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A Comparison of the Analgesic and Respiratory Effects of Epidural Nalbuphine or Morphine in Postthoracotomy Patients

Richard C. Etches, M.D., F.R.C.P.(C).,* Alan N. Sandler, M.Sc., M.B.ChB., F.R.C.P.(C).,†
Stephanie L. Lawson, R.N.‡

This randomized, double-blind study compared the analgesic and respiratory effects of lumbar epidural morphine 5 mg, nalbuphine 10 mg, and nalbuphine 20 mg in repeated doses in patients after thoracotomy; the first dose was administered intraoperatively. Pre- and postoperative monitoring included continuous pulse oximetry, respiratory inductance plethysmography, and repeated arterial blood gas analysis. Postoperatively, visual analogue pain scores, somnolence scores, respiratory rate, and arterial blood gases were determined for 16 h. Preoperatively, episodes of apnea were common during sleep but were not associated with low hemoglobin oxygen saturation or increased arterial carbon dioxide tension (Pa_{CO_2}). During sleep, some otherwise normal patients had increased Pa_{CO_2}, and 2 of 15 patients had episodes of hemoglobin oxygen saturation of less than 90%. Postoperatively, 1 and 2 h after arrival in the recovery room, patients who received morphine had lower pain scores than did those who received nalbuphine 10 or 20 mg ($P < 0.05$). All 6 patients who received morphine had satisfactory analgesia. Two of 4 patients who received nalbuphine 10 mg and all 5 who received nalbuphine 20 mg were withdrawn from the study because of inadequate analgesia (morphine *vs.* nalbuphine 10 mg, not significant; morphine *vs.* nalbuphine 20 mg, $P < 0.01$). Two patients who received morphine had persistently increased Pa_{CO_2} postoperatively. Two patients who received morphine had episodes of apnea and slow respiratory rate, which were most frequent 6 h after arrival in the recovery room. We conclude that lumbar epidural nalbuphine does not provide adequate analgesia after thoracotomy. Morphine is effective but may be associated with significant respiratory depression, which cannot be predicted on the basis of preoperative respiratory abnormalities, dose of drug, or hourly respiratory rate. (Key words: Analgesics: nalbuphine; morphine. Anesthesia: thoracic. Anesthetic techniques: epidural. Complications: respiratory depression; pain, postoperative. Ventilation, apnea: pattern.)

LUMBAR EPIDURAL MORPHINE can provide excellent postoperative analgesia of long duration in patients after thoracotomy but may be associated with unacceptable degrees of respiratory depression manifested by carbon dioxide retention, a flattening of the ventilation carbon dioxide response curve, and potentially dangerous transient episodes of apnea or slow respiratory rate.[1,2] This respiratory depression is a result of systemic uptake and/or cephalad spread in the cerebral spinal fluid (CSF) of epidurally administered morphine to the level of the respiratory control centers of the brain stem, where the drug exerts its depressant effects, primarily *via* its μ-receptor agonist activity.[1,3]

Nalbuphine (DuPont Pharmaceuticals, Toronto, Ontario, Canada) is a semisynthetic drug related to both naloxone and oxymorphone; it has a combination of opioid agonist and antagonist effects. In particular, nalbuphine is a relatively potent μ-antagonist and κ-agonist.[4] Parenterally administered nalbuphine in smaller doses (10–15 mg) has analgesic and respiratory effects similar to those of an equal dose of morphine. However, at larger doses, greater than 0.4 mg/kg, there is a ceiling effect on both analgesic effectiveness and respiratory depression.[5–8] Although this upper limit on respiratory depression is desirable, the problem of inadequate postoperative analgesia has limited the drug's popularity.[9,10]

Despite the frequent failure of nalbuphine as a parenteral analgesic, its combination of agonist and antagonist properties may enhance its benefit as an epidural analgesic. There is some evidence that κ receptors predominate in the human spinal cord, although the degree to which they mediate the analgesic effects of opioids is uncertain.[11] If spinal κ receptors are important mediators of analgesia in humans, then nalbuphine administered epidurally may provide analgesia with less risk of the clinically significant respiratory depression associated with epidural morphine. We therefore undertook a double-blind comparison of epidural nalbuphine *versus* morphine in patients undergoing thoracotomy.

