Reversal of epidural morphine-induced respiratory depression and pruritus with nalbuphine

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The effect of nalbuphine on the respiratory depression, pruritus and analgesia induced by epidural morphine was determined in a randomized, prospective, double-blind, placebo-controlled fashion. Twenty ASA physical status 1 women received 0.1 mg·kg^{-1} epidural morphine at induction of general anaesthesia for elective total abdominal hysterectomy. Group 1 (n = 14) received 0.3 mg·kg^{-1} nalbuphine intravenously six hours after the epidural morphine administration. Group 2 (n = 6) received saline. Prior to agent administration, six patients from the nalbuphine group and four patients from the saline group had respiratory depression indicated by a $PaCO_2$ greater than 45 mmHg. After nalbuphine administration the $PaCO_2$ (mean ± SE) decreased from 49.5 ± 1.2 mmHg to 42.5 ± 0.7 mmHg ($p < 0.005$) while there was no significant change after saline administration. Nine of the 14 patients receiving nalbuphine appeared to become more sedated, despite an improvement in ventilation. Pruritus was antagonized by 0.1 mg·kg^{-1} nalbuphine ($p < 0.006$). There was no reversal of analgesia after administration of 0.3 mg·kg^{-1} nalbuphine.

Key words

ANAESTHETIC TECHNIQUES: regional, epidural; ANALGESICS: morphine, respiratory depression, pruritus nalbuphine, sedation.

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Epidural morphine has become accepted as an efficient means of postoperative pain management. However, the problem of delayed respiratory depression has restricted its use, and in most centres patients are monitored for 24 hours following the last dose of epidural morphine, in an intensive care setting. Naloxone has been found to reverse this respiratory depression[1] but there are reported problems with reversal of analgesia.[2] Many investigators now believe naloxone to have significant effects on cardiovascular function with or without prior narcotic analgesia administration.[3–5]

Nalbuphine has been shown to reverse intravenous opioid-induced respiratory depression.[6,7] It might have a lesser tendency for reversal of analgesia since it is a partial agonist at the mu opioid receptor and an agonist at the Kappa opioid receptor.[12]

There have been no previous published studies of nalbuphine's effect on the respiratory depression and analgesia produced by epidural morphine. The purpose of our study was therefore to determine if intravenously administered nalbuphine could reverse epidural morphine-induced respiratory depression, pruritus and to assess its effects on analgesia.

Methods

After approval by our Human Research Ethics Committee, informed consent was obtained from 20 ASA physical status I patients scheduled for elective total abdominal hysterectomy. The study was prospective, randomized, double-blind and placebo controlled. Randomization was achieved using a random numbers table.

Premedication was with diazepam 5 mg PO 1.5 hours preoperatively. Ventilatory response to CO_2 was assessed using the rebreathing method described by Read.[8] A Portex epidural catheter was introduced 3–4 cm into the epidural space at spinal level L_{2-3} or L_{3-4} via a 17 gauge Touhy needle, the bevel of which faced cephalad. A test dose of 3 ml carbonated lidocaine with 1:200,000 epinephrine was then administered. While awaiting the development of some sensory block to confirm successful

