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Analgesic and Respiratory Effects of Epidural Sufentanil in Patients Following Thoracotomy

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Immediately following thoracotomy, 22 patients were entered into a randomized, double blind study comparing the effects of three lumbar epidural doses of sufentanil on postoperative pain and respiratory pattern. Patients were given either 30 μg (group I), 50 μg (group II), or 75 μg (group III) of epidural sufentanil in 20 ml N saline. Repeat doses were given on request for the 24-h study period. Linear analogue pain score (PS), heart rate (HR), and mean arterial pressure (MAP) were measured at 15-min intervals after each dose. Respiratory depression was assessed by the presence of: 1) slow respiratory rate (SRR—less than 10 breaths per minute for greater than 5 min), 2) apnea (AP—cessation of tidal ventilation for greater than 15 s), and 3) increased Pa_{CO_2} in arterial blood gases (ABG) drawn at regular intervals. SRR and AP were measured using respiratory inductive plethysmography (RIP). A further group of ten patients (group IV) underwent preoperative RIP monitoring during sleep and in the absence of any drug. Maximum analgesia was achieved within 15 min after a dose of sufentanil for all groups. Analgesia was not significantly prolonged by increasing the dose of sufentanil. SRR occurred in all four groups (group I: 2/9; group II: 2/6; group III: 7/7; group IV: 2/10 $P < 0.05$ I, IV:II, I, IV:III, II:III). The number of episodes of SRR/hr was highest in group II (group I: 0.6 ± 0.8, group II: 4.12 ± 0.6, group III: 1.8 ± 2.0, group IV: 0.5 ± 0.2) (NS). Mean onset time of SRR after a dose of sufentanil was 38 ± 12 min (group I), 17 ± 12 min (group II), and 19 ± 21 min (group III) (NS). AP occurred in all four groups (group I: 5/9, group II: 3/6, group III: 7/7, group IV: 6/10) (NS). The number of apneas per hour were significantly increased in group III (group I: 1.3 ± 1.2, group II: 3.0 ± 2.8, group III: 4.3 ± 3.7, group IV: 0.4 ± 0.5 $P < 0.05$ IV:III). Mean onset time of AP after a dose of sufentanil was 18 ± 15 min (group I), 32 ± 57 min (group II), and 10 ± 10 min (group III) (NS). Mean duration of AP was 19 ± 3 s (group I), 18 ± 3 s (group II), 22 ± 5 s (group III), and 17.5 ± 3 (group IV) (NS). Mean Pa_{CO_2} measured within 30 min of a dose of sufentanil was significantly increased in all groups receiving sufentanil (preoperative Pa_{CO_2}: group I: 37 ± 3, group II: 36 ± 4, group III: 35 ± 1, group IV: 36 ± 3, post-dose Pa_{CO_2}: group I: 41 ± 5, group II: 46 ± 8, group III: 49 ± 14, $P < 0.05$ I:III). Three patients receiving 75 μg developed life-threatening respiratory depression. Lumbar epidural sufentanil in patients following thoracotomy produced rapid onset of pain relief that was of short duration. Increasing the dose did not extend the duration of analgesia, but increased respiratory depression. (Key words: Analgesia: post-thoracotomy. Analgesics: sufentanil. Anesthesia: thoracic. Anesthetic techniques: epidural. Complications: respiratory depression; pain, postoperative. Ventilation, apnea: pattern.)

EPIDURAL ADMINISTRATION of opiates has achieved great popularity for postoperative analgesia, with morphine being the most widely used agent.[1-3] We have recently demonstrated in patients that, following thoracotomy, pulmonary function and analgesia was significantly improved by repeated doses of epidural morphine administered *via* a lumbar catheter when compared to intravenous morphine.[4] However, further investigation of this patient population using continuous monitoring of postoperative respiratory pattern revealed an unacceptably high incidence of respiratory depression (75%) in the patients receiving epidural morphine.[5] In this randomized, double-blind study, following thoracotomy, patients were given 5-mg doses of epidural morphine on demand over the first 24 h. Mean epidural morphine dose was 21.9 ± 2.1 mg/24 h.[5] Due to the slow onset of analgesia with epidural morphine, two to three doses of epidural morphine were often given early in the postoperative period.[5]

