A Randomized, Double-blind Comparison of Lumbar Epidural and Intravenous Fentanyl Infusions for Postthoracotomy Pain Relief

Analgesic, Pharmacokinetic, and Respiratory Effects

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Although epidural opioids frequently are used to provide postoperative analgesia, several articles have suggested that the analgesia after epidural fentanyl is similar to that after an equal dose of fentanyl given intravenously. To address this issue further, 29 postthoracotomy patients were studied in a randomized, double-blinded trial comparing a lumbar epidural fentanyl infusion with an intravenous fentanyl infusion for analgesia, plasma fentanyl pharmacokinetics, and respiratory effects for 20 h postoperatively. In all patients in both groups, good analgesia was achieved (pain score < 3, maximum 10) over a similar time course, although the patients receiving epidural infusion required a significantly larger fentanyl infusion dose than did the patients receiving intravenous infusion (group receiving epidural fentanyl infusion: 1.95 ± 0.45 $\mu g \cdot kg^{-1} \cdot h^{-1}$; group receiving intravenous fentanyl infusion: 1.56 ± 0.36 $\mu g \cdot kg^{-1} \cdot h^{-1}$; $P = 0.0002$). The time course for the plasma fentanyl concentrations was similar in the two groups, and plasma fentanyl concentrations were not significantly different at any sampling period (T7–T20; group receiving epidural fentanyl infusion: 1.8 ± 0.5 ng/ml; group receiving intravenous fentanyl infusion: 1.6 ± 0.6 ng/ml; $P = 0.06$). Similarly, calculated clearance values for the two groups were not significantly different (group receiving epidural fentanyl infusion: 0.95 ± 0.26 $l \cdot kg^{-1} \cdot h^{-1}$; group receiving intravenous fentanyl infusion: 0.87 ± 0.25 $l \cdot kg^{-1} \cdot h^{-1}$; $P = 0.3$). Both groups demonstrated a similar degree of mild to moderate respiratory depression postoperatively, which was assessed with continuous respiratory inductance plethysmography and sequential arterial blood gas analysis. Side effects (nausea, vomiting, pruritus) were mild and did not differ between groups. The authors conclude that lumbar epidural fentanyl infusions are equivalent to intravenous fentanyl infusions for postthoracotomy analgesia and that the mode of action of a lumbar epidural fentanyl infusion is primarily through systemic absorption. (Key words: Analgesia: postoperative. Analgesics, epidural: fentanyl. Analgesics, intravenous: fentanyl. Anesthetic techniques: epidural.)

PATIENTS undergoing thoracotomy experience severe postoperative pain and significant respiratory impairment for several days postoperatively.[1] Epidural opioids are extremely effective in providing postthoracotomy analgesia[1–3] and improving pulmonary function.[1] Additional effects of epidural opioids include pruritus, urinary retention, nausea, vomiting, and respiratory depression.[4,5] Because of its hydrophilic nature, morphine is thought to produce a greater incidence of respiratory depression than lipophilic opioids when administered by the epidural route.[5,6] This has led to increased use of short-acting, lipophilic opioids by epidural bolus injection and continuous infusion to control postthoracotomy pain. Fentanyl is used widely in this fashion and may be administered by lumbar[3,7,8] or thoracic epidural catheters.[9,10] Although epidural fentanyl has been shown to depress the ventilatory response to CO_2,[11,12] there have been few reports of clinically significant respiratory depression.[5] However, a relatively large dose is necessary when using a lumbar catheter to provide postthoracotomy analgesia,[3] and there are several reports of similar plasma concentrations achieved when intravenous and lumbar epidural fentanyl infusions were compared for postoperative pain relief.[13–16]

These observations have brought into question the mechanism of action of epidural fentanyl (*i.e.*, spinal uptake *versus* rapid systemic absorption). This study was conducted to compare the analgesic and respiratory effects

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and pharmacokinetic profiles of a lumbar epidural infusion *versus* an intravenous infusion of fentanyl for post-thoracotomy pain.

Materials and Methods

Patient Selection

Twenty-nine adult patients, ASA Physical Status 1 to 3, undergoing elective thoracotomy were studied after institutional ethics approval and written informed consent had been obtained. Exclusion criteria were age less than 18 or greater than 80 yr, weight greater than 100 kg, symptomatic coronary artery disease, congestive heart failure, poorly controlled hypertension, or significant renal, hepatic, or cerebrovascular disease.