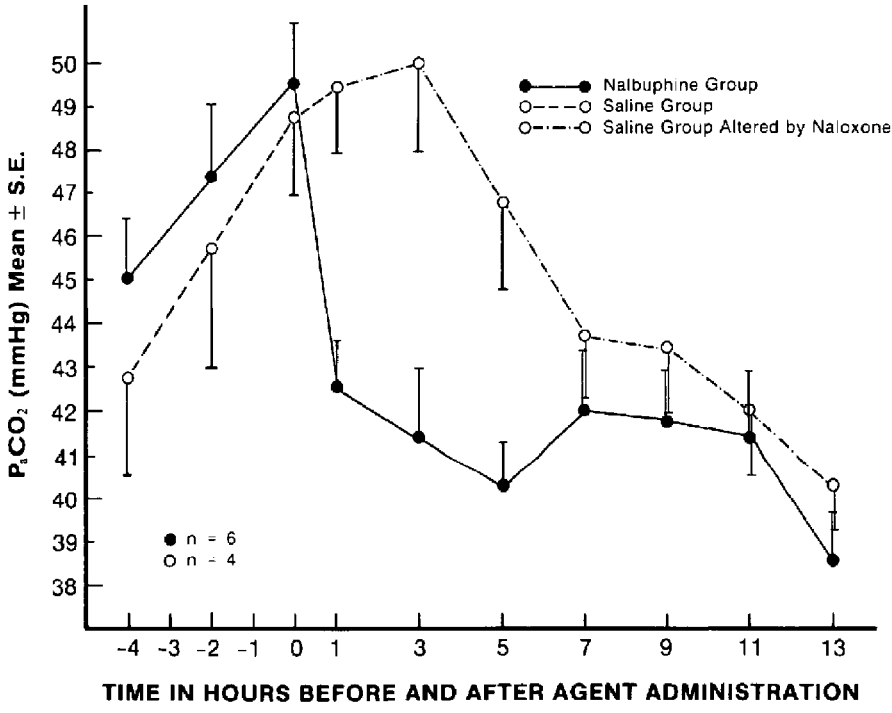

FIGURE Mean $PaCO_2$ in relation to the time the study agent was administered. At time = 1 hr after study agent administration, $p < 0.005$ for the nalbuphine group vs saline group.

placement of the epidural catheter, the patient was familiarized with the visual analogue pain scale[9] (0–10, 0 = no pain, 10 = agonizing pain) that would be employed in the postoperative period.

The standardized general anaesthetic consisted of 3 mg IV d-tubocurarine, thiopentone 4–6 $mg \cdot kg^{-1}$ IV, and succinylcholine 1.5 $mg \cdot kg^{-1}$ IV to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen and isoflurane. The radial artery was cannulated after induction. Preservative-free epidural morphine, 0.1 $mg \cdot kg^{-1}$, in a concentration of 0.5 $mg \cdot ml^{-1}$ was administered five minutes after induction to allow adequate time for the morphine to produce effective analgesia by the end of surgery. Additional d-tubocurarine was used for muscle relaxation and was reversed with neostigmine/atropine IV (2.5 mg/1.2 mg). No other narcotics were administered at any time during the perioperative period.

Patients remained in the Recovery Room for 24 hours postoperatively. Patients who graded their pain score as four or more out of ten in the first thirty minutes following awakening were given an additional 0.05 $mg \cdot kg^{-1}$ of epidural morphine. Arterial blood gases were drawn every two hours, for 18 hours.

Six hours after the patients had received the 0.1 $mg \cdot kg^{-1}$ epidural morphine given with induction, baseline resting arterial blood gas samples were drawn. (The $PaCO_2$ values determined at this time are represented at the point, time = 0, in the Figure.) Immediately after this blood sampling an assessment of ventilatory response to CO_2 was performed. Immediately on completion of the test, the patient received a series of three intravenous injections of study agent prepared by the pharmacy and labelled only with the patient's name and study number. The injections were 20 minutes apart and each consisted of 0.1 $mg \cdot kg^{-1}$ nalbuphine or an equivalent volume of saline. Fifteen minutes after each injection of study agent, a CO_2 response test was performed. Arterial blood gases were drawn ten minutes after the last of the four CO_2 response tests (time = +1 hr in Figure). Study agent

injections and the CO_2 response tests were performed by the principal author.

Any patient found to have a $PaCO_2$ greater than 49 mmHg at any time after study agent administration was treated with a bolus of 2 $\mu g \cdot kg^{-1}$ naloxone followed by a naloxone infusion of 2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$.

