Prevention of epidural morphine-induced respiratory depression with intravenous nalbuphine infusion in post-thoracotomy patients

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The efficacy of nalbuphine, an agonist/antagonist opioid, in preventing respiratory depression from epidural morphine analgesia after thoracotomy, was assessed in a randomized double-blind placebo controlled trial. After a standardized general anaesthetic and 0.15 mg·kg⁻¹ of epidural morphine, patients received a bolus and then a 24 h infusion of nalbuphine (200 µg·kg⁻¹ + 50 µg·kg⁻¹·hr⁻¹, 100 µg·kg⁻¹ + 25 µg·kg⁻¹·hr⁻¹, or 50 µg·kg⁻¹ + 12.5 µg·kg⁻¹·hr⁻¹) or placebo. Blood gases, analgesia, sedation, side effects, and blood nalbuphine concentrations were assessed every two hours for the next 24 h. Fifty-three per cent of placebo-treated patients had a PaCO₂ > 50 mmHg and 89 per cent of these received naloxone. A 200 µg·kg⁻¹ bolus of nalbuphine followed by a 50 µg·kg⁻¹·hr⁻¹ infusion achieved a mean steady state blood level of 38.2 ng·ml⁻¹ and prevented CO₂ retention greater than 50 mmHg in all but two patients, neither of whom required naloxone. There was no difference in the incidence of side effects among groups, and analgesia appeared to be unaffected by nalbuphine.

Key words

PAIN: postoperative; ANALGESICS: morphine, nalbuphine; ANAESTHETIC TECHNIQUES: epidural.

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Presented in part at the ASA Annual Meeting, Atlanta, October 1987.

Epidural opioids provide excellent postoperative analgesia¹ and facilitate the recovery of pulmonary function.² Side effects such as pruritus, nausea, vomiting and urinary retention, are common,¹ but the most serious problem is respiratory depression. While mild respiratory depression is common with any method of opioid administration, the occasional occurrence of delayed and unpredictable severe respiratory depression with the use of epidural opioids has been a major concern and has limited their use in many centres to areas where the patient can be closely monitored.^{3,4} While the incidence of severe respiratory depression is low,⁵ CO₂ retention and an abnormal respiratory pattern⁶ are seen much more frequently. This is a problem especially in patients needing larger doses of opioid, or repeated administration of smaller doses, to produce good analgesia, e.g., after thoracotomy⁶ or upper abdominal surgery.⁷

Nalbuphine hydrochloride, an opioid agonist/antagonist, has a plateau effect on respiratory depression when given on its own.⁸ It has been shown to reverse the respiratory depression from both intravenous⁹ and epidural opioids.¹⁰

This study was undertaken to determine whether a continuous intravenous infusion of nalbuphine would reduce the incidence and severity of respiratory depression in post-thoracotomy patients receiving epidural morphine analgesia. We were also interested to see if this combination could reduce the incidence of other side-effects, and to assess its impact on analgesia. Finally, we attempted to determine the dosage and serum levels required for optimal outcome.

Method

This was a double-blind placebo-controlled trial of three doses of nalbuphine, given as a loading bolus followed by a 24-hour infusion. Patients between the ages of 21 and 70

years with a body mass index less than $30 \text{ kg} \cdot \text{m}^{-2}$ and ASA physical status I-III presenting for elective thoracotomy were eligible for the study.

The study was approved by the hospital human experimentation committee. An explanation of the risks and benefits of the study was given, and informed consent was obtained from all subjects. Patients were allocated with a random numbers table to one of four treatment groups, to receive in a double-blind fashion either:

Group A $-200 \mu\text{g} \cdot \text{kg}^{-1}$ bolus of nalbupine and a $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion;

Group B $-100 \mu\text{g} \cdot \text{kg}^{-1}$ nalbupine bolus and a $25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion;

Group C $-50 \mu\text{g} \cdot \text{kg}^{-1}$ nalbupine bolus and a $12.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion;

Group D $-a$ saline bolus and infusion.

Preoperative investigations included haemoglobin, platelet count, electrolytes, urinalysis, electrocardiogram, chest x-ray, pulmonary function studies and arterial blood gas analysis. Pre-medication was with oral diazepam $0.1 \text{ mg} \cdot \text{kg}^{-1}$ and monitoring was with electrocardiogram, peripheral nerve stimulator, and oxygen analyzer. Prior to surgery, a radial arterial cannula was inserted; an epidural catheter was inserted at the L_{2-3} or L_{3-4} interspace and its position confirmed by injection of a test-dose of local anaesthetic containing epinephrine $1:200,000$.