Preoperative Evaluation

Preoperative respiratory pattern monitoring in this patient population in our institution has demonstrated abnormal respiratory patterns in many patients before thoracotomy, in some cases bordering on sleep apnea (AP).[17] To control for preexisting respiratory dysfunction, all subjects underwent a modified sleep study the night before surgery, in addition to their standard preoperative investigations. Respiratory pattern was assessed continuously with respiratory inductive plethysmography (NIMS, Miami Beach, FL) while the patients were asleep. Calibration and validation—as well as its application in previous clinical studies—have been described elsewhere.[6,18,19] Respiratory rate, episodes of slow respiratory rate (SRR = respiratory rate less than 10 breaths/min persisting for more than 5 min), and episodes of AP (AP = tidal volume of less than 100 ml for more than 15 s) were measured continuously and recorded in 5-min epochs. Patients were attended continuously by trained personnel during the entire preoperative and postoperative data-collection period. Respiratory pattern abnormalities were confirmed by analysis of real-time respiratory inductive plethysmography output and direct observation of the patient. Revalidation (using spirometric or spirobag techniques) was performed several times during the observation periods, and recalibration was instituted if error was greater than 20%. Arterial blood gases (ABGs) were drawn *via* an indwelling radial artery cannula while the patients were awake and at 2-h intervals while they were asleep.

Anesthesia

With the exception of optional vagolytic agents, the subjects received no preoperative medication. Immediately before anesthesia, an epidural catheter was inserted at the L2–3 or L3–4 interspace and its position verified by injection of a 3-ml test dose followed by 5–7 ml of 2% carbonated lidocaine. Anesthesia was induced with sodium thiopental and maintained with O_2/N_2O and halothane or isoflurane plus a nondepolarizing neuromuscular blocking agent. The trachea was intubated with either a double-lumen endotracheal tube or a single-lumen tube with bronchial blocker. At the conclusion of surgery, neuromuscular blockade was reversed with neostigmine and atropine. When the patient emerged from anesthesia and spontaneous breathing resumed, the trachea was extubated and the patient was taken to the postanesthetic care unit (PACU). During transport and throughout the postoperative period, subjects received supplemental O_2 by mask to ensure Pa_{O_2}s greater than 80 mmHg.

The hospital pharmacy assigned patients to one of two groups in a double-blind randomized fashion. Identical coded syringes of study drug and placebo were supplied by the pharmacy for each subject. Fentanyl was provided in a concentration of 10 $\mu g \cdot ml^{-1}$ for the infusion and 5 $\mu g \cdot ml^{-1}$ for bolus dosing, which has been shown in a previous study in our institution to provide good analgesia with lumbar catheters, as well as a reasonable onset time for analgesia.[5] One group received fentanyl by the epidural route and N saline intravenously (EP group), whereas the other group was given N saline by the epidural route and fentanyl intravenously (iv group). One hour after induction, *via* computerized infusion pumps (Harvard PCA Pump, Bard, Billerica, MA), both groups were given a fentanyl bolus of 1.5 $\mu g \cdot kg^{-1}$ (0.3 $ml \cdot kg^{-1}$), and a fentanyl infusion of 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (0.1 $ml \cdot kg^{-1} \cdot h^{-1}$) was begun *via* the assigned route. At the same time, an infusion of placebo (N saline) of identical volume was begun by the alternate route.

Plasma samples were collected 15, 30, and 60 min after each bolus administration, and hourly thereafter during surgery.

Postoperative Monitoring

When the patient arrived in the PACU, respiratory inductive plethysmography monitoring was started again, with repeat calibration performed as soon as the subject was awake enough to cooperate. For the purposes of data collection, arrival in the PACU was taken as time zero (T_0). ABG and plasma fentanyl samples were collected at T_0, hourly for 6 h, and then every 2 h until the end of the study, 20 h after arrival in the PACU.

Pain was assessed verbally with a numeric rating scale (0–10)[20] until the patients were recovered sufficiently to use a 10-cm visual analog scale (VAS)[21] (within the first postoperative hour). Patients had been familiarized preoperatively with both pain-rating methods. The two pain scales have been shown to yield similar results.[20] Pain assessments were made when the patient arrived in the PACU, hourly for 6 h, and then every 2 h until the end of the study. Pain ratings also were obtained in response

to spontaneous complaints of pain, which were treated as outlined below. Somnolence was recorded on a five-point scale (1: oriented and initiates conversation; 2: responds to all forms of stimulation, is well oriented but does not initiate conversation; 3: responds to verbal command and painful stimulation but is disoriented and does not initiate conversation; 4: responds to painful stimulation but not to verbal command; 5: unresponsive to painful stimulus) at the same times the VAS measurements were made.

Side effects (nausea, vomiting, pruritus) were recorded if present. All patients had indwelling urinary catheters.

Postoperative Pain Control

If patients recorded a VAS greater than 3.3 and had a somnolence score of 2 or less, an additional fentanyl bolus of 0.5 $\mu g \cdot kg^{-1}$ (0.1 $ml \cdot kg^{-1}$) was given by the prescribed route, and the infusion increased by 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (0.025 $ml \cdot kg^{-1} \cdot h^{-1}$) while similar volumes of N saline were given by the alternate route. This increase was repeated as required, at intervals of not less than 30 min. If the VAS remained greater than 3.3 and the somnolence score less than 2 after four increases, epidural catheter placement was reconfirmed with 2% lidocaine CO_2, 8–10 ml. Confirmation of the correct catheter position allowed additional bolus/infusion increases if necessary. The infusion was decreased with the same stepwise procedure if patients demonstrated increased somnolence (score greater than 3) or CO_2 retention ($Pa_{CO_2} > 55$ mmHg) in the face of adequate analgesia (*i.e.*, VAS < 3.3).

