Nalbuphine Antagonism of Ventilatory Depression Following High-dose Fentanyl Anesthesia

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Prolonged respiratory depression requiring overnight mechanical ventilation may follow the use of large doses of fentanyl for anesthesia. However, patients with stable cardiovascular and pulmonary function have been extubated within 8 h of aortocoronary bypass (ACB) surgery without significant morbidity or mortality.[1-3] Early extubation may improve patient comfort, decrease requirements for sedative drugs, and reduce intensive care unit (ICU) time and hospital costs.

In two recent studies,[4,**] nalbuphine antagonized respiratory depression induced by moderate doses of narcotic analgesics administered during general anesthesia for noncardiac surgery. No significant adverse consequences were reported. Our study evaluated the safety and efficacy of nalbuphine in antagonizing ventilatory depression following high-dose fentanyl anesthesia for ACB surgery.

METHODS

Following approval by the Human Investigations Committee, informed consent was obtained from 21 patients. Study 1 involved nine men and two women, ages 48–77 yr; and study 2 included ten men, ages 45–68 yr. (See table 1 for further description of the patients' characteristics.) Patients were excluded from the studies if they had a history of myocardial infarction within the previous 6 weeks, poor left ventricular function (left

ventricular end diastolic pressure > 18 mmHg and ejection fraction < 0.4), a bleeding diathesis, severely impaired pulmonary function (FEV_1/FVC or FVC < 70% of predicted or a preoperative resting Pa_{CO_2} > 48 mmHg), or a neuromuscular or central nervous system (CNS) disorder capable of compromising pulmonary function. In study 1, nalbuphine was administered the morning after surgery if spontaneous ventilation failed to maintain Pa_{CO_2} less than 50 mmHg. Based on the positive results of the first study, the second study was undertaken in which nalbuphine was administered to patients within several hours of their admission to the ICU if their spontaneous ventilation failed to maintain a Pa_{CO_2} of less than 50 mmHg.

Premedication for all patients consisted of oral diazepam 0.15 mg/kg, intramuscular morphine 0.1 mg/kg, and scopolamine 0.3 mg/70 kg. All patients received fentanyl as their primary anesthetic. In study 1, the patients received fentanyl in a total dose of 120 ± 7 μg/kg (mean ± SEM), and seven of the 11 patients also received diazepam 5–30 mg. Patients in study 2 received fentanyl (97 ± 5 μg/kg) but no diazepam (table 1). All patients received enflurane or vasodilators as indicated by increases in mean arterial pressure or heart rate 20% greater than control.

In the ICU, patients remained in the study if they had stable cardiovascular function (including a systolic blood pressure > 90 mmHg, pulmonary capillary wedge pressure < 18 mmHg, cardiac index > 2.2 $l \cdot min^{-1} \cdot m^{-2}$ without the use of large amounts of vasoactive drugs, and no serious dysrhythmias), satisfactory urine output (>0.5 $ml \cdot kg^{-1} \cdot h^{-1}$), no significant bleeding (mediastinal drainage < 2 $ml \cdot kg^{-1} \cdot h^{-1}$), and a rectal temperature > 36° C. Those patients unable to maintain Pa_{CO_2} < 50 mmHg by spontaneous ventilation were given nalbuphine in 15 μg/kg increments every 30–60 min (according to the laboratory time required for arterial blood gas analysis) until the Pa_{CO_2} decreased to <48 mmHg or until a total dose of 150 μg/kg had been administered. Systemic, pulmonary arterial, and central venous pressures; heart rate; cardiac output; and arterial blood gases were measured prior to and just after the administration of nalbuphine, then every 5–10 min for 3 h, and routinely for the remainder of the patient's stay in the ICU. Forced vital capacity (FVC), tidal volume, and inspiratory and expiratory force measurements were

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TABLE 1. Patient Characteristics (Mean ± SEM)

	Study 1 (n = 11)	Study 2 (n = 10)
Age (yr)	61 ± 3	58 ± 3
Weight (kg)	78 ± 4	80 ± 3
History of hypertension	4/11	5/10
No. of ACB grafts	3.9 ± 0.5	3.7 ± 0.4
Fentanyl (μg/kg)	120 ± 5	97 ± 5
Diazepam (mg)	18.6 ± 3.1	0

made prior to extubation. The electrocardiogram was monitored continuously for dysrhythmias. Throughout the study period the patients were kept in dimly lit rooms, and stimulation was limited to that essential for their care.