Induction of anaesthesia was with fentanyl $2-3 \mu\text{g} \cdot \text{kg}^{-1}$, droperidol 1 mg , d-tubocurarine $0.05 \text{ mg} \cdot \text{kg}^{-1}$, thiopentone $3-5 \text{ mg} \cdot \text{kg}^{-1}$, and succinylcholine $1.5-2 \text{ mg} \cdot \text{kg}^{-1}$. Airway management was with either tracheal tube and bronchial blocker, or a double-lumen endobronchial tube. Anaesthesia was maintained with nitrous oxide, oxygen, pancuronium, isoflurane, and additional fentanyl as required to a maximum of $5 \mu\text{g} \cdot \text{kg}^{-1}$ for the whole anaesthetic. As soon as convenient after induction of anaesthesia, $0.15 \text{ mg} \cdot \text{kg}^{-1}$ of preservative-free morphine, $0.5 \text{ mg} \cdot \text{ml}^{-1}$ was injected through the epidural catheter. At the end of surgery, muscle relaxation was reversed with neostigmine or edrophonium and atropine, and spontaneous ventilation resumed. The patient was then given an intravenous bolus of the test solution, and the 24-hour infusion was begun. The tracheas were extubated in the operating room or shortly after arrival in the recovery room. Any patient remaining intubated for more than two hours postoperatively was withdrawn from the study.

Patients remained in the recovery room or intensive care unit for 24 hours as is routine in this institution for patients receiving epidural opioid analgesia. Arterial blood gases were analyzed every two hours for 24 hours. Pain, sedation, pruritus, nausea and vomiting were recorded two hourly for 24 hours by recovery room nurses

who were trained in the use of the appropriate scales and were unaware of the patient's study medication. Pain intensity was scored on a visual analogue scale of 0 (no pain) to 10 (agonizing pain).¹²

Sedation was assessed using a 6-point scale:

- 1 = mostly awake
- 2 = asleep, opens eyes to surrounding noise
- 3 = asleep, opens eyes to name
- 4 = asleep, opens eyes to physical stimulus
- 5 = asleep, moves and makes noise to physical stimuli
- 6 = unconscious and unarousable

Pruritus, and nausea and vomiting, were rated on a 5-point scale:

- 1 = none
- 2 = mild
- 3 = moderate
- 4 = moderately severe
- 5 = severe

Additional fentanyl was administered intravenously by the recovery room nurses for a pain score > 4 , and anti-emetics were given as required.

Significant respiratory depression was defined as an arterial $\text{PCO}_2 > 50 \text{ mmHg}$ at any time after the first two hours postoperatively. If this occurred, then naloxone ($1 \mu\text{g} \cdot \text{kg}^{-1}$ bolus + $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion for the remainder of the 24-hour period) was substituted for the study agent infusion.

Pain scores, fentanyl requirements, sedation scores and haemodynamic changes were analyzed by repeated measures analysis of variance (ANOVA) or the Kruskal Wallis test for non-parametric data where appropriate. If the ANOVA was significant, individual means were compared by the Newman-Keuls test. The incidence of side-effects, the number of patients requiring antihypertensive therapy, and the number of patients with at least one $\text{PaCO}_2 > 50 \text{ mmHg}$ were analyzed by χ^2 test or the Fisher exact probability test. Power was calculated using the mean square between subjects and the mean square within subjects obtained from the repeated measures ANOVA.²²

Results

Sixty-three patients completed the trial and the demographic data are shown in Table I. There were no significant differences among the four groups with respect to age, sex, ASA status, preoperative pulmonary function tests, arterial blood gases, duration of surgery, or intraoperative fentanyl requirements. A further 22 patients agreed to participate but were withdrawn because of intraoperative protocol deviations (six), intraoperative surgical problems (eight), intraoperative arrhythmias

FIGURE 1 The number of patients yet to exceed a PaCO_2 50 mmHg during 24 hours after thoracotomy.

(two), recovery room nursing staff logistical problems (two), elective postoperative ventilation because of prolonged surgery (three), and return to operating room because of postoperative haemorrhage (one). No patient required ventilation because of postoperative CO_2 retention.