Analysis of Plasma Fentanyl Concentration

Plasma fentanyl concentrations were determined with a commercial radioimmunoassay kit[22] (Janssen Laboratories, Beerse, The Netherlands). In our laboratory, the assay is sensitive to 0.1 ng/ml, with intraassay and interassay coefficients of variation of 6.0% and 6.9%, respectively, at 1.0 ng/ml.

Pharmacokinetic Analysis

The clearance rate of fentanyl was calculated as the ratio between the dose rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$) and steady-state plasma concentration of the drug. The steady-state plasma concentration was defined by the mean of the first two successive plasma concentration measurements that differed by less than 10% after at least 8 h of infusion of an unchanged dose.

Data Analysis

All data are presented as standard error of the mean unless otherwise indicated. Demographic data were analyzed with unpaired two-tailed *t* tests for parametric variables and chi-square analysis for nonparametric variables. Somnolence was analyzed with the Kolmogorov–Smirnov test. Side effects were evaluated with chi-square analysis. VAS pain scores, episodes of AP, SRR episodes, ABGs, fentanyl infusion rates, and plasma concentration were analyzed by a two-way repeated measures analyses of variance with the use of group as the independent sample and time as the repeated-measurements factor. Significant main effects were analyzed by *post hoc* tests. Significant interaction effects were broken down into simple main effects and further analyzed by *post hoc* tests. Tukey's *post hoc* test was used for all *post hoc* tests. Pearson correlation coefficients were calculated between preoperative and postoperative measurements of episodes of AP and SRR. $P < 0.05$ was considered significant in all cases. Power analysis[23] was performed on those variables in which no significant between-group differences were detected (VAS pain score, fentanyl concentration; see Results).

Results

Demographics

Twenty-nine patients were recruited: 13 were randomized to the EP group and 16 to the iv group. All patients were studied for the full 20 h, although 1 patient in each group was excluded from postoperative ABG and plasma fentanyl analysis because of a lack of arterial access.

The two groups were equivalent in terms of gender, habitus, and particulars of surgery (table 1), as well as preoperative ABGs and respiratory variables.

Analgesia

All 13 patients in the EP group required bolus/infusion increases (mean number of increases = 4.4), whereas 10 of 14 patients in the iv group required bolus/infusion increases (mean number of increases = 4.0) (not significant [NS] for numbers of patients in each group or number of bolus/infusion increases). During the study, in 6 patients in the EP group and 5 patients in the iv group (NS), the infusion had to be decreased in a stepwise fashion only once, as described above, because of a somnolence score greater than 3 or Pa_{CO_2} greater than 55 mmHg. Despite the fentanyl dosing by the two routes intraoper-

Table 1. Patient Group Characteristics

	Intravenous Fentanyl	Epidural Fentanyl
Age (yr)	61 ± 13	59 ± 15
Male/female	8/8	9/4
Weight (kg)	69 ± 13	71 ± 11
Height (cm)	163 ± 10	168 ± 19
Duration of operation (min)	200 ± 52	203 ± 67

Values are mean ± SD. The differences are not significant.

atively, the VAS was relatively high in the early PACU period (fig. 1). There were no significant between-group differences in VAS for the entire postoperative data-collection period ($P = 0.79$; power = 0.57, *i.e.*, probability of detecting a difference in pain if a difference existed between the epidural and intravenous routes).[23] With this model of increasing fentanyl infusion in a stepwise manner every 30 min, if required, adequate analgesia (VAS < 3.3) was achieved slowly, between 4 and 6 h after T_0 for both groups (fig. 1).

Respiratory Effects

Episodes of Sleep Apnea

There was no difference in the AP rate between the two groups during the preoperative monitoring period (EP group: 1.6 ± 0.6 AP episodes/h; iv group: 1.9 ± 0.6 AP episodes/h; NS). The overall mean postoperative rate of AP episodes was 10.7 ± 1.8 AP episodes/h for the EP group and 6.3 ± 0.7 AP episodes/h for the iv group (NS). Four patients in the EP group and five patients in the iv group had a mean AP rate of less than 1 AP episode/h postoperatively, whereas four patients in the EP group and five patients in the iv group had an AP rate of greater than 10 AP episodes/h postoperatively, respectively (NS). There were significantly more within-group AP episodes in the EP group postoperatively when compared with preoperative data starting at postoperative hour 7 and concluding with the end of the study ($P = 0.04$) (fig. 2). Similarly, there were significant within-group differences between preoperative and postoperative AP rates in the iv group for the entire postoperative period ($P = 0.02$). Between postoperative hours 14 and 17, the EP group had a significantly higher AP rate than the iv group ($P = 0.001$) (fig. 2). In addition, there was no significant correlation between the preoperative AP rate and postoperative AP rate for any patient in both groups.