The high incidence of respiratory depression and the slow onset of analgesia of epidural morphine has prompted this study of epidural sufentanil for post-thoracotomy pain relief. Sufentanil is five to seven times more potent than fentanyl,[6] highly lipophilic, and has a high affinity for mu-opiate receptors.[7] These features, coupled with a slow receptor dissociation constant,[8] suggested that sufentanil might have a rapid onset of action, and a useful duration of analgesia. Theoretically, minimal respiratory depression was also possible, as the high receptor affinity and slow receptor/sufentanil dissociation might result in low CSF sufentanil concentrations.

In this study, we have investigated the analgesic properties, dose-response relationship, time to onset of analgesia, duration of analgesia, and side effects of lumbar epidural sufentanil for pain relief following thoracotomy.

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Materials and Methods

Patient Selection

Thirty-two ASA Physical Status I and II patients undergoing elective thoracotomy for pulmonary procedures gave informed consent for the study, which was approved by the Human Experimentation Committee of Toronto General Hospital.

Based on previously published work,[9-11] we chose to evaluate three doses. Each patient receiving epidural sufentanil was randomly assigned by the Hospital Pharmacy using a table of random numbers[12] to one of three groups: group I = 30 μg, group II = 50 μg, and group III = 75 μg per dose. All doses of epidural sufentanil were made up in 20 ml of normal saline. The randomization code was available to the investigators at all times in event of an emergency (*e.g.*, severe respiratory depression). Neither investigator nor patient was aware of the dose of sufentanil being used.

Instruments and Calibration

The breathing pattern was continuously measured postoperatively for 24 h using a respiratory inductive plethysmograph (RIP)[13] (NIMS, Miami, Florida).

Setup and calibration of the RIP have been described in previous communications.[5,14,15] After calibration, the RIP was programmed to compute the following variables: 1) slow respiratory rate (SRR)[16]—respiratory frequency of less than 10/min for at least 5 min; and 2) apnea (AP)—negligible tidal volume signals lasting 15 s or longer. Apnea was analyzed by the system and classified as obstructive or central. Central apnea had negligible abdominal, rib cage, and tidal volume signals. Obstructive apnea had a negligible tidal volume signal despite the rib cage and abdominal signals showing persistent out-of-phase respiratory movements.[16] The incidence of SRR and AP was recorded by the printer at 5-min intervals. After calibration and programming of the RIP, preoperative data collection was made over a 15-min period. The position of the two RIP transducer bands was marked on the skin and the bands removed.

Anesthesia

No preoperative medication was given. Preoperative vital signs and arterial blood gases were obtained the day before surgery. Immediately preoperatively, an epidural catheter was inserted *via* either the L2–3 or L3–4 interspace. Following a test dose of 3 ml of 2% carbonated lidocaine, the patients received a total of 10–12 ml of 2% carbonated lidocaine. Upper levels of segmental block ranged between T8 and T4, and provided analgesia during the initial part of the thoracotomy. All patients had radial artery catheters inserted for arterial blood gas sampling and pressure monitoring. General anesthesia was induced with thiopental, and either succinylcholine or pancuronium was administered to facilitate endotracheal intubation. The tracheas of all patients were intubated with either a Robertshaw double-lumen tube or a single lumen tube and a bronchial blocker. Patients were ventilated with nitrous oxide and oxygen in varying concentrations to maintain adequate hemoglobin saturation, and one-lung ventilation was conducted when necessary. Isoflurane or halothane were used in varying concentrations to provide analgesia and hypnosis. No opiate or intravenous sedative/hypnotic agents were used during anesthesia. In addition, no other analgesic or sedative/hypnotic drugs were given in the postoperative period while epidural sufentanil was being administered. At the end of surgery, neuromuscular blockade was reversed with neostigmine and atropine. Once spontaneous ventilation was established, the patients' tracheas were extubated and the patients taken to the recovery room. Due to the nature of the surgery, all patients received supplemental oxygen by face mask for at least 24 h at whatever concentration was necessary to maintain arterial p_{O_2} above 100 mmHg.