The patients graded their pain and pruritus every two hours while awake and also immediately before and ten minutes after each administration of the study agent. The pain scores were determined by the patients using the linear analogue pain scale, graded from 0 to 10, with which they had been familiarized preoperatively. The pruritus score was attained from the patient in response to direct questioning: "Do you itch?" It was graded according to severity: zero when not present, one when mild, two when moderate and three when distressingly severe. The patients' scores were reported to the principal investigator at the times just before and after study agents were administered. Other scores were obtained from the patients by the recovery room nurses assigned to the patient.

Data for the arterial blood gases and the duration of adequate analgesia after epidural morphine were analyzed using a two-tailed Student's t test for two independent samples. The pruritus data were analyzed using the Chi-square test. Statistical significance was assumed when $p < 0.05$.

Results

There were no significant differences between the two groups (Table I) regarding age, weight and height.

Six patients from the nalbuphine group and four patients from the control group had a $PaCO_2 > 45$ mmHg immediately prior to the first postoperative assessment of ventilatory response to CO_2 (six hours after 0.1 $mg \cdot kg^{-1}$ epidural morphine). Four of the six patients in the nalbuphine group, and three of the four patients in the saline group had received a further 0.05 $mg \cdot kg^{-1}$ of epidural morphine, 30 minutes postoperatively, because of pain scores greater than four out of ten.

The Figure shows the mean $PaCO_2$ for these two sub-groups before and after the administration of the study agent. The six patients from the nalbuphine group had a statistically significant ($p < 0.005$) mean correction of 7 mmHg in their $PaCO_2$ while the mean $PaCO_2$ for the saline group remained elevated.

TABLE I Demographic data (mean ± SD)

	Nalbuphine (n = 14)	*Saline (n = 6)*
Age (yr)	42 ± 3.4	38 ± 4.4
Weight (kg)	60 ± 7.0	65 ± 7.8
Height (cm)	161 ± 4.0	161 ± 6.0

Three of the four patients with respiratory depression in the saline subgroup required naloxone for $PaCO_2$ greater than 49 mmHg after saline was administered. None of the nalbuphine patients required naloxone. Administration of nalbuphine to patients with $PaCO_2 <$ 45 mmHg did not significantly change the mean $PaCO_2$ (before 40.5 mmHg, after 40.0 mmHg). Only ten patients were able to perform the CO_2 response tests in an acceptable fashion, therefore we lacked sufficient data to perform a valid statistical analysis.

Eleven patients needed additional epidural morphine to achieve satisfactory analgesia in the early postoperative period. Seven of these were in the nalbuphine group, and four in the saline group. All patients except one from the saline group subsequently enjoy excellent postoperative analgesia.

Table II shows pain scores before and after administration of the study agent. The administration of 0.3 $mg \cdot kg^{-1}$ nalbuphine did not diminish the analgesia reported by our patients. The duration of analgesia after epidural morphine (i.e., the time to first request for additional analgesia), is shown in Table III. The duration of adequate analgesia in the nalbuphine group was 5.4 hours longer than in the saline group, but this difference was not statistically significant.

Six hours after the administration of 0.1 $mg \cdot kg^{-1}$ epidural morphine 50 per cent of patients in both groups had pruritus (Table II). There was a dramatic improvement after 0.1 $mg \cdot kg^{-1}$ nalbuphine IV ($p < 0.006$) but not with saline.

Discussion

Our data indicate that intravenously administered nalbuphine will antagonize epidural morphine-induced respiratory depression. This was the main question for which this study was designed. Based on the low incidence of delayed respiratory depression reported in early papers (as low as 0.33 per cent[10]) we felt it was necessary to perform assessments of ventilatory response to CO_2 in order to quantify respiratory depression in our patients. In retrospect this test may have needlessly complicated our study design. Our arterial blood gas data proved adequate to answer our principal question with a surprisingly small number of patients. The degree of respiratory depression experienced by our patients corresponds well with those of Rawal and Wattwil,[1] whose post-cholecystectomy patients experienced a mean increase in end–tidal CO_2 of 15 per cent five hours after administration of 10 mg epidural morphine.