Patients were extubated if they had a FVC > 8 ml/kg, an inspiratory force > −20 mmHg, and if they were able to maintain Pa_{CO_2} < 48 mmHg, pH > 7.33 and Pa_{O_2} > 90 mmHg while breathing a mixture of 60% oxygen or less on no more than 5 cmH$_2$O of continuous positive airway pressure (CPAP).

RESULTS

After receiving nalbuphine, all 11 patients in study 1 and nine of 10 patients in study 2 met the criteria for extubation. One patient in the second study required ventilatory support for 48 h postoperatively. His data are excluded because of the likely occurrence of a perioperative neurologic insult unrelated to nalbuphine. The dose of nalbuphine ranged from 1 to 10 mg (66 ± 13 μg/kg) in study 1 and 1.5–9 mg (46 ± 10 μg/kg) in study 2. After entry into the study, the time from the first dose of nalbuphine to extubation was 1.8 ± 0.3 h in the first and 1.3 ± 0.3 h in the second study. The time from the effective or final dose of nalbuphine to extubation was 20.5 ± 2.1 min in the first group and 18.9 ± 1.5 min in the second group of patients. Four patients in the first and three in the second study were extubated after only one dose of nalbuphine. Only one patient in each group received a total dose of 150 μg/kg. In patients receiving nalbuphine the day of surgery, the mean time from the end of surgery to extubation was 7.7 ± 0.3 h. Delays in starting the study on the day

TABLE 2. Side Effects of Antagonism of Narcotic Analgesics

	Study 1 (n = 11)	Study 2 (n = 10)
Nausea and vomiting	2	0
Restlessness	1	1
Pain after first dose of nalbuphine	3	0
Pain requiring morphine	0	1
Renarcotization	0	3
Hypertension (>25% ↑ MAP)	3	1
Tachycardia, dysrhythmias	0	0

of surgery were most commonly due to hemodynamic instability, excessive bleeding, or incomplete rewarming (rectal temperature < 36° C).

One patient in the second group was weaned successfully to a Pa_{CO_2} of 48 mmHg without nalbuphine and extubated on the day of surgery. After extubation his Pa_{CO_2} increased to 61 mmHg and he was given one dose of nalbuphine that promptly reduced his Pa_{CO_2} to 47 mmHg.

The side effects of nalbuphine administration are noted in Table 2. Two patients in study 1 experienced nausea and had large gastric air bubbles; insertion of a nasogastric tube reduced gastric distention and relieved the nausea. Three patients in study 1 had an immediate increase in pain after receiving nalbuphine, and it was relieved with additional nalbuphine. One patient in each group became restless after nalbuphine, although neither patient required any sedation or other treatment. Three patients in study 1 and one patient in study 2 had transient increases of greater than 25% in mean arterial pressure (MAP) after nalbuphine administration (fig. 1). In only one of the three patients in study 1 did the increase in blood pressure exceed his range of pressures measured preoperatively (and his MAP remained less than 100 mmHg). None of the three patients required vasodilator therapy. The one patient in study 2 who experienced a 69% increase in mean arterial pressure after nalbuphine required therapy with nitroprusside for 10 min on the day of surgery.

Renarcotization occurred only in patients studied the day of surgery approximately 2 to 3 h after the administration of nalbuphine; it was treated easily with another 15 μg/kg dose of nalbuphine. None of the patients receiving doses of nalbuphine ≤ 30 μg/kg experienced this problem. However, three of four patients in study 2 who required doses ≥ 60 μg/kg initially had to be treated for renarcotization (Pa_{CO_2} > 55 mmHg).