Postoperative Analgesia

The first dose of epidural sufentanil (either 30, 50, or 75 μg) was given in the recovery room as soon as the patient complained of pain. This constituted time zero (T_0) for the study. After 2–4 h in the recovery room, the patients were transferred to an Intensive Care Unit. The study was continued for 24 h from T_0. Further doses of epidural sufentanil were given on demand for analgesia, with a minimal interval of 30 min between doses. The same dose of sufentanil was given each time analgesia was requested, depending on the group (I, II, or III) to which the patient belonged. The epidural catheter was removed after 24 h and further analgesia provided with intramuscular or intravenous morphine.

Postoperative Measurements

Pain scores were obtained using a 10-cm linear analog scale.[17,18] A score of 10 indicated maximum pain, whereas 0 correlated with no pain. Pain scores were measured immediately before a dose and at 15-min intervals after each dose until there was no further improvement in analgesia.

Vital signs (heart rate, blood pressure) were recorded at 15-min intervals after each dose for the first hour and at hourly intervals thereafter until the next dose.

Arterial blood gases (ABG) were measured at 30 min and 1 h after T_0, and then at 4-h intervals for the 24-h

TABLE 1. Demographic Data

	Group I	Group II	Group III	Group IV*
N	9	6	7	10
Age (yr)	60 ± 8	63 ± 8	56 ± 9	58 ± 9
Sex	7M, 2F	5M, 1F	2M, 5F	7M, 3F
Height (cm)	170 ± 9	175 ± 9	170 ± 7	174 ± 6
Weight (kg)	70 ± 12	71 ± 13	68 ± 11	73 ± 8
FEV_1/FVC	0.63 ± 0.08	0.66 ± 0.13	0.78 ± 0.18	0.69 ± 0.11

* Preoperative respiratory monitoring during sleep only. Demographic data (mean ± SD) (age, sex, height, weight, FEV_1/FVC). There were no significant differences between the four groups.

period. If SRR or AP were present, ABG sampling frequency was increased.

Serum Concentrations

Arterial blood samples were drawn for analysis of serum sufentanil concentrations after the first three and the last two doses in all patients. Following a dose, arterial blood was sampled at 2.5, 5, 7.5, 10, 15, 30, and 60 min during the first hour, and every 30 min thereafter until the next dose was given.

Measurement of Sufentanil Serum Concentrations

Analysis of serum sufentanil levels was performed using a commercial radioimmunoassay[19] kit (Janssen Laboratories, Beerse, Netherlands). Cross-reactivity experiments performed by Janssen Laboratories demonstrated the specificity of the sufentanil antibodies by their ability to differentiate between the parent drug and other closely related compounds, including metabolites and other fentanyl-like analgesics. The limit of detection of the assay, *i.e.*, the amount of sufentanil that caused at least a 10% decrease of the initial tracer binding ability, was 0.05 ng/ml of sample. Within the assay, the coefficient of variation was 4.5–7.5% when the mean of the determination was 0.1 ng/ml.

Side effects (nausea, vomiting, pruritis) were recorded if present. All patients had an indwelling urinary catheter postoperatively.

Respiratory pattern. At the end of the surgical procedure, with the dressing in place, the RIP abdominal and rib cage transducer coils were replaced and aligned with the skin markings made preoperatively during the calibration procedure. The RIP coils were then taped to the skin to prevent movement away from the alignment markings. The taping did not impede expansion of the chest or abdomen. In the recovery room, the RIP coils were re-attached to the Respitrace monitor and the calibration factors previously derived entered into the microprocessor. Respiratory pattern was continuously monitored with the RIP for 24 h from T_0. The RIP was programmed to compute and print SRR and AP at 5-min intervals (see Instruments and Calibration).