Methods and Materials

PATIENT SELECTION

The study protocol was approved by the Human Experimentation Committee of the Toronto General Hospital and the Canadian Health Protection Branch, a division of Health and Welfare Canada.

* Assistant Professor of Anesthesia, University of Alberta, Alberta, Canada.

† Assistant Professor of Anesthesia, University of Toronto; Anaesthetist-in-Chief, Toronto General Hospital.

‡ Research Assistant, Toronto General Hospital.

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Address correspondence to Dr. Sandler: Department of Anesthesia, Toronto General Hospital, GW 2-502, 200 Elizabeth Street, Toronto, Ontario, Canada, M5G 2C4.

Fifteen ASA physical status 1 and 2 patients undergoing elective thoracotomy gave written informed consent to participate in the study.

Patients were excluded from the study if they were greater than 65 yr of age or obese or if they had other significant medical problems (including evidence of ischemic heart disease). Patients scheduled for pneumonectomy were excluded.

Patients were randomly assigned to one of three groups: group M received epidural morphine 5 mg, and groups N10 and N20 received nalbuphine 10 and 20 mg, respectively. Nalbuphine was supplied by the manufacturer as sterile lyophilized powder. Drugs were prepared by the hospital pharmacy in 20-ml vials of preservative-free normal saline and identified only with the subject number. Only the hospital pharmacy was aware of the contents.

Preoperative Monitoring

Because preexisting respiratory abnormalities may affect postoperative respiratory function,[1,12] patients were monitored overnight prior to surgery. An arterial catheter was inserted, and arterial blood gases were determined prior to sleep and repeated at 2-h intervals during the night; in all cases patients were breathing room air. Continuous pulse oximetry was used throughout the night, and all episodes of hemoglobin oxygen saturation (Sp_{O_2}) less than 90% were noted. Continuous respiratory inductance plethysmography (RIP) was used to record average respiratory rate at 5-min intervals. In addition, the RIP equipment was programmed to record all episodes of apnea (defined as any 15-s interval with no tidal volume greater than 100 ml) and slow respiratory rate (defined as any 5-min interval with an average respiratory rate of less than 10 breaths per min). The setup and calibration of RIP have been described in detail previously.[2,13,§] For both preoperative and postoperative monitoring, a trained nurse or physician observer was present continuously to exclude artifact.

Anesthesia

With the exception of two group N10 patients who received diazepam 7.5 or 10 mg orally, patients received no preanesthetic medication. Immediately prior to anesthesia, an epidural catheter was inserted at the L2–L3 or L3–L4 interspace and its position verified by injection of a 3-ml test dose followed by 12–17 ml carbonated lidocaine with 1/200,000 epinephrine. Each patient's trachea was intubated after induction of general anesthesia and muscle relaxation with thiopental and pancuronium. Anesthesia was maintained with halothane or isoflurane and oxygen. The first dose of study drug was administered 2 h prior to the anticipated completion of surgery. No other sedative drugs or opioids were administered during surgery. At the completion of surgery, muscle relaxation was reversed, and the trachea of each patient was extubated in the operating room. Patients were then transferred with oxygen to the recovery room.

§ Watson H.: Technology of respiratory inductive plethysmography. Third International Symposium on Ambulatory Monitoring. Harrow, Middlesex, United Kingdom, 1979, pp 537–558.

Postoperative Monitoring

After surgery all patients received supplemental oxygen *via* mask or nasal prongs for at least 30 h.

Pain was assessed using a 10-cm visual analogue score (VAS) with zero and 10 labeled as "no pain" and "worst pain imaginable," respectively.[14] Pain scores were recorded as soon as possible after arrival in the recovery room. If the patient was unable to give a VAS during the first 15 min in the recovery room, no VAS was recorded for this epoch. The VAS was recorded immediately prior to each additional dose of drug (excluding the intraoperative dose) and then at 15, 30, 45, and 60 min and hourly thereafter. If analgesia was inadequate by the patient's assessment, an additional dose of study drug was administered. Doses were not repeated at intervals of less than 30 min. Any patient who did not have adequate analgesia after three doses was withdrawn from the study and analgesia supplemented with epidural local anesthetic or epidural or intravenous opioids.