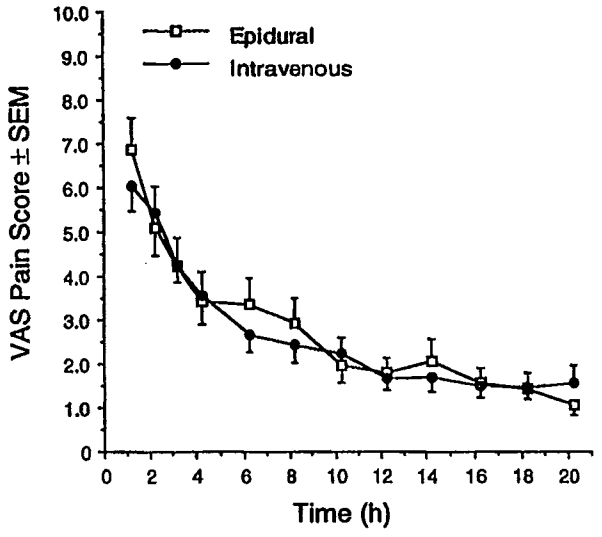


FIG. 1. Pain score (VAS) for both groups. The time course of postoperative analgesia showed no significant between-group differences.

Slow Respiratory Rate

There were no between-group differences in preoperative SRR episodes, which were uncommon in this study (EP group: 0.02 ± 0.01 SRR episodes/h; iv group: 0.4 ± 0.2 SRR episodes/h). Within-group analysis for the EP group showed a significantly higher hourly rate of SRR episodes postoperatively, from hour 10 onward ($P = 0.0002$) (fig. 3). Similarly, the iv group had a significantly higher rate of SRR episodes from hour 7 onward postoperatively ($P = 0.007$) (fig. 3). Between-group analysis demonstrated a higher rate of SRR episodes in the EP group postoperatively, although this was significant only at hour 15 ($P = 0.001$) (fig. 3).

Arterial Blood Gases

The EP and iv groups were similar in both *p*H ($P = 0.28$) and Pa_{CO_2} ($P = 0.87$) during the preoperative monitoring period (fig. 4). Both groups had a significantly decreased *p*H postoperatively for the duration of the study ($P = 0.0001$). The iv group had a significantly lower postoperative *p*H than the EP group between hours 1 and 3 ($P = 0.05$) (fig. 4). Similarly, both groups had significantly higher postoperative Pa_{CO_2}s compared with preoperative values for the entire study ($P = 0.0001$) (fig. 4). Between-group analysis showed significantly higher Pa_{CO_2}s in the iv group only at hour 1 postoperatively ($P = 0.03$) (fig. 4).

Somnolence

In general, patients scored between 0 and 2 for somnolence during the study. There was no difference in somnolence scores between the two groups at any time postoperatively.

Pharmacokinetics

Two hundred eighty-seven blood samples were collected for the plasma fentanyl assay for both groups. Infusion rates (fig. 5) and fentanyl concentrations (fig. 6) reached fairly stable levels approximately 8 h postoperatively for both groups. Between 8 and 20 h postoperatively, the mean plasma fentanyl concentration was similar at 1.8 ± 0.5 ng/ml for the EP group and 1.6 ± 0.6 ng/ml for the iv group, respectively ($P = 0.064$; power = 0.54, *i.e.*, probability of detecting a between-group difference in fentanyl concentration if a difference existed between epidural and intravenous route)[23] (fig. 6). The analysis of variance showed a significant interaction (*P*

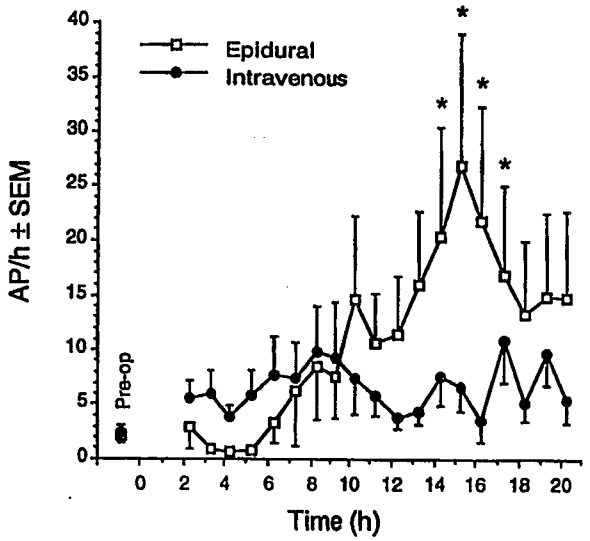


FIG. 2. Apneic episodes (Ap/h) for both groups. Significant between-group differences occurred at hours 14–17 (*$P < 0.05$, between groups).