Preoperative Respiratory Pattern

To control for abnormal respiratory patterns that have been demonstrated in patients with severe chronic obstructive pulmonary disease,[20] ten patients fulfilling the selection criteria for this study and scheduled for thoracotomy were monitored preoperatively during sleep using RIP. This group of patients (group IV) were enrolled after completion of the drug phase of the study. All the patients in this group were free of sedative drugs or opiates for at least 24 h prior to the sleep monitoring period, and were treated with iv analgesia post-thoracotomy. The demographic data from this group (group IV), which was not given epidural sufentanil, were compared to the patients who underwent thoracotomy and were given epidural sufentanil (groups I, II, and III).

Data Analysis

Data are expressed as mean ± 1 SD. Parametric data were analyzed using analysis of variance. Further analysis using Tukey's test or Duncan's test pinpointed within- and between-group significant differences. Chi-square was used in the analysis of non-parametric data. $P < 0.05$ was taken to indicate significant differences in all cases.

Results

Patient Population

Demographic data for the four groups of patients are shown in table 1. There were no significant differences between the groups with regard to age, height, weight, or FEV1/FVC. There was a preponderance of females in group III, but sex distribution was not significantly different between the groups. All patients were ASA Physical Status 1 or 2, with no significant differences in the distribution between the groups. In addition, there

were no significant differences in the distribution of surgical procedures between groups I, II, and III (thoracic exploration, wedge resection of the lung, lobectomy, and pneumonectomy). There were no significant differences between the four groups for the preoperative mean arterial pressure and heart rate. In addition, no significant changes were seen in heart rate from preoperative values either within groups or between groups for up to 30 min after every dose of sufentanil, by which time maximum analgesia was achieved (see Analgesia and Pain Score). Mean arterial pressure decreased by small but significant amounts in all the groups (I, II, III) at 15 and 30 min after a dose of sufentanil, probably reflecting the onset of adequate analgesia.

Analgesia and Pain Score

Mean pain scores pre-dose and 15 min and 30 min after every dose of sufentanil are shown in table 2. Although the scores are slightly lower at 30 min after each dose, they are not significantly different from the 15 min scores in each group. There was no significant improvement in pain score at later time intervals after each dose, indicating that the onset of satisfactory analgesia occurred within 15 min of a dose in each group.

The mean number of doses given over the 24-h assessment period was 11 ± 3 in group I, 8 ± 1 in group II, and 8 ± 1 in group III (NS).

The d. ation of analgesia per dose was defined as the time between administration of a dose and the next request for analgesia by the patient. The mean duration of analgesia per dose was 2.1 h ± 1.4 for group I, 2.8 h ± 1.9 for group II, and 3.2 h ± 1.3 for group III (NS).

Three patients are excluded from group III in the calculation of the mean number of doses received and the mean duration of dose, as they received only one, two, and four doses, respectively, before developing severe respiratory depression (see Severe Ventilation Disturbances).

Ventilation Disturbances

Preoperative Respiratory Rate. Mean preoperative respiratory rate was 19 ± 3 for group I, 18 ± 4 for group II, 16 ± 2 for group III, and 17 ± 3 for group IV. There was no difference between the groups, although the resting rate was slightly above normal,[21] and this may reflect the high proportion of smokers in this patient population.[22]

Apnea (AP) and Slow Respiratory Rate (SRR). All patients in groups I and II were monitored for 24 h postoperatively. Three patients in group III did not complete the 24-h postoperative monitoring period, as they only received one, two, and four doses of sufentanil before developing severe respiratory depression, and were then removed from the study. Patients in group IV undergoing preoperative sleep monitoring were usually only monitored for 6–8 h (*i.e.*, while asleep). To compensate for the difference in monitoring time periods, the number of episodes of AP and SRR were expressed as AP/h and SRR/h.

Preoperative Respiratory Pattern (Group IV). Sixty percent (6/10) of patients in group IV demonstrated episodes of AP during sleep, whereas 20% (2/10) of patients in this group had episodes of SRR (table 3).

Postoperative Respiratory Pattern. Slow Respiratory Rate (SRR): Episodes of SRR occurred in some patients in all three postoperative groups (table 3). There was a significant increase in the number of patients developing SRR in groups II and III compared to groups I and IV (control). Onset of SRR in relation to dose is shown in figure 1. With increasing dose, the onset of SRR occurred as early as the first dose.