Figure 1 shows the number of patients in each group whose PaCO_2 had not yet exceeded 50 mmHg from two to 24 hours after the administration of the study agent. This corresponds to approximately four to 26 hours after the injection of epidural morphine. After achieving this threshold value, the PaCO_2 values were reduced by naloxone therapy towards the normal range. A dose of $1 \mu\text{g} \cdot \text{kg}^{-1}$ was adequate in all but two patients whose infusions were increased to $2 \mu\text{g} \cdot \text{kg}^{-1}$.

Patients considered to be therapeutic failures because of having at least one $\text{PaCO}_2 > 50$ mmHg during the period from 2–24 hours are shown in Table II. There were only two therapeutic failures in Group A, and neither of these was given naloxone. The difference between the high dose (A) and both low dose (B and C) and placebo (D) groups is significant ($P < 0.01$). Although our

FIGURE 2 Pain scores (mean $\pm$ SD) v time during 24 hours after thoracotomy. There is no significant difference between the four groups.

TABLE II Therapeutic failures

Group	A	B	C	D
$\text{PaCO}_2 > 50$ mmHg	2*	7	12	9
Naloxone therapy	0	6	7	8

* $P < 0.01$.

Respiratory depression was significantly less frequent in Group A.

protocol dictated that naloxone be given on achieving a $\text{PaCO}_2 > 50$ mmHg, this was not always adhered to by the attending staff because of the general well-being of individual patients, adequate level of consciousness, cardiovascular stability and adequate oxygenation despite the elevated PaCO_2 .

There was no statistically significant difference in mean pain scores (Figure 2) among the groups (power 92 per cent for detecting a difference in pain score of 1.29). Significantly ($P < 0.05$) more fentanyl was required postoperatively (Table III) by placebo patients (mean 24-hour total $330 \pm 195 \mu\text{g}$ SD) than patients in either

TABLE I Demographic data (mean $\pm$ SD)

Group	A	B	C	D
n	15	16	17	15
Males/Females	8/7	10/6	8/9	9/6
Age—years	60.8 $\pm$ 7.7	53.5 $\pm$ 11.8	57.2 $\pm$ 7.6	56.7 $\pm$ 8.6
ASA I/II/III	0/12/3	1/12/3	1/12/4	1/10/4
Weight—kg	67.1 $\pm$ 16.8	71.4 $\pm$ 17.2	69.3 $\pm$ 15.0	70.1 $\pm$ 14.0
Pre-op FVC L	3.01 $\pm$ 1.0	3.30 $\pm$ 1.2	3.12 $\pm$ 1.1	3.29 $\pm$ 0.9
FEV ₁ L	2.25 $\pm$ 0.9	2.37 $\pm$ 0.9	2.17 $\pm$ 0.6	2.48 $\pm$ 0.8
PaCO_2 mmHg	38.7 $\pm$ 2.37	39.3 $\pm$ 2.1	40.1 $\pm$ 2.90	37.5 $\pm$ 3.2
PaO_2 mmHg	80.5 $\pm$ 11	81.1 $\pm$ 11.3	80.3 $\pm$ 18.4	80.3 $\pm$ 8.44
Fentanyl μg :				
Induction	148 $\pm$ 67.1	168.8 $\pm$ 70.4	129.4 $\pm$ 50.2	145 $\pm$ 46.5
Maintenance	105 $\pm$ 55.3	125 $\pm$ 114.0	111.8 $\pm$ 122.6	96.7 $\pm$ 99.5
Duration of surgery (min)	132.7 $\pm$ 37.8	146.7 $\pm$ 51.4	128.9 $\pm$ 45.2	129.9 $\pm$ 40.5

FIGURE 3 Sedation scores (mean $\pm$ SD) v time during 24 hours after thoracotomy. There is no significant difference between the four groups.

group A ($220 \pm 142 \mu\text{g}$) or group C ($157 \pm 132 \mu\text{g}$) but there was no significant difference between placebo and group B ($264 \pm 218 \mu\text{g}$). Within groups, patients who received naloxone did not consistently require more fentanyl than those not receiving naloxone, and there was no significant difference in any group (power 92 per cent for detecting a difference of $144 \mu\text{g}$).

There was no correlation between PaCO_2 and fentanyl requirements for individual patients, which suggests that fentanyl supplementation was not the cause of the elevation of PaCO_2 .

