Published in final edited form as:

J Pain. 2008 April ; 9(4): 337–341.

A Subanalgesic Dose of Morphine Eliminates Nalbuphine Anti-analgesia in Postoperative Pain

Robert W. Gear, DDS, PhD¹, Newton C. Gordon, DDS, MS¹, Mehran Hossaini-Zadeh, DMD¹, Janice S. Lee, DDS, MD, MS¹, Christine Miaskowski, RN, PhD², Steven M. Paul, PhD³, and Jon D. Levine, MD, PhD⁴

¹Department of Oral and Maxillofacial Surgery, University of California, San Francisco 94143

²Department of Physiological Nursing, University of California, San Francisco 94143

³Department of Physiological Nursing, Epidemiology and Biostatistics, University of California, San Francisco 94143

⁴Department of Oral and Maxillofacial Surgery, Medicine, Graduate Program in Neuroscience, University of California, San Francisco 94143

Abstract

The agonist-antagonist kappa-opioid nalbuphine administered for postoperative pain produces greater analgesia in females than in males. In fact, males administered nalbuphine (5 mg) experience pain *greater* than those receiving placebo, suggesting the existence of an anti-analgesic effect. These sexually dimorphic effects on postoperative pain can be eliminated by co-administration of a fixed ratio of the prototypical opioid receptor antagonist naloxone with nalbuphine, implying a role for opioid receptors in the anti-analgesic as well as analgesic effects of nalbuphine. In the present study, we further evaluated the role of opioid receptors in the sex-specific effects on pain produced by nalbuphine by co-administering a dose of morphine low enough that it does not produce analgesia. Following extraction of bony impacted third molar teeth, nalbuphine (5 mg) was administered alone or in combination with either of two low doses of morphine (2 mg or 4 mg). Both doses of morphine reversed nalbuphine-induced anti-analgesia in males, but only the lower dose (2 mg) reached statistical significance. Neither dose affected nalbuphine-induced analgesia in females, and when administered alone in either males or females, morphine (2 mg) had no analgesic effect. Though not observed in females, the effect of morphine in males argues that, like naloxone, low dose morphine may act as an anti-analgesia opioid receptor antagonist.

Perspective—Previously we reported that the nalbuphine produces both analgesic and anti-analgesic effects, and that the opioid antagonist naloxone can enhance nalbuphine analgesia by selectively antagonizing the anti-analgesic effect. Here we show that morphine, given in a subanalgesic dose, reverses nalbuphine-induced anti-analgesia in males, perhaps by a similar mechanism.

Keywords

kappa opioid; sexual dimorphism; analgesia; gender

Correspondence: Jon D. Levine, M.D., Ph.D., Box 0440, 521 Parnassus Avenue, Room, C-522, University of California San Francisco, CA 94143-0440. Tel #: (415) 476-5108; FAX # (415) 476-6305; E-mail: jon.levine@ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The agonist-antagonist kappa (κ)-opioids—nalbuphine, pentazocine, and butorphanol—produce greater postoperative analgesia in females than in males^{6,9,12}. We have proposed that this sexually dimorphic effect results from the ability of κ -opioids to produce anti-analgesia as well as analgesia. In a placebo-controlled study of postoperative pain, we observed that males receiving nalbuphine (5 mg) actually experienced greater pain than those receiving placebo¹⁰. In subsequent studies, co-administration of a low dose of the opioid antagonist naloxone was shown to enhance nalbuphine analgesia in both females and males, and eliminate this sexual dimorphism^{7,8,11}, suggesting that anti-analgesia induced by nalbuphine is sensitive to naloxone and is present in both females and males, though more so in males. We proposed that nalbuphine produces two opposing effects, “analgesia” and “anti-analgesia,” by acting at distinct opioid receptors, and that anti-analgesia is more sensitive to naloxone antagonism than is analgesia¹¹. To further test the possibility that nalbuphine produces anti-analgesia by action at an opioid receptor, we investigated the effect of subanalgesic doses of morphine, an opioid that binds to μ -, κ -, and δ -opioid receptors¹⁹, on nalbuphine analgesia.

Methods and Materials

In this study, 116 patients underwent surgery for removal of third molar teeth, including at least one bony impacted mandibular third molar (see Table 1 for group characteristics). The surgical protocol includes intravenously administered diazepam, nitrous oxide and oxygen administered by inhalation, and local anesthetic injection (mepivacaine without vasoconstrictor to obtain a nerve block of shorter duration)^{6,13,14}. Following surgery, groups of males and females received nalbuphine (5 mg) alone, morphine (2 mg) alone or nalbuphine (5 mg) combined with either of two doses of morphine (2 mg or 4 mg). This double-blind, randomized study, in which all patients were studied in an interspersed fashion, conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Committee on Human Research at the University of California, San Francisco. Written informed consent was obtained from each research subject.