Apnea (AP). Apneic episodes were present in 56% (5/9) patients in group I, 50% (3/6) in group II, 100% (7/7) in group III, and 60% (6/10) in group IV (control), respectively (NS). The incidence of apnea/h

TABLE 2. Pain Score after Epidural Sufentanil

Time (min)	Pain Score (cm)		
	Group I	Group II	Group III
N	97	48	38
Pre-dose	6.0 ± 2.4*	5.5 ± 2.2*	6.2 ± 2.8*
Post-dose			
15 min	2.4 ± 2.7	3.6 ± 3.4	2.0 ± 2.3
30 min	1.9 ± 2.7	2.1 ± 2.9	0.8 ± 1.8

10 = maximum pain; 0 = no pain; N = number of observations. Pain scores (mean ± SD) obtained using a linear analog scale. Adequate to very good analgesia is achieved within 15 min of a dose in all three groups receiving epidural sufentanil.
* $P < 0.05$, pre-dose:post-dose 15, 30 min.

TABLE 3. Respiratory Pattern Preoperatively (Group IV) and after Epidural Sufentanil (Group I, II, III)

	Group I	Group II	Group III	Group IV*
APNEA/h	1.3 ± 1.2	3.0 ± 2.8	4.3 ± 3.7†	0.4 ± 0.5
N	5/9	3/6	7/7	6/10
SRR/h	0.6 ± 0.8	4.1 ± 0.6	1.8 ± 2.0	0.5 ± 0.2
N	2/9‡	2/6§	7/7¶	2/10‡

APNEA/h = number of apneic episodes (mean ± SD) per hour of monitoring (see text); SRR/h = number of episodes of slow respiratory rate (mean ± SD) per hour of monitoring (see text); N = number of patients with APNEA/h or SRR/h/total patients in the group.
* Preoperative respiratory monitoring only.
† $P < 0.05$ (group III:IV).
‡ $P < 0.05$ (group I, IV:II).
§ $P < 0.05$ (group II:III).
¶ $P < 0.05$ (group III:I, IV).

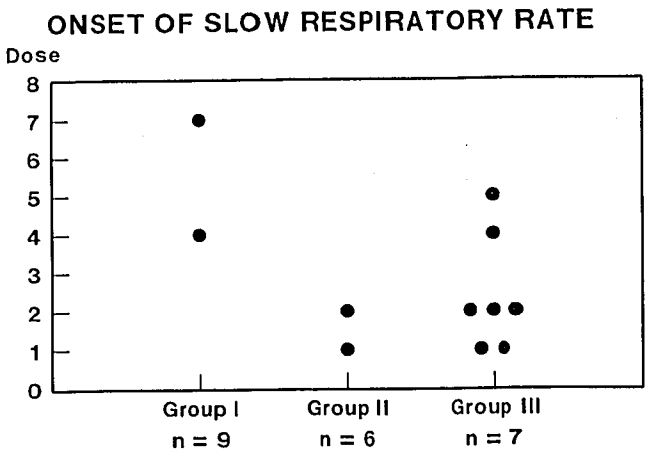

FIG. 1. Relationship between first appearance of slow respiratory rate (SRR) and number of doses of sufentanil given. Each dot represents one patient. SRR occurs after only one to two doses in increasing numbers of patients as the dose increases from 30 μg to 75 μg.

showed a steady increase from group IV (control) (0.4 ± 0.5) to group III (4.3 ± 3.7) (table 3), with group III having a significantly greater incidence than group IV (control). The mean duration to onset of apnea after a dose ranged from 18 ± 15 min in group I to 32 ± 57 min in group II and 10 ± 10 min in group III (NS). The mean duration of apnea was 19 ± 3 s in group I, 18 ± 3 s in group II, 22 ± 5 s in group III, and 17.5 ± 1.5 s for group IV (control) (NS).

Onset of apnea in relation to dose is shown in figure 2. Patients receiving epidural sufentanil developed episodes of apnea very early in the dosing schedule, the majority demonstrating apneic episodes after three doses. Obstructive and central apnea occurred with approximately the same frequency in each group, with no significant differences within or between the groups.