Somnolence was recorded on a five-point scale (1 = oriented and initiates conversation; 5 = unresponsive to painful stimulus) at the time pain scores were measured. Vital signs, including blood pressure, heart rate, and respiratory rate, were recorded at the same time as pain and somnolence scores. Arterial blood gases were determined immediately prior to repeated doses of the study drug and then at 30 and 60 min, and hourly thereafter.

RIP and monitoring of Sp_{O_2} were recommenced immediately upon arrival in recovery room and were continued for at least 18 h. Monitoring was done as described for preoperative monitoring. The respiratory rate was measured also by direct observation, and this value was entered into the data set.

Side effects were recorded if present. All patients had indwelling urinary catheters. After completion of the study all patients were asked to rate the quality of their analgesia on a five-point scale (1 = excellent; 5 = poor).

Data Analysis

Demographic data, data from preoperative monitoring, duration of anesthesia, and elapsed time from first dose administered to arrival in the recovery room were analyzed using a one-way analysis of variance. VAS of the three groups were compared using the Kruskal-Wallis

analysis of variance by ranks. Where this was significant, the Mann-Whitney U test was then used for individual comparisons. Fisher's exact test was used to compare group M patients with group N10 and N20 patients with respect to frequency of analgesic success or failure. Pa_{CO_2} for the group M patients was compared to control values using Student's t test adjusted for multiple comparisons.

Results

Before beginning the study, a power analysis was performed. Based on the author's (ANS) previous experience, it was determined that 11 patients per group would be adequate to demonstrate a significantly smaller increase in postoperative carbon dioxide in patients receiving nalbuphine compared to morphine. However, for clinical reasons the study was terminated after 15 patients. (See Discussion.)

Demographic Characteristics

Demographic data for the three groups are summarized in table 1. There were no significant differences among groups with respect to age, sex, weight, procedures undertaken, or duration of surgery. No patient had evidence of significant obstructive or restrictive lung disease based on history, physical examination, or chest x-ray.

Preoperative Monitoring

There were no significant differences among groups, and the resting, awake Pa_{CO_2} was within the normal range for all subjects. No episodes of slow respiratory rate were detected. However, in all three groups some patients had increased Pa_{CO_2} (up to 50 mmHg) during sleep, and 10 of 15 subjects had from 1 to 66 apneic episodes of 15–20 s duration. Two patients had periods of Sp_{O_2} of less than 90% (86 and 88). There was no discernible relationship among the maximum detected Pa_{CO_2}, apneic episodes, and decreased Sp_{O_2}.

Perioperative Period

In all patients lumbar epidural catheters were inserted without difficulty and the position verified as described above.

Postoperative Period

The times from the administration of the study drug until arrival in the recovery room were 167 ± 41, 95 ± 41, and 144 ± 43 minutes for groups M, N10, and N20, respectively (no significant differences). Each patient's trachea was extubated prior to arrival in the recovery room, and all patients had somnolence scores of 3 (not oriented, but responding to verbal commands) or less.

One patient in group N10 and two in group N20 were unable to provide VAS within 15 min of arrival in the recovery room, and these patients are not included in the intergroup data analysis of the first VAS. Some patients who received nalbuphine were withdrawn from the study before they had spent a full 2 h in the recovery room. For these patients the last VAS measured, rather than the 2-h score, is included. Using the Kruskal-Wallis test, there was a significant difference in the VAS among the three groups at 1 h $P < 0.05$) and 2 h ($P < 0.025$) but not for the first VAS in the recovery room. Individual intergroup comparisons (Mann-Whitney U test) at 1 and 2 h revealed significant differences in VAS between group M and both nalbuphine groups but no difference between the two nalbuphine groups (table 2).