There was no significant difference among the groups for sedation scores (power 99 per cent for detecting a difference in sedation score of 0.48) (Figure 3) or other side effects (Table IV). There was no significant difference in the perioperative changes in heart rate (power 98 per cent for detecting a ten per cent heart rate difference) and mean arterial pressure (power 98 per cent for detecting an eight per cent difference in pressure) between the groups (Table V), nor in the incidence of arrhythmias or requirement for antihypertensive medication (Table IV).

The mean nalbuphine plasma profile at each dose level is shown in Figure 4. The loading dose and infusion produced steady state levels of $38.2 \pm 5.6 \text{ ng} \cdot \text{mL}^{-1}$ (mean

FIGURE 4 Plasma nalbuphine concentrations (mean $\pm$ S.D.) v time during 24 hr after thoracotomy.

$\pm$ standard deviation) in Group A, $21.2 \pm 5.5 \text{ ng} \cdot \text{mL}^{-1}$ in Group B, and $9.4 \pm 2.1 \text{ ng} \cdot \text{mL}^{-1}$ in Group C.

Discussion

The occurrence of delayed respiratory depression after administration of epidural opioids continues to be of concern and in many centres restricts the use of this analgesic technique to situations where patients can be closely monitored for up to 24 hours after the last dose of morphine administration.^{3,4} If there was a reliable method of preventing this serious side effect, then epidural opioids could be a useful analgesic technique for patients who did not otherwise require intensive monitoring. This would considerably enhance the safety and availability of this otherwise excellent analgesic technique.

If the incidence of respiratory depression is dose dependent,¹² it is more likely to occur in situations requiring a higher dose of morphine, given as a higher initial dose or repeated smaller (e.g., 5 mg) doses.^{2,6} In our practice, we too have invariably found it necessary to give repeated small doses of epidural morphine to achieve adequate analgesia after thoracotomy. Based on our

TABLE III Fentanyl requirements

Group	A	B	C	D
Total μg mean $\pm$ SD	220 ± 142	264 ± 218	157 ± 132	330 ± 195
(number of patients)	(15)	(16)	(17)	(15)
Patients who received naloxone	—	212 ± 259	171 ± 153	400 ± 172
		(6)	(7)	(8)
Patients who did not receive naloxone	220 ± 142	295 ± 199	147 ± 124	250 ± 200
	(15)	(10)	(10)	(7)

Supplementary intravenous fentanyl — total mean $\pm$ SD for each group, plus means within groups for patients who did/did not receive naloxone.

TABLE IV Postoperative side effects

Group	A	B	C	D
No. of patients with:				
Nausea	3	0	5	2
Vomiting	1	0	2	1
Pruritus	0	3	1	3
Arrhythmias	4	2	1	3
Antihypertensive medication administered	5	1	2	2

There was no statistically significant difference in the incidence of side-effects between the four groups.

previous clinical experience, and for the purposes of standardization, we elected to give a single dose of $0.15 \text{ mg} \cdot \text{kg}^{-1}$ morphine. We anticipated that most of our patients would then have adequate analgesia with only a small amount of intravenous narcotic supplementation, and this is what happened. To obtain complete analgesia with epidural morphine alone, a higher dose would have been necessary, and this would likely have caused even more respiratory depression.

The incidence of respiratory depression found with the use of epidural opioids is dependent on the definition thereof, and varies greatly from series to series. Rawal⁵ estimated the incidence to be of the order of one in 1100, using the definition of a slow respiratory rate or a clinical problem requiring opioid antagonist therapy. Unfortunately, respiratory rate is not predictably slowed by increasing respiratory depression from epidural opioids.^{14,15} We elected to define significant respiratory depression as a PaCO_2 above 50 mmHg, as levels higher than this are not frequently found with other analgesic techniques. The incidence of CO_2 retention in this study was 53 per cent overall. While patients with such mild elevation of PaCO_2 might not exhibit a clinical problem, there is clearly interference with central respiratory control.¹⁷

After demonstrating the occurrence of respiratory depression following epidural morphine first in volunteers and then in patients undergoing cholecystectomy, Rawal¹² found that the respiratory depression could be reversed with naloxone 5 or $10 \mu\text{g} \cdot \text{kg}^{-1}$. However, naloxone has been found to reverse analgesia in doses ($0.4\text{--}4 \mu\text{g} \cdot \text{kg}^{-1}$) used to prevent respiratory depression.¹³ Other problems which have arisen with naloxone therapy for reversal of respiratory depression after surgery include hypertension¹⁹ and pulmonary oedema.²⁰