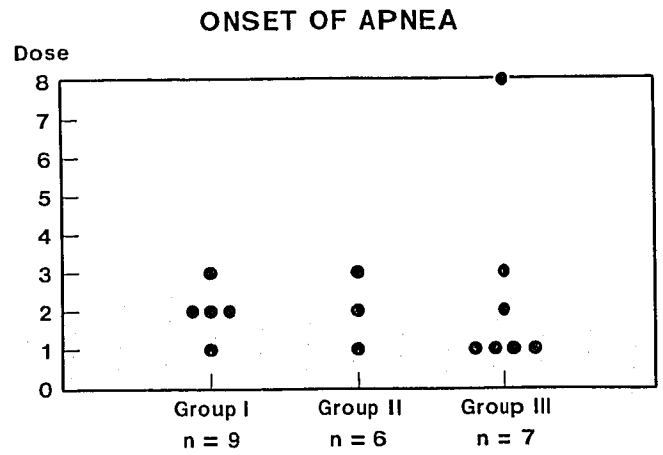

FIG. 2. Relationship between first appearance of apnea (AP) and number of doses of sufentanil given. Each dot represents one patient. Apnea was present in a greater percentage of patients in group I and group II than SRR, and occurred after one to three doses in patients in all three groups.

Arterial Blood Gases. Preoperative Pa_{CO_2} and *p*H showed no significant differences between patients in the four groups (table 4). Mean values for Pa_{CO_2} and *p*H sampled within 30 min after a dose of sufentanil was given are shown in table 4. Pa_{CO_2} was significantly elevated compared to preoperative values for all three groups, but between-group analysis showed only group III significantly higher than group I. *p*H was significantly lower than preoperative values for all three groups, but there were no between-group significant differences.

Severe Ventilation Disturbances. Three patients in group III (75 μg) developed severe respiratory depression. Two patients had severe respiratory acidosis after two and four doses of epidural sufentanil, respectively, requiring repeated doses of naloxone to antagonize the respiratory depression. In addition, one patient suffered 19 apneic episodes after the first postoperative dose of epidural sufentanil, culminating in total respiratory arrest 30 min after the dose, and required tracheal intubation and positive pressure ventilation for 1 h, followed by naloxone to correct the respiratory depression. The position of all three epidural catheters was verified with 2% carbonated lidocaine once the respiratory depression had been reversed, excluding accidental intravascular or intrathecal administration in all three cases. The study was terminated after the episode of respiratory arrest, as was dictated by the study protocol.

Serum Concentrations. A total of 566 blood samples were collected for serum sufentanil analysis after the first three and the last two doses in all patients in groups I, II, and III. Sixty-one samples were obtained at the time when AP was present. The mean serum concentrations of sufentanil in these samples was 0.43 ± 0.27 ng/ml, compared to 0.37 ± 0.30 ng/ml in those samples collected when AP was absent (NS, $P < 0.08$). Thirty-five serum samples were obtained at periods when SRR occurred. The mean serum level for these samples was 0.47 ± 0.26 ng/ml, which was significantly increased compared to those samples collected when no SRR was present (0.37 ± 0.30 ng/ml).

Minor Side Effects. Pruritus, nausea, and vomiting occurred in five patients in groups I and II only. All patients had indwelling urinary catheters postoperatively, and, thus, the incidence of urinary retention was not measured.

Discussion

ANALGESIA

All three doses of lumbar epidural sufentanil produced rapid onset of pain relief in the thoracic

TABLE 4. Arterial Blood Gases (Mean ± SD) Measured Within 30 Min of a Dose of Epidural Sufentanil

	Group I	Group II	Group III	Group IV*
Preop Pa_{CO_2} (mmHg)	37 ± 3	36 ± 4	35 ± 1	36 ± 3§
Postop Pa_{CO_2} (mmHg)	41 ± 5†	46 ± 8†	49 ± 14†‡	
Preop *p*H	7.43 ± 0.2	7.44 ± 0.03	7.43 ± 0.03	7.43 ± 0.04§
Postop *p*H	7.36 ± 0.04†	7.35 ± 0.06†	7.32 ± 0.08†	

Pa_{CO_2} was significantly elevated and *p*H was significantly decreased in all three groups receiving epidural sufentanil compared to preoperative values. Group III (75 μg) had significant higher mean Pa_{CO_2} than group I (30 μg) postoperatively.