= 0.0002) between infusion rates, with the EP group requiring a higher infusion rate ($1.95 \pm 0.45\ \mu g \cdot kg^{-1} \cdot h^{-1}$) than the iv group ($1.56 \pm 0.36\ \mu g \cdot kg^{-1} \cdot h^{-1}$) after hour 8.5 (fig. 5). The fentanyl clearance after intravenous use was $0.87 \pm 0.25\ l \cdot kg^{-1} \cdot h^{-1}$ and was not significantly different from that calculated for the EP group ($0.95 \pm 0.26\ l \cdot kg^{-1} \cdot h^{-1}$).

SIDE EFFECTS

There were no significant between-group differences in the incidence of nausea and vomiting (EP group: four cases; iv group: two cases) or pruritus (EP group: one case; iv group: three cases). All side effects were mild in nature and easily treated. All patients had indwelling urinary catheters for 24 h postoperatively.

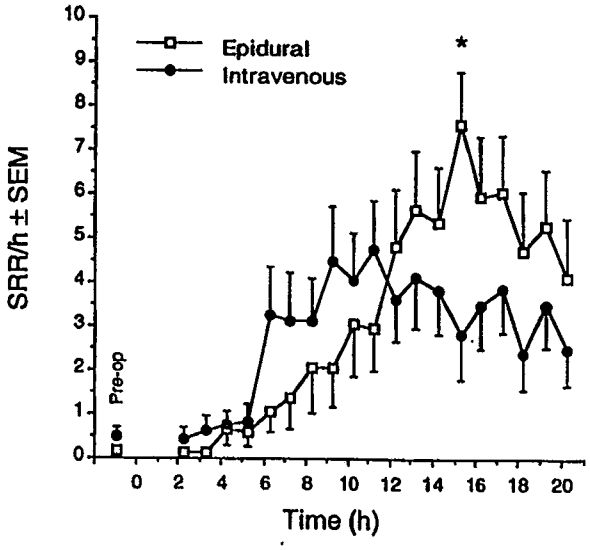
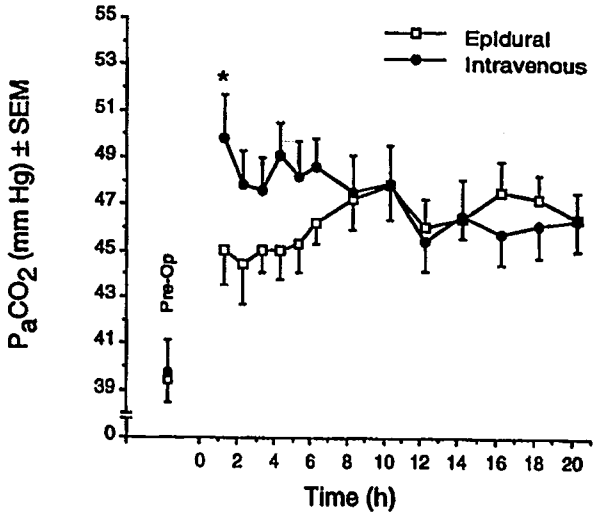


FIG. 3. Slow respiratory rate (SRR/h) for both groups. Between-group differences occurred only at hour 15 (*$P < 0.05$, between groups).



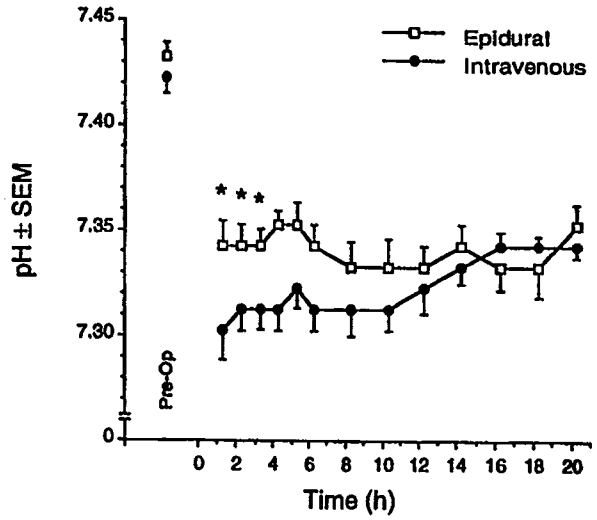


FIG. 4. ABG results postoperatively. Pa_{CO_2} was increased and *p*H decreased significantly at all times postoperatively relative to preoperative measurements, but there were only minor between-group significant differences (*$P < 0.05$, between groups).