Pain intensity was quantified by asking patients to place a mark on a 10 cm visual analog scale (VAS), which was anchored on the left side with the words “No Pain” and on the right with the words “Worst Pain Imaginable.” Pain ratings were obtained at 20 minute intervals beginning 50 minutes after the onset of local anesthesia (i.e., the beginning of the surgical procedure). The study drug(s) was administered through an indwelling intravenous line 10 minutes after the “baseline” VAS pain rating, which was defined as the first VAS pain rating ≥ 3 cm occurring at least 70 minutes after the start of surgery. The duration of the experiment, measured from the time of study drug administration, was three hours.

Data analysis

Differences in demographic characteristics among the treatment groups were determined using separate one-way analyses of variance (ANOVAs) for each sex. The between-subjects factor for each of these ANOVAs was treatment with four levels.

Analgesic response was defined as the difference (cm) between the VAS pain rating at each time point following study drug administration and the baseline VAS pain rating just prior to drug administration. Differences in analgesic responses among the treatment groups were determined using separate two-way repeated measures ANOVAs for each sex with one within-subjects factor (time with 9 levels) and one between subjects factor (treatment with four levels). For each ANOVA, the Mauchly criterion was used to determine if the assumption of sphericity for the within-subjects effects was met. If the Mauchly criterion was not satisfied, Greenhouse-Geisser adjusted *p* values are presented. If significant treatment group $\times$ time interaction

occurred, the simple main effects were examined over time to help explain the significant interaction.

Results

Males

One-way ANOVAs for males showed a significant difference among the four treatment groups in only the age variable ($p=0.037$). However, none of the six possible pairwise contrasts showed significant differences using the Scheffé criterion. Also, since age is not significantly related to pain score, it was not used as a covariate in the subsequent repeated measures ANOVA analysis.

The response of males who received nalbuphine (5 mg) or morphine (2 mg) alone, or nalbuphine combined with morphine (2 mg or 4 mg) are depicted in Figure 1. Two-way, repeated measures ANOVA demonstrated a significant main effect of treatment ($F(3,52) = 4.364$; $p = 0.008$) as well as time ($F(8,416) = 10.460$; $p < 0.001$). The treatment by time interaction was not significant. Post hoc analysis (Scheffé) revealed that on average the nalbuphine alone group was significantly different from the nalbuphine plus morphine (2 mg) group ($p=0.014$) but not significantly different from the nalbuphine plus morphine (4 mg) group ($p=0.079$), the group that received only morphine was not significantly different from any of the other groups.

Females

One-way ANOVAs for females showed a significant difference among the four treatment groups in only the baseline VAS pain variable ($p = 0.007$). Post hoc pairwise contrasts using the Scheffé criterion indicated that baseline VAS pain was approximately 1.7 centimeters higher in the group that received nalbuphine (5 mg) combined with morphine (4 mg) than the group that received nalbuphine alone. Consequently, baseline VAS pain was included as a covariate in the subsequent repeated measures ANOVA analysis.

The responses of females who received nalbuphine (5 mg) or morphine (2 mg) alone, or nalbuphine combined with morphine (2 mg or 4 mg) are depicted in Figure 1. Two-way, repeated measures ANOVA did not demonstrate either significant main effects of time or treatment or a time $\times$ treatment interaction.

Discussion

In a previous study that did not examine for sex differences we reported that morphine (2 mg) enhanced the analgesic effect of the agonist-antagonist κ -opioid pentazocine¹⁴. In the present study, we found that morphine reversed the anti-analgesic effect of nalbuphine, but that this effect was statistically significant only in males. Neither dose of morphine produced a significant effect in females.

The effect of morphine on the ability of nalbuphine to produce analgesia could be due to the summation of separate analgesic effects of morphine acting at μ -opioid receptors and nalbuphine at κ -receptors, but examination of the data does not support this explanation in the current study. While, an additive effect of morphine might be expected to be similar in both sexes, this was not the case; the effect of morphine was significant only in males. Also, with analgesic summation the higher (4 mg) dose of morphine should have produced greater enhancement than the lower (2 mg) dose, but if anything the opposite was observed. In combination with nalbuphine only the 2 mg morphine dose significantly improved the analgesic effect of nalbuphine alone in males.

An alternative explanation—one that is more consistent with the current findings—is that nalbuphine analgesia is unmasked by morphine blockade of the action of nalbuphine at an anti-analgesia receptor. Previously, we showed that the opioid receptor antagonist naloxone enhances nalbuphine analgesia in both sexes (males > females)¹¹, a finding that formed the basis of a two-receptor hypothesis for the effect of nalbuphine on postoperative pain^{5,7,8,11}. According to this hypothesis, nalbuphine induces anti-analgesia as well as analgesia by acting at distinct “anti-analgesia” and “analgesia” opioid receptors. Thus, the effect of nalbuphine alone on pain is observed as the sum of these two opposing actions. To account for the sexually dimorphic analgesic effect of κ -opioids, the hypothesis proposes that males have more “anti-analgesia” receptors than females. The ability of naloxone to enhance κ -opioid analgesia and eliminate the sexual dimorphism results from naloxone’s greater affinity for the anti-analgesia receptor.