With the exception of one patient in group M, all patients required additional study drug within the first two postoperative hours. Group M patients received an average of 2.3 (range 1–4) doses during the 18-h period of postoperative monitoring, and all had adequate analgesia after the second dose. In contrast, two of the four N10 patients and all five N20 patients were withdrawn from the study within the first three postoperative hours because of inadequate analgesia after three doses of the study drug. One N20 patient was withdrawn from the study

Table 1. Demographic Characteristics

	Group M	Group N10	Group N20
n	6	4	5
Age (yr)	53 ± 12.5	56 ± 4.7	57 ± 6.1
Sex	4 M, 2 F	2 M, 2 F	2 M, 3 F
Weight (kg)	71 ± 7.9	70 ± 13.3	73 ± 11.6
Procedure	4 TTHH 1 L lobectomy 1 R bilobectomy	2 TTHH 1 L lobectomy 1 chest wall resection	3 TTHH 1 R lobectomy 1 R segmental lobectomy
Duration of surgery (min)	222 ± 36	207 ± 11	198 ± 25

Plus/minus values are mean ± SD.
There were no significant differences between groups.
TTHH = transthoracic hiatus hernia repair; L = left; R = right.

TABLE 2. VAS and Somnolence Scores

	Group M	Group N10	Gropu N20
First VAS	3.5 (0.5–8.5)	9.4 (5.7–9.6)	10 (5.0–10)
1 h*	3.0 (1.3–7.0)	9.0 (7.5–10)†	9.5 (2.5–10)‡
2 h*	3.0 (0.3–5.0)	6.2 (3.2–10)‡	9.5 (6.0–10)†
Somnolence scores at			
RR arrival	2 (2–3)	3 (2–3)	3 (2–3)
1 hr	2 (1–3)	2 (2–3)	2 (2–3)
2 hr	2 (1–3)	2 (–)	2 (2–3)

VAS shown are for the first VAS determined in the recovery room (RR) and at 1 and 2 h after arrival. Somnolence scores shown were determined immediately upon arrival in the RR and at 1 and 2 h thereafter. All values are medians (ranges in parentheses).

* $P < 0.25$ among all three groups.

† $P < 0.01$ *versus* group M.

‡ $P < 0.05$ *versus* group M.

after only two doses because of severe pain associated with agitation and hypertension (Fisher's exact test: group M *vs.* group N10, no significant difference; group M *vs.* group N20, $P < .01$). The two group N10 patients who completed the study both rated their analgesia as good (3 on a 5-point scale). However, the average VAS for hours 3–16 inclusive were 3.4 and 3.8. In contrast, only one of six group M patients had a score greater than 3.0 at any time during this period, but only on 5 of the 14 VAS recorded.

Somnolence scores were not different among groups. Subjectively, however, the patients who received nalbuphine were much more sedated than the patients who received morphine (table 2).

Providing adequate rescue medication for some of the patients withdrawn from the study was difficult. For example, one patient in the N10 group required morphine 70 mg and fentanyl 0.2 mg intravenously over 3 h to achieve only fair analgesia. Other patients responded adequately to epidural lidocaine and/or bupivacaine followed by a combination of epidural and intravenous opioids.

Two of the six group M patients (patients 1 and 4) had Pa_{CO_2} measurements greater than 50 mmHg throughout much of the study period. In addition, two patients (1 and 2) had numerous apneic episodes and periods of slow respiratory rate during the study. (No RIP data was available for patient 4 because of equipment malfunction.) At no time during the postoperative study period did any patient have a low respiratory rate based on hourly direct observation. There was no demonstrable relationship between the apneic episodes or periods of slow respiratory rate and the degree of hypercapnia. There also was no relationship between the number of doses of morphine and the Pa_{CO_2}; in fact, the most severe hypercapnia occurred in the patient who received only a single dose throughout the study period (fig. 1).

SIDE EFFECTS

Two group M patients received a single dose of diphenhydramine 25 mg intravenously for pruritus. No other side effects were noted.