Discussion

This study compared two administration routes for fentanyl (intravenous or lumbar epidural) when used as a postthoracotomy analgesic opioid. The study design was controlled rigidly and followed a randomized, double-blind format. With this regimen, all patients achieved high-quality analgesia, the primary end-point. The current results demonstrate that comparing fentanyl administration *via* a lumbar epidural catheter with that *via* an intra-

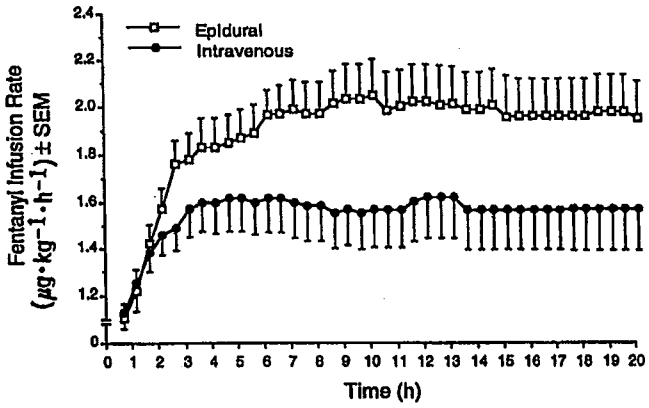


FIG. 5. Fentanyl infusion rates postoperatively. The epidural group required a significantly higher infusion rate at plateau.

venous infusion and regulating the increment/decrement of the dose in exactly the same fashion for both produced the following features: First, the analgesic profiles appeared to be similar (fig. 1), indicating that the administration route was not important for the onset and maintenance of analgesia. Second, the adherence to a 30-min interval between additional fentanyl boluses and infusion increases may have delayed the onset of high-quality analgesia for both groups in the PACU. Thus, larger bolus doses and/or larger stepwise increases in infusion rate may have shortened the onset of analgesia. Third, there were no significant between-group differences between plasma fentanyl concentrations at any sampling period during the postoperative period (fig. 6), although this required higher infusion rates for the EP group (fig. 5). Fourth, the primary adverse effect, respiratory depression, as measured by CO_2 retention and respiratory pattern abnormalities, was similar for both the iv and EP groups.

ANALGESIA

This study has demonstrated that lumbar epidural fentanyl given by bolus/infusion produces a similar analgesic profile in postthoracotomy patients as intravenous fentanyl given by the same bolus/infusion regimen but requires a significantly increased epidural dose. Several other studies, in which epidural fentanyl was given by bolus dosing alone or bolus plus infusion regimens, have demonstrated effective postthoracotomy analgesia irrespective of catheter placement at the lumbar[3,7,24] or thoracic segments.[9,10,24,25] In a retrospective study, Mackersie *et al.*[8] found lumbar epidural fentanyl infusions to be an effective analgesic regimen for blunt chest trauma resulting in multiple rib fractures.

Several controlled studies have compared intravenous with epidural fentanyl infusions for pain relief and pharmacokinetic analysis in different surgical populations.[7,10,13,14,16] In a randomized, blinded study, Loper *et al.*[14] administered fixed-dose infusions of fentanyl (100 μg/h) either epidurally (lumbar catheter) or intravenously to patients after anterior cruciate ligament repair performed while the patients were under epidural anesthesia. The fixed-dose infusions were supplemented with 50-μg doses of fentanyl, either epidurally or intravenously, when requested by the patient. There were no significant differences in pain scores at 18 h postoperatively, although other time periods were not reported. Also, there were no differences between the number of supplementary doses requested by each group or the incidence of side effects (pruritus, nausea, urinary retention). In a similar randomized, blinded study, Ellis *et al.*[13] compared lumbar epidural fentanyl infusions and intravenous infusions after cesarean sections for 24 h postoperatively. In most of the patients in the two groups, similar analgesic effects were achieved 12 h after the infusions were started, although there were three patients in the group receiving intravenous infusions who were eliminated from the study because of inadequate pain control at the highest permitted infusion rate. Glass *et al.*[16] used a double-blind crossover design to compare lumbar epidural fentanyl with intravenous fentanyl in patients after lower-extremity or abdominal surgery for 12 h postoperatively. Patients self-administered fentanyl, using patient-controlled analgesia (PCA) pumps. Sixty minutes after the procedure was finished, analgesia was equivalent in both groups and was not affected by group crossover 6 h postoperatively.

Two studies have specifically addressed patients postthoracotomy: Salomaki *et al.*[10] compared epidural (thoracic catheter) and intravenous infusions of fentanyl after thoracotomy in a randomized, double-blind trial. As in

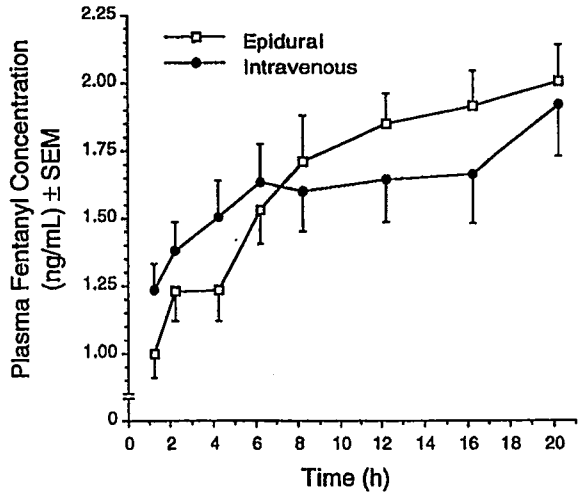


FIG. 6. Plasma fentanyl concentration postoperatively. Analgesic plasma fentanyl levels were achieved by both groups. There were no significant between-group differences.