In the ICU, none of the patients required any analgesics prior to extubation. After extubation, analgesia was provided with nalbuphine for the first 24 h. Patients in the first study required 6.7 ± 2.1 mg nalbuphine (zero to six doses) and those studied on the day of surgery required 4.7 ± 1.4 mg nalbuphine (zero to five doses), except for one patient, whose pain was not relieved by 20 mg nalbuphine administered within 10 min. He then was treated with morphine 20 mg in five divided doses. Although he continued to complain of pain, no additional morphine was thought to be necessary, as he would fall asleep within 5 min if left alone. He continued to complain of pain of similar character and intensity throughout his 7-day hospitalization, despite additional doses of morphine, oxycodone with acetaminophen, and propoxyphene with acetaminophen. None of the patients experienced tachycardia or dysrhythmias following the injection of nalbuphine.

Statistical analysis of the hemodynamic variables using multiple analyses of variance showed no significant changes from prenalbuphine levels in heart rate, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, or cardiac index. Although there was no significant increase in mean arterial pressure for either group, one patient in study 2 did experience a clinically significant increase in mean arterial pressure, as noted above (fig. 1).

DISCUSSION

High-dose narcotic anesthesia, especially with fentanyl, frequently is used for patients with cardiac disease undergoing cardiac and major noncardiac surgery in order to avoid cardiovascular depression. One disadvantage of this technique is postoperative ventilatory depression due to residual narcotic drug and necessitating mechanical ventilation, in some cases for prolonged periods. It has been demonstrated that patients can be extubated safely early after cardiac surgery with inhalational or balanced narcotic anesthesia.[1-3] Early extubation should minimize patient discomfort, hospital costs, sedative/analgesic requirements, and the risks of airway obstruction or accidental extubation.

Antagonism of narcotic-induced respiratory depression with naloxone has been fraught with complications, including the unmasking of pain, severe hypertension,[5] acute pulmonary edema,[6] ventricular dysrhythmias,[7] and cardiac arrest.[8] Prior to naloxone, overdoses of narcotics were treated with agonist–antagonists such as nalorphine and levallorphan.[9] The poor analgesic qualities of these drugs together with the high incidence of psychotomimetic reactions markedly limited their use. Presently, three agonist–antagonists are used widely as analgesics: pentazocine, butorphanol, and nalbuphine. Both pentazocine and butorphanol can cause unpleasant psychic effects, although to a lesser extent than nalorphine. Patients receiving nalbuphine exhibit psychic side effects infrequently and to a much lesser degree than after any of the other antagonist–analgesics.[10]

Nalbuphine has a half-life of 3–6 h,[9,11] which compares favorably with the terminal half-life of fentanyl of 3.7 h in volunteers,[12] and 5.2–7.1 h following cardiopulmonary bypass.[13,14] It produced minimal hemodynamic changes in patients with coronary artery disease undergoing cardiac catheterization or surgery or experiencing an acute myocardial infarction.[15,16],†† This is in contrast to pentazocine and butorphanol, which were associated
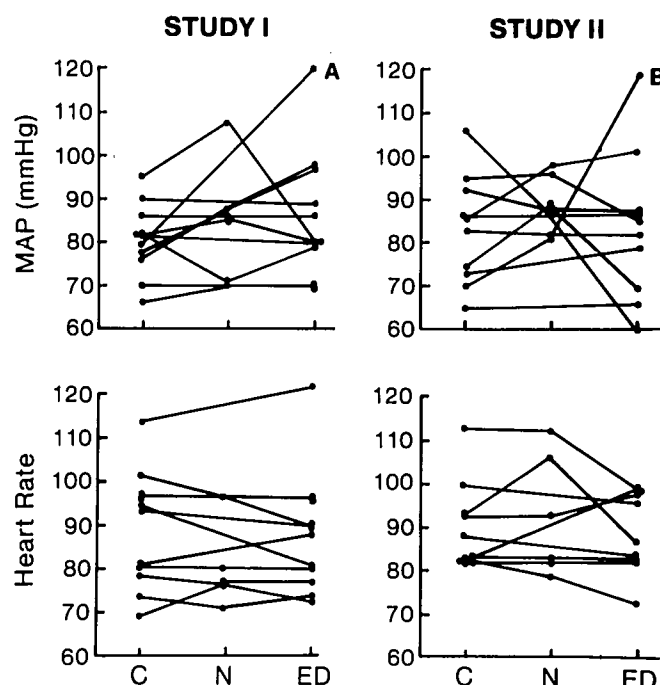