Nalbuphine has mild to moderate intrinsic respiratory depressant activity that is limited by a "ceiling effect" at 0.4 $mg \cdot kg^{-1}$.[11] The mechanism by which it antagonizes epidural morphine-induced respiratory depression is

TABLE II Pain scores before and after study agents

Patient	Study agent	Total dose of epidural morphine $mg \cdot kg^{-1}$	Pain score*		Time in hours† duration of analgesia	Pain score‡
			pre	post		
4	Nalbuphine	0.15	0	0	17	3
5	Nalbuphine	0.15	0	0	21	4
7	Nalbuphine	0.15	0	0	25	–
8	Nalbuphine	0.15	0	0	16	6
9	Nalbuphine	0.15	2	2	32	–
11	Nalbuphine	0.15	0	0	24	8
19	Nalbuphine	0.15	1	2	14	4
1	Nalbuphine	0.10	2	3	16	5
2	Nalbuphine	0.10	0	2	19	5
3	Nalbuphine	0.10	1	1	14	5
13	Nalbuphine	0.10	0	1	30	–
14	Nalbuphine	0.10	1	1	36	–
15	Nalbuphine	0.10	0	1	15	3
20	Nalbuphine	0.10	1	1	32	–
6	Saline	0.15	0	0	19	3
10	Saline	0.15	0	0	16	4
12	Saline	0.15	0	0	8	5
18	Saline	0.15	2	2	14	3
16	Saline	0.10	5	4	8	3
17	Saline	0.10	0	0	36	–

*Pain scores around the time of study agent administration: "pre" immediately before first postoperative CO_2 response test and before agent administration, "post" 20 minutes after third injection of 0.1 $mg \cdot kg^{-1}$ study agent.
†Time (hrs) to first request for analgesia.
‡Pain score at time of first request for analgesia.

probably by the displacement of morphine from brainstem receptors. Therefore in order for nalbuphine to antagonize narcotic-induced respiratory depression, the degree of depression must be beyond that which would be present with nalbuphine alone.

The arterial blood analysis at the one-hour point in the Figure was ten minutes after a CO_2 challenge test. This time interval is probably long enough for the arterial CO_2 to have returned to the pre-test level, but should this not be the case, then all patients should be equally affected by any error as they all experienced the same CO_2 challenge ($ETCO_2$ 60 mmHg).

TABLE III Duration of adequate analgesia* after epidural morphine

	No. of patients	Hours, mean ± SD
Nalbuphine group		
Total dose epidural morphine		
0.15 $mg \cdot kg^{-1}$	7	20.0 ± 6.3
0.10 $mg \cdot kg^{-1}$	7	23.1 ± 9.2
Combined	14	22.2 ± 7.6
Saline group		
Total dose epidural morphine		
0.15 $mg \cdot kg^{-1}$	4	14.3 ± 4.6
0.10 $mg \cdot kg^{-1}$	2	22.0 ± 19.8
Combined	6	16.8 ± 10.4

*Time from epidural morphine at induction of anaesthesia to first postoperative parenteral or oral analgesia.

Nine patients in the nalbuphine group became more sedated after the second and/or third injection of 0.1 $mg \cdot kg^{-1}$ study agent. These patients were still arousable to verbal command, but during the CO_2 response tests, they were breathing around the mouthpiece of the CO_2 rebreathing circuit, invalidating the test. We felt that this increased level of sedation was more than desired and therefore we stopped the study after 20 patients (yielding 14 nalbuphine and six saline controls). This phenomenon had not been anticipated and the study was not designed to study sedation. No change in sedation was observed in the saline group. The sedative effect of nalbuphine is thought to be mediated by its agonist activity at certain kappa receptors throughout the brain.[12] Thus, perhaps by interacting with separate receptors mediating separate clinical responses, nalbuphine can produce a divergence of sedation and respiratory depression when given to patients treated with epidural morphine.