While nalbuphine, morphine, and naloxone all bind to μ -, δ -, and κ -opioid receptors^{3,18}, the efficacy of each drug as an agonist is markedly different. Naloxone, the prototypical opioid receptor *antagonist* is essentially devoid of agonist efficacy at any opioid receptor¹⁵. The efficacy of nalbuphine is relatively low at the μ -opioid receptor, which is consistent with its ability to antagonize some actions of morphine^{2,21} and still act as a low efficacy μ -agonist, for example in producing mild respiratory depression, when administered alone²⁰. In contrast, morphine is well known as a highly efficacious μ -opioid receptor agonist with little if any efficacy at κ -opioid receptors^{16,17}.

If the anti-analgesia receptor is an opioid subtype, morphine, like naloxone, appears to function as an *antagonist* at this receptor blocking the anti-analgesic effect of nalbuphine. However, since higher doses of morphine produce analgesia, the analgesic effect of a combination of any given pair of μ and κ opioid agonists likely depends on an array of factors, including the dose ratio of the two drugs, and their relative binding affinities for the relevant opioid receptor subtype. Different dose ratios could result in enhanced analgesia, diminished analgesia, or no change in analgesia compared to either drug alone^{1,14,22}. In addition, the relatively short plasma half-lives of both morphine and naloxone imply that plasma concentrations of these drugs do not correspond well with the prolonged time course of analgesia. Future studies to address the optimal dose ratio for morphine to enhance nalbuphine analgesia in both males and females should provide useful information with respect to properties of the receptor at which drugs such as morphine and naloxone act to block nalbuphine-induced anti-analgesia.

In summary, doses of morphine well below the lowest dose that produces analgesia reversed nalbuphine-induced anti-analgesia in both females and males with postoperative pain. Further investigation is needed to determine the optimal dose ratio that provides maximum enhancement of nalbuphine analgesia in males and females. Identification of the receptor(s) at which agonist-antagonist κ -opioids act to induce anti-analgesia is important in order to understand the mechanism(s) underlying sexual dimorphism in opioid analgesia and might aid in the development of novel analgesic drugs selectively targeted at the analgesia receptors and/or antagonists selectively targeted at anti-analgesia receptors. Eliminating agonist-antagonist κ -opioid-induced anti-analgesia would not only produce greater analgesia using lower doses of opioids, but potentially also decrease side effects, including abuse liability.

Acknowledgements

We thank Gretchen Summer, R.N., Ph.D., for excellent technical assistance. This work was supported by National Institutes of Health (DE018526).

References

1. Baxter AD, Samson B, Penning J, Doran R, Dube LM. Prevention of epidural morphine-induced respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients. *Can J Anaesth* 1989;36:503–509. [PubMed: 2507181]
2. Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR. Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. *Anesth Analg* 1992;75:747–752. [PubMed: 1416128]
3. De Souza EB, Schmidt WK, Kuhar MJ. Nalbuphine: an autoradiographic opioid receptor binding profile in the central nervous system of an agonist/antagonist analgesic. *J Pharmacol Exp Ther* 1988;244:391–402. [PubMed: 2826773]
4. Faucett J, Gordon N, Levine J. Differences in postoperative pain severity among four ethnic groups. *J Pain Symptom Manage* 1994;9:383–389. [PubMed: 7963791]
5. Fillingim RB, Gear RW. Sex differences in opioid analgesia: clinical and experimental findings. *Eur J Pain* 2004;8:413–425. [PubMed: 15324773]
6. Gear RW, Gordon NC, Heller PH, Paul S, Miaskowski C, Levine JD. Gender difference in analgesic response to the kappa-opioid pentazocine. *Neurosci Lett* 1996;205:207–209. [PubMed: 8852594]
7. Gear RW, Gordon NC, Miaskowski C, Paul SM, Heller PH, Levine JD. Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003;351:5–8. [PubMed: 14550900]
8. Gear RW, Gordon NC, Miaskowski C, Paul SM, Heller PH, Levine JD. Sexual dimorphism in very low dose nalbuphine postoperative analgesia. *Neurosci Lett* 2003;339:1–4. [PubMed: 12618286]
9. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med* 1996;2:1248–1250. [PubMed: 8898754]
10. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain* 1999;83:339–345. [PubMed: 10534607]
11. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Action of naloxone on gender-dependent analgesic and anti-analgesic effects of nalbuphine in humans. *J Pain* 2000;1:122–127.
12. Gordon NC, Gear RW, Heller PH, Paul S, Miaskowski C, Levine JD. Enhancement of morphine analgesia by the GABAB agonist baclofen. *Neuroscience* 1995;69:345–349. [PubMed: 8552232]
13. Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. *Nature* 1984;312:755–756. [PubMed: 6514008]
14. Levine JD, Gordon NC. Synergism between the analgesic actions of morphine and pentazocine. *Pain* 1988;33:369–372. [PubMed: 3419842]
15. Martin WR. Pharmacology of opioids. *Pharmacol Rev* 1983;35:283–323. [PubMed: 6144112]
16. Matthes HW, Maldonado R, Simonin F, Valverde O, Slowe S, Kitchen I, Befort K, Dierich A, Le Meur M, Dollé P, Tzavara E, Hanoune J, Roques BP, Kieffer BL. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. *Nature* 1996;383:819–823. [PubMed: 8893006]
17. Matthes HW, Smadja C, Valverde O, Vonesch JL, Foutz AS, Boudinot E, Denavit-Saubié M, Severini C, Negri L, Roques BP, Maldonado R, Kieffer BL. Activity of the delta-opioid receptor is partially reduced, whereas activity of the kappa-receptor is maintained in mice lacking the mu-receptor. *J Neurosci* 1998;18:7285–7295. [PubMed: 9736649]
18. Pasternak GW. Pharmacological mechanisms of opioid analgesics. *Clin Neuropharmacol* 1993;16:1–18. [PubMed: 8093680]
19. Pasternak GW, Gintzler AR, Houghten RA, Ling GS, Goodman RR, Spiegel K, Nishimura S, Johnson N, Recht LD. Biochemical and pharmacological evidence for opioid receptor multiplicity in the central nervous system. *Life Sci* 1983;33:167–173. [PubMed: 6319856]
20. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980;27:478–485. [PubMed: 7357806]