* Preoperative monitoring only.

† $P < 0.05$ = within-group postoperative to preoperative value for Pa_{CO_2} and *p*H.

‡ $P < 0.05$ = group III:I.

§ $P < 0.05$ = group IV preoperative:I, II, III postoperative.

dermatomes. The rapid onset of analgesia in post-thoracotomy patients is similar to that found when epidural sufentanil was administered to patients who had undergone abdominal or lower extremity surgery.[9-11,23] Most studies have administered only one dose, varying from 10 μg[10] to 75 μg.[23] Parker *et al.*[10] administered one dose of 10 μg of sufentanil with or without epinephrine to patients who had undergone general or orthopedic procedures. These procedures were performed during epidural anesthesia, and epidural sufentanil was given in the postoperative period. Although the degree of analgesia was not reported, the duration of analgesia varied from 1.6 to 2.4 h, suggesting that, for lower extremity and general surgical procedures, 10 μg of epidural sufentanil has a similar duration of action to 30 μg in our study.

Donadoni *et al.*[9] also gave only one dose of sufentanil to their patients postoperatively, but the dosage range was similar to that used in our study (15 μg, 30 μg, 50 μg, and 75 μg). The duration of analgesia increased with increasing dose (4.4–6.2 h of pain relief with 30–75-μg doses). In general, Donadoni *et al.*[9] described a much longer duration of analgesia with each dose for lower extremity orthopedic procedures than we found in post-thoracotomy patients. Duckett *et al.*[11] compared thoracic *versus* lumbar administration of 50 μg of sufentanil after major abdominal surgery. More than one dose of sufentanil was given, although the exact number of doses were not specified. As in our study, onset of analgesia was rapid (within 30 min). Duration of analgesia was prolonged with thoracic epidural administration (9.9 h) compared to lumbar administration (5.4 h). Verborgh *et al.*[23] also reported rapid onset of analgesia with 30, 50, or 75 μg of sufentanil, but shorter durations of analgesia than Donadoni *et al.*[9] in post-abdominal surgery patients. Epidural sufentanil has also been given postoperatively as a continuous infusion, usually after an epidural loading dose.[24,25] This regimen provided good analgesia, although further intermittent doses were needed for breakthrough pain.[24] Epidural sufentanil has also been recently investigated by several groups for analgesia after cesarean section.[26-29] These studies used doses varying from 25 to 100 μg administered *via* a lumbar catheter. In general, onset of analgesia was rapid (6–30 min), with durations of analgesia varying from 3 to 7 h in these studies. Increasing the dose from 50 to 100 μg did not increase the duration of analgesia.[26]

VENTILATORY PATTERN AND RESPIRATORY DEPRESSION

The advantages of using RIP to assess the effects of drugs on respiration have been reviewed by Jordan.[30] Using impedance pneumography, Wynne *et al.*[20] have shown that patients with severe chronic obstructive pulmonary disease (COPD) commonly have apneic episodes and oxygen desaturation during sleep. In their study, FEV1/FVC was less than 0.5 in all patients (mean = 0.39 ± 0.08); whereas, in our study, FEV1/FVC was greater than 0.5 in all the patients (mean = 0.68 ± 0.1), indicating a lesser degree of COPD in our patients. Nonetheless, 60% of patients in our study monitored during sleep preoperatively (group IV) demonstrated apneic episodes, and 20% had episodes of SRR. In our study, epidural sufentanil was associated with SRR and AP in patients in all three postoperative groups. The number of apneas/h appears to be the most useful predictor of severe respiratory depression. Patients demonstrating more than three apneas/h had marked CO_2 retention (tables 3 and 4), and, thus, three apneas/h in this patient population indicates significant respiratory depression. The number of episodes of SRR/h was not as useful in predicting respiratory depression (table 3). The value for SRR/h was lowest in group III, who received the largest dose of epidural sufentanil. Three of the seven patients in group III did not complete the 24-h postoperative monitoring period (see Severe Ventilation Disturbances), and the remaining four patients had the highest incidence of AP/h. Thus the opportunity to exhibit SRR was markedly decreased in group III. These results are in contrast to those of Donadoni *et al.*,[9] who did not find any evidence of respiratory depression after epidural sufentanil. Donadoni's study is very comparable to ours in terms of

