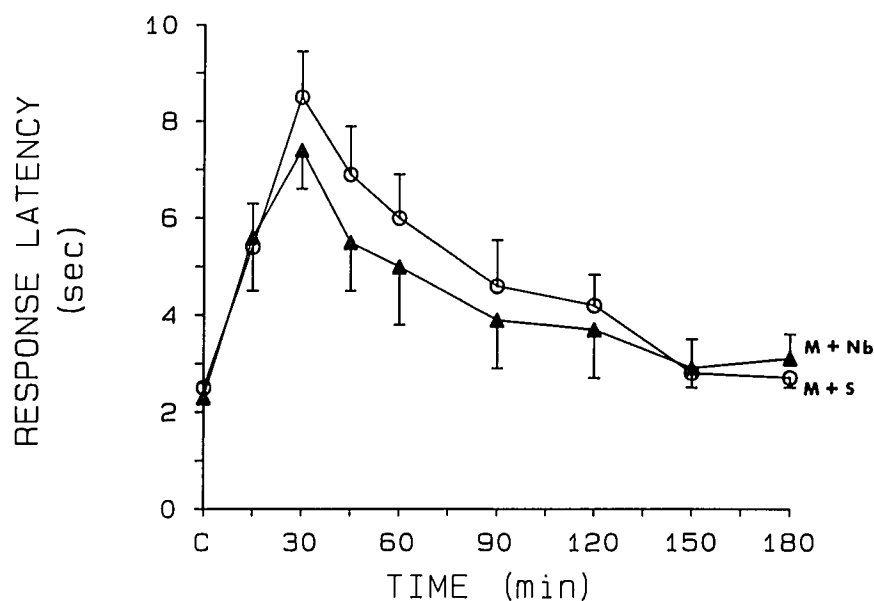


FIG. 5. The effect of intrathecal morphine (M; 4 μ g) injected immediately after baseline testing (C), followed 30 min later by sc nalbuphine (0.5 mg/kg; Nb) or saline (S) on the time course of tail flick latency. Data are presented as the mean \pm SEM of seven rats. All points were significantly different from their respective baseline value except for 90–180 min in the M + Nb group and 150–180 min in the M + S group. There were no significant differences between the two treatment groups at the individual time points.

a thermal (TF) and a mechanical (PP) pain test could be measured concurrently in the same animals to assess the interaction using different nociceptive stimuli. Second, repeated determinations in the TF and PP tests could be easily performed to study the interaction over the complete time course of antinociception. This is important because the net effect of a partial agonist (*e.g.*, agonism, no change, or antagonism) is determined by the magnitude of effect of the full agonist at the time the interaction is measured. Third, changes in experimentally induced pain are easier to measure objectively than changes in clinical pain because the former can be quantitated with respect to the intensity of the stimulus evoking a response

(PP test) or the latency of the response evoked by a fixed stimulus intensity (TF test). Finally, the reliability of this model in predicting the pharmacology of spinal opioid analgesia in humans is well documented.²⁶

In this study nalbuphine antagonized the antinociceptive effect of intrathecal morphine in the TF test while concurrently enhancing the effect of intrathecal morphine in the noninflamed PP test. The absence of hyperalgesia after nalbuphine (and naloxone) indicates that the former effect was due to pharmacologic antagonism at μ -receptors and was not secondary to the inhibition of tonically active endogenous opioid modulation (*e.g.*, physiologic antagonism). These results are in agreement with previous

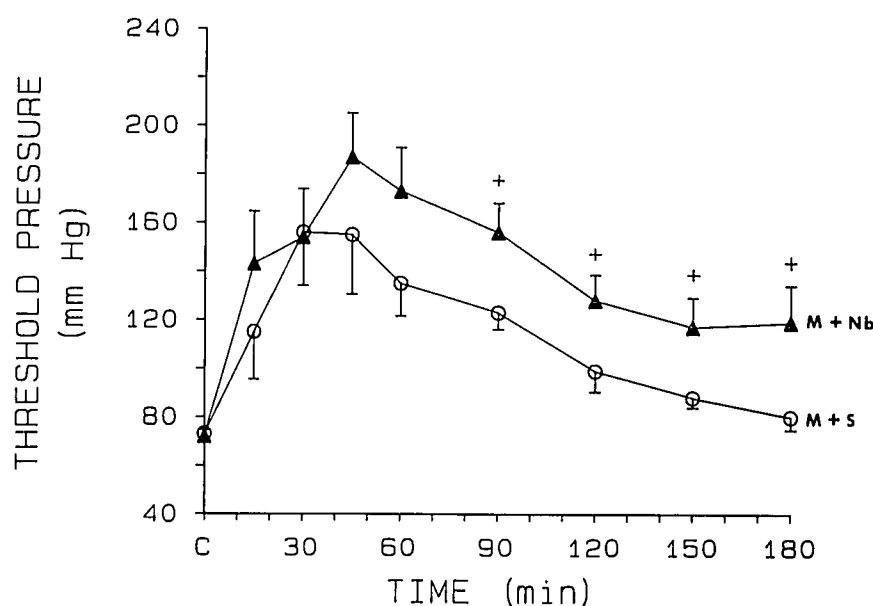


FIG. 6. The effect of intrathecal morphine (M; 1.5 μ g) injected immediately after baseline testing (C), followed 30 min later by sc nalbuphine (0.5 mg/kg; Nb) or saline (S) on the time course of paw pressure threshold in the noninflamed hind paw. Data are presented as the mean \pm SEM of nine and six rats for the M + Nb and M + S groups, respectively. All points were significantly different from their respective baseline value except 180 min in the M + S group. *Significant difference from the M + S group at the individual time points.