21. Wang JJ, Ho ST, Tzeng JI. Comparison of intravenous nalbuphine infusion versus naloxone in the prevention of epidural morphine-related side effects. *Reg Anesth Pain Med* 1998;23:479–484. [PubMed: 9773701]
22. Wittels B, Glosten B, Faure EA, Moawad AH, Ismail M, Hibbard J, Amundsen L, Binstock W, Senal JA, Cox SM. Opioid antagonist adjuncts to epidural morphine for postcesarean analgesia: maternal outcomes. *Anesth Analg* 1993;77:925–932. [PubMed: 8214728]

Figure 1.

The effect of nalbuphine (5 mg) alone, morphine (2 mg) alone, and nalbuphine (5 mg) plus morphine (2 mg or 4 mg) on post operative pain in males and females. Data were plotted as analgesia scores calculated as baseline VAS pain score (dashed horizontal line) minus the post administration VAS pain scores at various time points over the 3 hours following administration (see legend in figure). See Table 1 for number of study participants in each group. Data are plotted as mean $\pm$ sem.

Table 1

Study participant sample characteristics

Males	Nalb alone	Nalb 5 mg Mor 2 mg	Nalb 5 mg Mor 4 mg	Mor alone
Sample size (n)	14	14	14	14
Age (years)	21.86 ± 3.86	26.3 ± 4.5	24.7 ± 4.7	26 ± 4
Weight (kg)	71.0 ± 9.82	76.5 ± 13.9	74.2 ± 7.1	86.5 ± 24.2
Surgical severity *	4.55 ± 0.34	4.32 ± 0.94	4.5 ± 0.17	4.43 ± 0.51
Baseline VAS pain (cm)	4.76 ± 1.47	5.8 ± 1.5	5.2 ± 1.5	5.1 ± 0.9
Females	Nalb alone	Nalb 5 mg Mor 2 mg	Nalb 5 mg Mor 4 mg	Mor alone
Sample size (n)	15	15	15	15
Age (years)	22.5 ± 3.6	23 ± 4	23.2 ± 2.9	22.6 ± 5
Weight (kg)	60.8 ± 13.8	59.1 ± 8.2	56.9 ± 6.9	60.5 ± 9.8
Surgical severity *	4.58 ± 1.4	4.33 ± 0.65	6.07 ± 6.44	4.37 ± 0.8
Baseline VAS pain (cm)	5.1 ± 1.2	5.9 ± 1.4	6.8 ± 1.1	6 ± 1.4

Data are presented as mean ± s.d. Abbreviations: "Nalb", nalbuphine; "Mor", morphine.

* Surgical severity scores⁴ were assigned as follows: Upper third molar extractions: uncomplicated or tissue impacted teeth = 0.25, partial or full bony impacted teeth = 0.50. Lower third molar extractions: uncomplicated or tissue impacted teeth = 1, partial or full bony impacted teeth = 2. The surgical severity score for each patient is the sum of the assigned values for each extracted tooth.