Nalbuphine hydrochloride, an opioid agonist/antagonist with approximately equal analgesic potency to morphine,²¹ has been shown by Romagnoli and Keats⁶ to have a plateau effect on respiratory depression. Moldenhauer⁹ demonstrated that nalbuphine $0.1 \text{ mg} \cdot \text{kg}^{-1}$ IV was effective in reversing opioid-induced respiratory depression while preserving analgesia. Penning¹⁰ demonstrated that in patients given epidural morphine, nalbuphine was effective in reversing respiratory depression as well as nausea and pruritus. Also, he showed that nalbuphine in doses of up to $0.3 \text{ mg} \cdot \text{kg}^{-1}$ did not reverse analgesia, but caused increased sedation. Therefore in seeking a dose range that would be effective prophylactically without causing sedation, we chose to use doses below $0.3 \text{ mg} \cdot \text{kg}^{-1}$. We also took into account the antagonist potency ratio of nalbuphine to naloxone of 1:34.²¹ Our highest dosage group of nalbuphine (group A) was equivalent to naloxone $5.9 \mu\text{g} \cdot \text{kg}^{-1} + 1.48 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$, i.e., much higher than the equivalent doses of naloxone which other investigators have found to reverse analgesia.¹³ This dose of nalbuphine, $200 \mu\text{g} \cdot \text{kg}^{-1}$ IV followed by a $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion, produced a mean serum level of $38.2 \text{ ng} \cdot \text{ml}^{-1}$ and was effective in maintaining a lower PaCO_2 . There were significantly fewer patients with a $\text{PaCO}_2 > 50 \text{ mmHg}$ while analgesia was maintained.

Interestingly, prophylaxis was not entirely successful by our strict criteria, since two patients in Group A had

TABLE V Perioperative haemodynamic variables

Group	A	B	C	D
Mean arterial pressure mmHg $\pm$ SD				
Preop	96.1 $\pm$ 10	92.8 $\pm$ 5	91.2 $\pm$ 8	93.4 $\pm$ 10
15 min postop	104.5 $\pm$ 17	98.3 $\pm$ 6	103.0 $\pm$ 13	97.4 $\pm$ 20
75 min postop	91.2 $\pm$ 15	94.0 $\pm$ 11	104.0 $\pm$ 14	102.2 $\pm$ 19
135 min postop	85.3 $\pm$ 10	91.1 $\pm$ 14	95.9 $\pm$ 13	96.0 $\pm$ 15
Heart rate $\text{b} \cdot \text{min}^{-1} \pm$ SD				
Preop	85.3 $\pm$ 8.6	80.8 $\pm$ 9.3	81.3 $\pm$ 8.3	79.7 $\pm$ 10.7
15 min postop	87.9 $\pm$ 18.8	84.8 $\pm$ 19.4	88.7 $\pm$ 14.9	79.8 $\pm$ 17.1
75 min postop	88.7 $\pm$ 20.5	88.5 $\pm$ 21.7	87.8 $\pm$ 16.3	84.5 $\pm$ 15.3
135 min postop	89.5 $\pm$ 20.4	89.8 $\pm$ 16.6	88.9 $\pm$ 16.5	87.1 $\pm$ 13.5

There was no statistically significant difference in mean arterial pressure or heart rate between the four groups.

PaCO₂ of 51 and 54 mmHg at isolated times during the observation period. The effects of sleep, sedation, other drugs, variations in the rate of CSF flow, morphine absorption, etc., may be important in affecting the incidence and severity of respiratory depression, and we were not able to correlate individual PaCO₂'s with individual blood nalbuphine concentrations. All of the failures (PaCO₂ > 50 mmHg) in our study occurred within four hours of the end of surgery (approximately seven hours from the administration of epidural morphine) except for one patient with a single PaCO₂ of 52 mmHg at 12 hours and a second patient with a PaCO₂ of 51 mmHg at 20 hours. This is similar to Rawal's findings that clinically significant respiratory depression usually occurs within 12 hours of epidural morphine administration.⁵