our study, fentanyl by both routes was titrated to produce equivalent analgesia. With the use of a thoracic catheter, there were significantly lower fentanyl requirements and lower plasma fentanyl concentrations in the group receiving epidural administration. In addition, there were fewer side effects in this group. Using a randomized double-blind trial, Grant *et al.*[7] compared PCA plus infusions of fentanyl administered *via* a lumbar epidural catheter or intravenously after thoracotomy. Infusion dosing was increased to achieve maximum analgesia in all patients (*i.e.*, minimal PCA use) and then decreased once adequate analgesia was achieved. Over the 20-h postoperative data-collection period, all patients achieved high-quality analgesia with no significant between-group differences. However, fentanyl infusion rates were significantly lower in the group receiving epidural infusion.

Pharmacokinetics

Dosage Requirements

With epidural administration, it is difficult to compare dosage requirements between studies because experimental regimens differ and the amounts (if any) of preoperative or intraoperative opioid used are different; these factors also may influence postoperative analgesia. In addition, the fentanyl concentration used (and thus the volume of diluent) differs in many of the studies (*e.g.*, Loper *et al.*[14] used a fentanyl concentration of 25 $\mu g \cdot ml^{-1}$ [bolus] and 50 $\mu g \cdot ml^{-1}$ [infusion], whereas other investigators used concentrations of 10–15 $\mu g \cdot ml^{-1}$[13,7,10]).

In the two postthoracotomy controlled studies, Salomaki *et al.*[10] used an epidural fentanyl concentration of 12.5 $\mu g \cdot ml^{-1}$ and Grant *et al.*[7] used a concentration of 10 $\mu g \cdot ml^{-1}$. We used fentanyl concentrations of 5 $\mu g \cdot ml^{-1}$ for bolus dosing and 10 $\mu g \cdot ml^{-1}$ for infusion, which are similar to those used by Salomaki *et al.*[10] and Grant *et al.*[7] The steady-state lumbar epidural dosage requirements for fentanyl (1.9 $\mu g \cdot kg^{-1} \cdot h^{-1}$) observed in the current study are higher than fentanyl doses required when thoracic catheters are used after thoracic or abdominal surgery.[9,10,24] For example, the study by Salomaki *et al.*[10] demonstrated that good analgesia was achieved with thoracic catheter placement and an epidural infusion rate of 0.95 $\mu g \cdot kg^{-1} \cdot h^{-1}$, which was approximately half that required with a lumbar catheter in this study. In addition, for postoperative analgesia supplied by lumbar epidural fentanyl infusions or epidural PCA for procedures involving lumbar dermatomes (orthopedic surgery[14,16] and abdominal surgery[13,26]), lower dosages have been required. Postthoracotomy analgesia provided by lumbar epidural fentanyl administered by PCA/infusion also was associated with reduced dose requirements.[7]

The steady-state requirements for good analgesia with the intravenous infusion of fentanyl in this study (1.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were very similar to those quoted by other investigators[10,27–29] after various forms of surgery, including thoracotomy and abdominal and orthopedic procedures. However, in studies in which PCA was used alone[16] or in combination with an infusion,[7] considerably lower intravenous dose requirements were recorded.

Plasma Concentration

The results of the current study show that administration of fentanyl by the lumbar epidural or intravenous route produced identical analgesic effects and similar (no significant differences between groups) plasma fentanyl concentration curves. These results confirm findings of similar less-intensive studies by Loper *et al.*[14] in orthopedic patients and Ellis *et al.*[13] in patients after cesarean section, both of which used minimal plasma sampling data. However Ellis *et al.*[13] removed three patients in the group receiving intravenous administration because of inadequate analgesia at the maximum dosage level; retention of these patients may have resulted in higher plasma concentrations in the group receiving intravenous administration. Glass *et al.*[16] also found between-group plasma fentanyl concentrations to be similar in their study, which compared epidural PCA fentanyl with intravenous PCA fentanyl after abdominal and lower limb surgery. In contrast to observer-controlled fentanyl infusion studies, much lower dose requirements and plasma concentrations were recorded in those studies in which PCA was used.[16] The levels and time course of the plasma fentanyl concentrations found after epidural administration in this study were very similar to those observed in our earlier study of patients postthoracotomy,[8] although other reports of plasma fentanyl concentrations after epidural administration (usually as a constant infusion) have varied widely from undetectable levels to 4–5 ng/ml.[10,11,13–15] However, plasma fentanyl concentrations in our iv group were very similar to results from other studies investigating intravenous fentanyl infusions for postoperative analgesia.[10,14,27–29]

Clearance

Our values for fentanyl clearance are similar to those calculated by Duthie *et al.*,[29] Varvel *et al.*,[30] and Mclain and Hug[31] for patients undergoing a variety of surgical procedures. In addition, the clearance rate after intravenous or epidural use also was similar, indicating that the systemic bioavailability of the epidurally administered fentanyl tends to be complete, with essentially all drug reaching the systemic circulation to achieve a steady state comparable to that observed after intravenous administration.