FIG. 1. Hemodynamic variables before and after nalbuphine. Control (C) values were obtained immediately before the first dose. Hemodynamic measurements also were made after the first dose (N) and again after the effective dose (ED) of nalbuphine that reduced the $Pa_{CO_2} \leq 48$ mmHg (and before extubation). The values shown represent the maximum increase in heart rate and MAP immediately after N and ED. Since the first dose also was the effective dose for four patients in study 1 and three patients in study 2, no data are shown at N for these patients. Two patients had increases in MAP to approximately 120 mmHg (A and B). Although patient A experienced a 50% increase in his MAP above prenalbuphine control values, his blood pressure remained within the range of MAP recorded preoperatively and he received no vasodilator therapy. Patient B experienced a 69% increase in her MAP from her prenalbuphine control values. Since this was greater than her preoperative values, she was treated with nitroprusside for 10 min until her MAP decreased below 100 mmHg. C = prenalbuphine control; N = after the initial dose of nalbuphine; ED = after the effective dose of nalbuphine; MAP = mean arterial pressure.

with increases in pulmonary and systemic vascular resistance and a decrease in cardiac index.[17-19] Unlike butorphanol, nalbuphine is postulated to act as an antagonist at the mu opiate receptor, suggesting its use to antagonize narcotic-induced respiratory depression.[9,10] In two recent studies[4] (Magruder et al.‡‡), large doses of nalbuphine (0.1–0.3 mg/kg intravenously) were used to antagonize respiratory depression in noncardiac patients, following narcotic anesthesia, who then were extubated without any adverse sequelae. In our study nalbuphine, in 15 μg/kg increments effectively antagonized the ventilatory

†† Romagnoli A, Keats AS: Comparative hemodynamic effects of nalbuphine and morphine in patients with coronary artery disease. Cardiovascular Disease Bulletin, Texas Heart Institute 5:19–24, 1978.

‡‡ Magruder MR, Delaney RD, Di Fazio CA: Reversal of narcotic-induced respiratory depression with nalbuphine hydrochloride. Anesthesiology Review 9: 34–37, 1977.

depressant effects of large anesthetic doses of fentanyl following cardiac surgery. The doses of nalbupine ranged from 1 to 10 mg (66 ± 13 μg/kg) in patients studied the day after surgery and 1.5–9 mg (46 ± 10 μg/kg) in patients extubated within 7.7 ± 0.3 h after surgery.

In contrast to the previous work cited, our patients did experience some side effects after receiving nalbuphine, although few of these were clinically important. Nausea and vomiting occurred in two patients receiving nalbuphine the morning after surgery. These patients had evidence of gastric distension, and the nausea subsided quickly once a nasogastric tube was inserted. Hypertension requiring treatment with sodium nitroprusside occurred in one patient who received nalbuphine on the day of surgery.

Three of the nine patients extubated the day of surgery experienced episodes of renarcotization occurring 2–3 h after receiving nalbuphine. This was readily apparent by clinical observation (respiratory rate, sedation degree of) and confirmed by arterial blood gas analysis; it was treated easily with additional nalbuphine. Renarcotization occurred only in the patients of study 2 who initially required large doses of nalbuphine. The need for larger doses implies the following: 1) there were greater narcotic analgesic (fentanyl) concentrations still present to be antagonized, and 2) higher fentanyl concentrations require a longer time to be eliminated and thereby increase the chances of renarcotization.

In summary, nalbuphine can effectively antagonize the ventilatory depression due to residual fentanyl effect following high-dose fentanyl anesthesia. In contrast to previous reports of this use of nalbuphine, our study indicates that renarcotization may occur. Although our study failed to demonstrate a significant increase in the group mean arterial pressures, one patient did experience a transient, clinically significant degree of hypertension that required treatment. No dysrhythmias occurred following nalbuphine administration, and there were few other clinically important side effects. We administered nalbuphine in small doses that were titrated to a satisfactory level of ventilation. It is possible that larger doses of nalbuphine would have a longer duration of action and decrease the incidence of renarcotization. However, this might also increase the incidence and/or severity of side effects. Studies to determine the optimum dose and timing relative to the last dose of a narcotic anesthetic are required.

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