It has been suggested that there may be reversal of analgesia with intravenous boluses of nalbuphine,^{16,18} but we found no evidence to support this. In our experimental design, we planned to assess the contribution of nalbuphine to analgesia by comparing the intravenous fentanyl supplementation required to achieve adequate analgesia, and similar pain scores, in each group. Since there was no increase in fentanyl requirements in patients receiving nalbuphine, there did not appear to be any negative effect of nalbuphine on analgesia. This discrepancy with other reports may be due to the epidural route of administration of morphine resulting in a higher concentration of the μ agonist at the opioid receptors than after intravenous administration. Alternatively, it is possible that morphine has a higher intrinsic activity at the μ receptors than fentanyl since the reversal of analgesia reported was in patients who received fentanyl.^{16,18} Finally, it is possible that nociception is more κ -mediated in lateral thoracotomy patients than after median sternotomy, since the κ -agonist nalbuphine appeared to augment analgesia in this study, contrary to the reversal reported in patients after median sternotomy.¹⁸

After previous reports of cardiovascular stimulation following nalbuphine administration,¹⁸ we were interested to observe that there was no statistically significant correlation between the dose of nalbuphine administered and elevation of blood pressure during emergence from anaesthesia and the postoperative period (Table V), the incidence of arrhythmias, or in the requirements for antihypertensive medication (Table IV). The patients in this study appeared to be mildly sedated, but there was no apparent increase in sedation with increasing doses of nalbuphine.

Conclusion

In this series of thoracotomy patients, epidural morphine

at a dose of 0.15 mg · kg⁻¹ caused significant increases in postoperative PaCO₂ with acceptable though incomplete analgesia. Fifty-three per cent of patients who did not receive postoperative nalbuphine had PaCO₂ > 50 mmHg and most of these required treatment with naloxone. Low doses of nalbuphine attenuated the morphine-induced increase in PaCO₂ but only to a degree that was neither clinically nor statistically significant. Bolus administration of 200 μ g · kg⁻¹ followed by infusion of 50 μ g · kg⁻¹ · hr⁻¹ of nalbuphine, significantly attenuated the increased PaCO₂ without causing unacceptable sedation nor antagonizing epidural morphine induced analgesia. A 200 μ g · kg⁻¹ bolus followed by a 50 μ g · kg⁻¹ · hr⁻¹ infusion of nalbuphine may be administered to post-thoracotomy patients receiving epidural morphine, to prevent respiratory depression without causing significant side-effects or cardiovascular stimulation.

Acknowledgements

We are grateful to our colleagues in the Anaesthesia Department and the Recovery Room nursing staff for their cooperation during this study; Drs. Crepeau, Belanger, and Hooper, Division of Thoracic Surgery, for cooperation with this study on their patients; Sylvie Paquette for secretarial assistance; DuPont Pharmaceuticals for a grant to cover operating costs; Jeremy Hill, BSc for statistical analysis of data; and to Drs. R. Dales and R. Nair (University of Ottawa) for statistical consultation.

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Résumé

Une étude à double-insue et avec placebo a été faite pour évaluer la nalbuphine, un opioïd agoniste-antagoniste, comme agent prophylactique de la dépression respiratoire subséquente à l'injection épidurale de morphine après une thoracotomie. Après une anesthésie générale uniformisée et une injection épidurale de 0.15 mg · kg⁻¹ de morphine, un bolus suivi d'une infusion de nalbuphine ou placebo pendant 24 heures furent administrés aux patients (soit 200 µg · kg⁻¹ + 50 µg · kg⁻¹ · hr⁻¹, ou 100 µg · kg⁻¹ + 25 µg · kg⁻¹ · hr⁻¹, or 50 µg · kg⁻¹ + 12.5 µg · kg⁻¹ · hr⁻¹ ou un placebo). La gazométrie, l'analgésie, la sédation, les effets secondaires, et les niveaux sanguins de nalbuphine furent évalués aux deux heures pendant 24 heures. Cinquante-trois pourcent des patients ayant reçu le placebo eurent un PaCO₂ > 50 mmHg et 89% de ces patients eurent besoin de naloxone. Les patients ayant reçu un bolus de 200 µg · kg⁻¹ et une infusion de 50 µg · kg⁻¹ · hr⁻¹ eurent des concentrations sanguines stables de 38.2 ng · ml⁻¹; de plus, aucun de ces patients n'eut besoin de naloxone et tous sauf deux eurent des PaCO₂ < 50 mmHg. L'incidence des effets secondaires fut la même dans tous les groupes et l'analgésie de base de ces patients ne fut pas modifiée par la nalbuphine.