Nalbuphine did not antagonize epidural morphine's analgesia. Epidural morphine acts as an analgesic via its action on opioid receptors located in the substantia gelatinosa of the spinal cord.[13] Morphine is carried with the cerebrospinal fluid to the area related to respiratory function near the floor of the fourth ventricle. A consider-

TABLE IV Pruritus scores

Patient number	*Pruritus score* before agent*	*Pruritus score after first injection of study agent*
Nalbuphine		
1	2	0
2	1	0
5	2	0
8	2	0
9	2	0
11	2	1
13	3	1
14	1	0
Saline		
12	1	1
17	1	1
18	2	2

*Pruritus score: 0 – nil, 1 – mild, 2 – moderate, 3 – severe.

able concentration gradient exists between morphine at the opioid spinal receptors and the receptors for respiratory depression in the brainstem.[14,15] Therefore, with intravenous nalbuphine administration the nalbuphine: morphine ratio at the spinal opioid receptor favours morphine, while at the brainstem respiratory centre the ratio favours nalbuphine. However, if there is a common opioid receptor conformation for the mediation of respiratory depression and the modulation of nociception in the substantia gelatinosa of the spinal cord, then it should be possible to antagonise epidural morphine's analgesia with nalbuphine. This may occur with a larger dose or more rapid administration of nalbuphine.

Pruritus was effectively antagonized by the first administration of 0.1 $mg \cdot kg^{-1}$ nalbuphine. At this dose no change in level of sedation was observed, unlike after the second and/or third nalbuphine administrations. Therefore, this seems to be an antagonist action of nalbuphine and not just secondary to increasing sedation.

We conclude that in patients receiving epidural morphine, intravenous nalbuphine had the following effects:

1 Reversal of respiratory depression to clinically acceptable levels.
2 No detectable change in degree of analgesia with 0.3 $mg \cdot kg^{-1}$ nalbuphine intravenously.
3 Reversal of pruritus with 0.1 $mg \cdot kg^{-1}$ nalbuphine.

Also, we observed an apparent increase in sedation in a dose-related fashion. However, this important clinical issue must be specifically addressed with further study.

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Résumé

Les auteurs ont étudié l'effet de la nalbuphine sur la dépression respiratoire, le prurit et l'analgésie produits par la morphine administrée par voie épidurale. L'étude fut conduite à double insu, prospectivement et avec placebo. Vingt patientes ASA I reçurent 0.1 $mg \cdot kg^{-1}$ de morphine par voie épidurale à l'induction de l'anesthésie générale pour une hystérectomie abdominale élective. Les patientes du groupe I (n = 14) reçurent

0.3 mg·kg^{-1} de nalbuphine intraveneusement six heures après l'administration de la morphine épidurale. Les patientes du group II (n = 6) reçurent du placebo. Avant l'administration de ces agents, six patientes du premier groupe et quatre du deuxième groupe avaient une dépression respiratoire manifestée par un $PaCO_2$ plus élevé que 45 mmHg. Les patientes furent assignées l'un ou l'autre de ces groupes au hazard. Après l'administration de la nalbuphine, le $PaCO_2$ fut réduit de 49.5 ± 1.2 mmHg à 42.5 ± 0.7 mmHg ($p < 0.005$) alors qu'il n'y eut aucune amélioration après l'administration du placebo. L'amélioration du $PaCO_2$ démontrée après l'administration de la nalbuphine se manifesta en dépit d'une augmentation du niveau de sédation observé chez ces patientes. Le prurit fût antagonisé par 0.1 mg·kg^{-1} de nalbuphine ($p < 0.005$). L'analgésie produite par la morphine épidurale ne fût pas antagonisée après l'administration intraveneuse de 0.3 mg·kg^{-1} de nalbuphine.