animal^{11,26} and clinical studies^{13,14} of nalbuphine, and are in keeping with its partial agonist activity at the μ -receptor and the predominant role of μ -receptors in cutaneous thermal nociceptive tests (where κ -receptors have no role).²⁶ The dose of nalbuphine used in this experiment and the intrathecal route of morphine administration suggest that the locus of action of nalbuphine was probably at the spinal cord.

Nalbuphine (10 mg/kg) alone produced significant antinociception in the noninflamed PP but not the TF test. These data are consistent with its enhancement of intrathecal morphine in the PP test (fig. 2) and with the autoradiographic distribution of [³H]nalbuphine binding sites in areas of the CNS known to mediate analgesia.¹² Previous studies have reported the potent antinociceptive effect of systemic and intrathecal κ -agonists in mechanical (inflamed and noninflamed PP tests) and visceral chemical (acetic acid- and phenylquinone-induced writhing tests) nociceptive tests.^{11,17,27} Nalbuphine has no antinociceptive activity in thermal nociceptive tests (where μ -receptors predominate), suggesting that its activity in the PP test was not mediated by μ -receptors.

We believe that this is the first report of the analgesic interaction between intrathecal morphine and systemic nalbuphine in animals, and the differential effect of nalbuphine on a thermal *versus* mechanical nociceptive test measured concurrently in the same animals. To the extent that nalbuphine-induced elevation of PP threshold was mediated by κ -receptors, the data suggest that κ -opioid receptors subserve an inhibitory role on neurons activated by somatic mechanical nociceptive stimulation. They also provide further evidence that κ -opioid receptors are coupled differently to neural substrates that process information about mechanical and thermal nociception in the rat.

In comparing the PP values for morphine (4 μ g) + saline treatment in figure 2 and nalbuphine alone (10 mg/kg) in figure 4 with those of morphine (4 μ g) + nalbuphine (10 mg/kg) at individual time points (fig. 2), the analgesic interaction appeared to be additive at 90 and 120 min and greater than additive from 150 to 240 min. That is, the most pronounced effect of the combination was observed in the latter part of the time course when the individual effects of morphine and nalbuphine were returning to baseline. To further investigate the interaction between nalbuphine and morphine in the PP test, an inactive dose of nalbuphine (0.5 mg/kg) was combined with a lower dose of intrathecal morphine (1.5 μ g). The results in figures 3, 4, and 5 confirmed that nalbuphine (0.5 mg/kg) had no significant agonist or antagonist activity in either the TF or PP test. As shown in figure 6, this same dose of nalbuphine significantly enhanced the effect of intrathecal morphine (1.5 μ g) in the PP test, suggesting potentiation between the two drugs. An earlier study reported potentiation between intrathecal nalbu-

phine and intrathecal morphine in the rat using the acetic acid-induced writhing test.²⁸ Nalbuphine concentrations were not determined in the present study; thus, a pharmacokinetic interaction cannot be ruled out. However, this explanation seems unlikely considering the route of morphine administration and the factors affecting drug clearance from the subarachnoid space. Complete dose-response and pharmacokinetic data are required to confirm the nature of this interaction.

Doses of 0.5 and 10 mg/kg nalbuphine are large compared with those normally administered for reversal of opioid-induced respiratory depression in humans (5–10 mg/70-kg man). However, the elimination half-life of nalbuphine in rats is approximately 12 min²⁹ compared with 3–6 h in humans.³⁰ To compensate for this marked difference, doses of 0.5 and 10 mg/kg were used, the latter being approximately 7 times greater than the ED₅₀ of sc nalbuphine in the rat phenylquinone-induced writhing test.¹¹ Nalbuphine is unlikely to have produced respiratory depression in this analgesic study because sc doses up to 124 mg/kg were reported to have no significant effects on measures of respiratory function in rats.¹¹

The reversal of analgesia in patients with severe pain is unacceptable in terms of patient discomfort and the corresponding stress response that is evoked. The results of this animal study suggest that systemic nalbuphine can augment antinociception while antagonizing spinal morphine activity mediated by μ -receptors. The data indicate that the individual doses of morphine and nalbuphine, the time of testing after nalbuphine treatment, and the nature of the nociceptive stimulus are critical factors in determining the net analgesic effect during the interaction. Whether a comparable analgesic interaction occurs in humans during the antagonism of respiratory depression remains to be determined.

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