Discussion

This study was terminated after only 15 subjects because of the clear clinical impression that the majority of the patients were not obtaining a degree of analgesia consistent with safe, humane medical care. This decision was made by an independent third party after a preliminary analysis of the data; the investigators remained blinded to the patient group assignments and to the preliminary results until the final decision had been made.

There is evidence that κ receptors exist in greatest number within the dorsal columns of the human spinal cord, but their function has not been determined with certainty.[11] Nalbuphine is a κ-agonist/μ-antagonist drug that should be an effective epidural analgesic if spinal κ receptors mediate analgesia in humans. In this study, lumbar epidural nalbuphine did not provide effective postoperative analgesia after thoracotomy. These results suggest that in this setting, κ-agonist activity alone, without μ-agonist activity, will not provide adequate analgesia. Alternatively, this failure to achieve adequate analgesia may be attributed to an inappropriate dose or inadequate cephalad spread of the drug within the neuraxis.

Several studies suggest that in smaller doses (less than 0.2 mg/kg), nalbuphine is approximately equipotent to morphine. In larger doses there appears to be a ceiling effect to both its analgesic and to its respiratory depressant effects.[5–8] In this study, no patient who received 60 mg of epidural nalbuphine had adequate analgesia. This is in contrast to the patients who received morphine, all of whom had adequate analgesia after 10 mg. Therefore, it is unlikely that the inadequate analgesia associated with nalbuphine can be attributed to inadequate dose. Conversely, Pugh and Drummond[10] suggested that the analgesic effects of nalbuphine may peak with smaller doses and that the pain may again increase as additional doses are given. It is therefore possible that the dose administered was too large. However, we believe that this is unlikely. All but one patient who received morphine required 10 mg to obtain good analgesia; this is equal to the initial dose of nalbuphine given to patients in group N10. In addition, based on what is known of the pharmacokinetics of spinal opioids, it is probable that patients in group N10 had not achieved peak tissue levels of nalbuphine at the level of the thoracic spinal cord by the time they arrived in the recovery room.[1] Finally, the data do not suggest that analgesia was less with additional doses; VAS for patients receiving nalbuphine were either improved or unchanged after repeated doses.