sample size (five per group) and dosage range (15, 30, 50, and 75 μg), although only *one dose* was given. Measurement of respiratory rate at 30, 60, 120, 180, and 240 min after sufentanil revealed no differences to preoperative values in all four groups. It is possible that discrete measurements of respiratory rate at specific time intervals resulted in any abnormalities of respiratory pattern being missed.

Similarly, Duckett *et al.*,[11] after one or more doses of 50 μg of sufentanil after abdominal surgery, did not report any changes in respiratory pattern or evidence of respiratory depression. Assessment of respiratory changes was not clearly documented in this report.[11]

Of the studies assessing the effect of epidural sufentanil following cesarean section,[26–29] only that by Naulty *et al.*[26] clearly outlines when measurements of respiratory rate were measured. It is interesting that, even after 100 μg of sufentanil and fairly frequent bedside monitoring for the first 60 min, no abnormalities of respiration or decrease in rate were reported. A very small sample size (35 patients divided into ten groups) coupled with the administration of only one dose and non-continuous monitoring of respiratory pattern may explain these results.

In contrast, bradypnea has been noted after continuous infusion of epidural sufentanil[25] and after a single dose of 75 μg of epidural sufentanil.[23] In addition, Blackburn[31] has reported two patients who presented with respiratory arrest after four doses and seven doses, respectively, of 50 μg of epidural sufentanil after abdominal surgery. In children given 0.75 μg/kg of epidural sufentanil for postoperative analgesia, a marked decrease in the ventilatory response to CO_2 was noted without overt changes in respiratory rate.[32] In our study, the most severe problems followed epidural administration of 75 μg. One patient developed severe respiratory acidosis after two doses (Pa_{CO_2} 65, *p*H 7.17), and another after four doses (Pa_{CO_2} 59, *p*H 7.25) of sufentanil, requiring cessation of further doses of epidural sufentanil and treatment with intravenous naloxone. In addition, one patient who received 75 μg developed respiratory arrest approximately 30 min after the first dose, and required tracheal intubation, artificial ventilation, and intravenous naloxone. In all three cases, catheter position was verified to be in the epidural space.

Serum Concentrations

Mean serum concentrations of sufentanil, which coincided with time periods when AP and SRR occurred, were higher than serum levels taken when AP and SRR were absent, although only the concentrations measured during SRR reached statistical significance. However, mean serum concentrations at both times (with or without AP or SRR) were higher than those required for analgesia after systemic use.[27] This finding in our study using repeated pulse administration of sufentanil epidurally agrees with similar serum concentrations produced by continuous infusion of epidural sufentanil.[24] Our results suggest that absorption into the systemic circulation may play a part in the analgesic and respiratory effects seen after epidural sufentanil, especially in the patients receiving 50–75 μg of sufentanil per dose. High serum levels of sufentanil (and possibly high CSF levels as well) may interact synergistically with other factors, such as sleep, to produce ventilatory depression. Although the EEG was not measured in this study, following thoracotomy, patients spend much of their time sleeping in the first 24 h, particularly when provided with adequate analgesia.

The results of this study suggest that, in our patient population, 30 μg of lumbar epidural sufentanil given as repeated doses for 24 h produced adequate analgesia after thoracotomy. In addition, 30 μg was associated with no significant changes in respiratory pattern and only minimal elevation of Pa_{CO_2}. Larger doses may produce severe respiratory depression, which may result in respiratory arrest. Although the onset of analgesia is very rapid, the duration of analgesia is fairly short.

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