Respiratory Depression

In this study, continuous electronic monitoring of respiratory pattern with constant attendance by a trained observer and intermittent ABG sampling was used to define respiratory depression. Mild to moderate respiratory depression occurred in both the EP and iv groups postoperatively, although the EP group had a significantly higher rate of episodes of AP and SRR in the later time periods of the study. However, the EP group had significantly lower Pa_{CO_2}s and significantly higher *p*H values early in the postoperative period. In addition, respiratory depression was increased significantly in both groups in relation to preoperative findings. Clinically significant respiratory depression rarely has been reported after epidural fentanyl.[5] Although sensitive tests of respiratory depression such as CO_2-response curves have demonstrated respiratory depression after a bolus dose of 200 μg of epidural fentanyl[12] and after an epidural bolus of 1 μg/kg followed by an infusion of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$, this was not of clinical significance. Nonetheless, clinically significant respiratory depression definitely can occur with epidural fentanyl, especially if dosage requirements are increased rapidly.[3]

The published controlled studies comparing epidural with intravenous fentanyl[7,21,25,26] had differing results regarding respiratory depression. Loper *et al.*[14] relied on hourly respiratory rate to detect respiratory depression, which may be unreliable,[5,6] but recorded no respiratory rate < 8 breaths/min in any patient. Ellis *et al.*[13] measured end-tidal CO_2 concentrations frequently during the postoperative period and reported no evidence of respiratory depression in the groups receiving epidural or intravenous administration. In contrast, Salomaki *et al.*[10] recorded a 40% incidence of SRR episodes in their group receiving intravenous administration and 15% in the group receiving epidural administration. Respiratory rate presumably was measured by direct observation, although measurement intervals were not specified clearly. In addition, the incidence of hypercapnia and severe respiratory insufficiency was significantly higher in the group receiving intravenous administration. Grant *et al.*[7] found no difference in between-group Pa_{CO_2}s or intermittent respiratory rates in their postthoracotomy study.

Clinical Significance

This study provides strong evidence that lumbar administered epidural infusions of fentanyl required for severe postoperative pain after thoracotomy act primarily *via* a systemic reabsorption route because similar analgesic, pharmacokinetic, and respiratory effects were produced when compared with the intravenous route. The study by Salomaki *et al.*[10] provided important evidence that the siting of the epidural catheter is critical for the action of epidural fentanyl. With thoracic placement, the dose requirements and plasma concentration are decreased significantly, although the plasma concentration is still high enough to contribute significantly to any analgesic effect.

It is also of interest that, when lumbar epidural fentanyl is administered by PCA and infusion for postthoracotomy analgesia, significantly lower dose requirements were seen in contrast to those in a group treated similarly by intravenous administration.[7] These findings, reported by Grant *et al.*,[7] are in direct contrast to those reported here and may represent better control or prevention of central nervous system sensitization theorized to occur in the spinal cord in response to the afferent noxious input.[32] Thus, the ability of PCA to respond much more rapidly than the fixed protocol we used may have prevented "up-regulation" of the spinal cord analgesic pathways.[33] The lack of plasma sampling in the study by Grant *et al.*,[7] however, precludes discussion of mode of action when PCA epidural fentanyl is used after thoracotomy. However, Glass *et al.*[16] provided good evidence that PCA epidural fentanyl and PCA intravenous fentanyl are equivalent when used after abdominal or orthopedic surgery. It is of note that the dose requirements and plasma concentrations in their study were decreased significantly as well. After epidural bolus injections of 1 $\mu g \cdot kg^{-1}$, fentanyl has been shown to appear in lumbar cerebrospinal fluid in quantities high enough to produce analgesia and migrate cephalad to the cervical cerebrospinal fluid.[34] However, evidence from animal experiments has indicated that lipid-soluble opioids have significantly decreased potency when given epidurally, probably because of accumulation at nonspecific binding sites in white matter.[35] This nonspecific binding of fentanyl in the spinal cord, possible fentanyl uptake by dural fat tissues, and systemic reabsorption of the drug, when fentanyl is given as an epidural infusion, are possible reasons for the significantly higher epidural dose requirement and high plasma concentrations associated with analgesia in our study.

In conclusion, the data from this study support the concept that epidural fentanyl given by an observer-controlled infusion acts primarily by systemic reabsorption to provide postoperative analgesia and, therefore, provides little advantage over an intravenous fentanyl infusion.

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