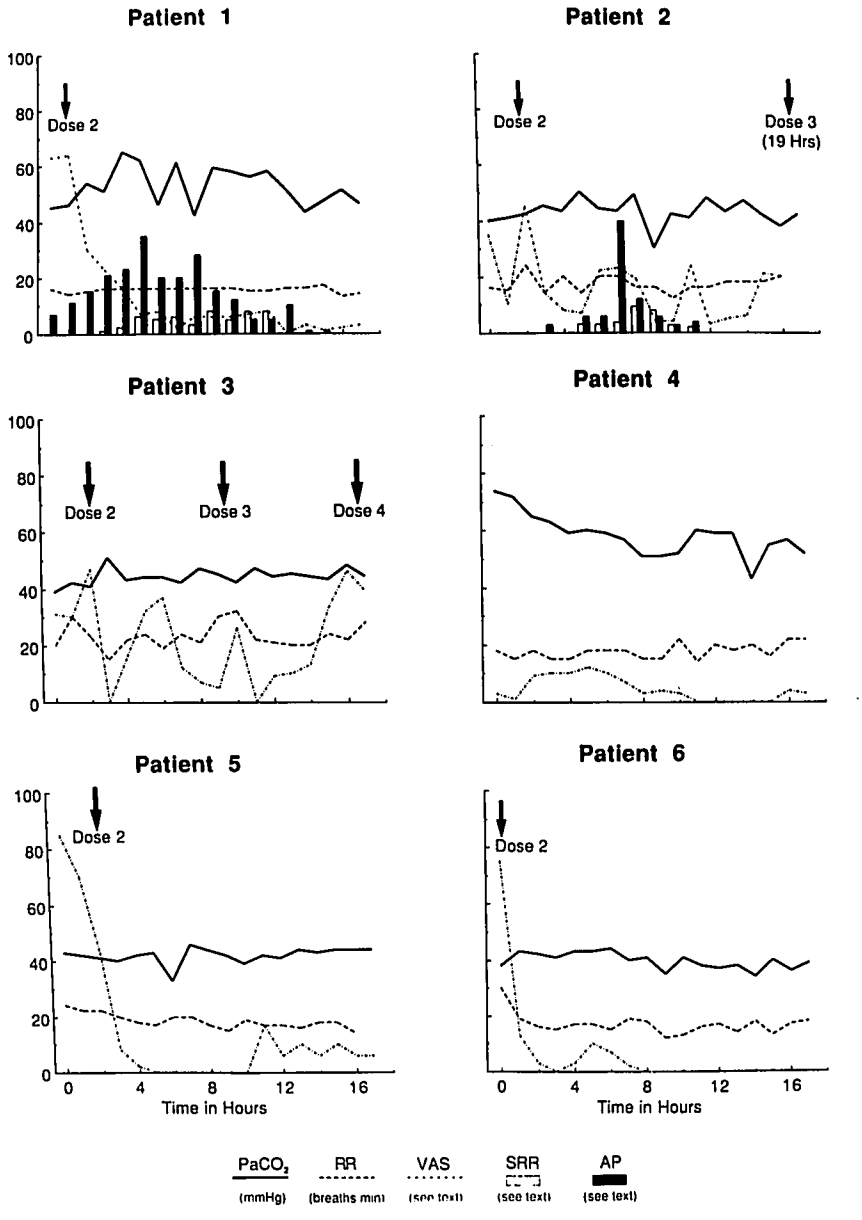

FIG. 1. Individual data for all group M patients: hourly measured Pa_{CO_2}, VAS, and respiratory rate, and hourly frequency of SRR and AP. (Note: patient 4 had only one dose intraoperatively.) See text for discussion.

Lumbar epidural opioids must move cephalad in the CSF to the midthoracic region if effective spinal analgesia is to occur after thoracotomy.[3] This cephalad spread is inversely related to the lipophilicity of the drug.[1] The lipophilicity of nalbuphine is low—intermediate between morphine and meperidine,¶ both of which have been shown to move cephalad from the lumbar level to C7–T1 within 2–3 h.[15,16] The rate of the cephalad spread of nalbuphine in the CSF to the midthoracic regions should be similar. Therefore, it is improbable that the failure to obtain adequate analgesia with nalbuphine can be explained on the basis of inadequate cephalad spread.

All patients who received morphine rated their analgesia as good to excellent. With the exception of patient 3, all group M patients had VAS pain scores of less than 3.0 from the fourth postoperative hour until the completion of the study. Patients received an average of 2.3 doses (11.5 mg) over the 18 h of the postoperative study period. Although persistent and clinically significant carbon dioxide retention occurred in two of the six group M patients, there was no relationship between the Pa_{CO_2} and the total dose. In fact, the patient with the most marked and prolonged elevation of Pa_{CO_2} in the postoperative

¶ Octanol/water solubility coefficients for morphine, meperidine, and nalbuphine are approximately 0.98, 39, and 9.75 respectively. Data supplied by manufacturer (DuPont Pharmaceuticals, Toronto, Ontario, Canada).

period received only a single dose (*i.e.*, intraoperatively). Respiratory rate also was not a predictor of Pa_{CO_2}; no patient had any hourly recorded respiratory rate of less than 12. Episodes of apnea and periods of slow respiratory rate were detected in two of the six patients who received epidural morphine; again, there was no detectable relationship to Pa_{CO_2} (fig. 1). This is consistent with other data[1] that illustrate that respiratory rate, except at its extremes, is not a useful indicator of respiratory depression or of carbon dioxide retention in patients after thoracotomy.

In conclusion, lumbar epidural nalbuphine 30–60 mg in divided doses did not provide adequate analgesia after thoracotomy. In contrast, lumbar epidural morphine provided excellent analgesia but was associated with significant hypercapnia in some patients. Pre- and postoperative monitoring using RIP to detect episodes of apnea or slow respiratory rate was not predictive of the degree of postoperative hypercapnia.

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