The Pharmacokinetics of Continuous Epidural Sufentanil and Bupivacaine Infusion After Thoracotomy

Vigdís Hansdóttir, MD, PhD*, Robert Woestenborghs, MS ChE†, and Gunnar Nordberg, MD, PhD*

*Departments of *Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden, and †Department of Pharmacokinetics, Janssen Research Foundation, Beerse, Belgium

In a double-blind, randomized study in patients undergoing thoracic surgery the plasma and cerebrospinal fluid (CSF) pharmacokinetics of epidural sufentanil were studied by using radioimmunoassay analysis. Sufentanil was given as an infusion (1 μg/mL) at the lumbar (Ls; $n = 11$), or thoracic (Ts; $n = 12$) level, or epidural sufentanil combined with bupivacaine (1 mg/mL) at the thoracic level (Tsb; $n = 14$). Postoperatively, the infusion was adjusted to optimize analgesia. During the infusion, the sufentanil plasma concentrations were related to the rate of epidural infusion and unrelated both to the epidural infusion regimen and to the postoperative pain scores. The elimination half-life in plasma (mean ± SEM) was 9.9 ± 1.7 h (Ls), 8.6 ± 0.7 h (Ts), and 11.7 ± 2.2 h (Tsb). The distribution volume was 15.2 ± 3.5 L/kg (Ls), 14.8 ± 2.4 L/kg (Ts), and 12.9 ± 1.2 L/kg (Tsb). Total sufentanil clearance was 17.8 ± 1.4 and 16.9 ± 2.0 mL · kg^{-1} · min^{-1} (Ls), 22.9 ± 3.5 and 20.0 ± 2.6 mL · kg^{-1} · min^{-1} (Ts), and 22.4 ± 3.0 and 14.5 ± 1.3 mL · kg^{-1} · min^{-1} (Tsb). The terminal elimination half-life of sufentanil in CSF was 7.2 ± 0.6 h. During steady state the CSF concentrations were not homogeneously distributed and they were higher than those in plasma. These pharmacokinetic findings support the concept that epidural sufentanil analgesia is optimal when administered segmentally and tailored to the surgical incision.

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Epidural opioids offer excellent postoperative analgesia. However, occasional reports of late respiratory depression (1) have indicated that epidural morphine is not altogether safe and optimal but that lipophilic opioids would offer a safer alternative for epidural administration (2).

One advantage of morphine is its enhanced potency when given epidurally as compared with the intravenous route. This property is less evident with other opioids (2). Small differences in dose efficacy and plasma concentrations after epidural and intravenous administration of, for example, fentanyl and sufentanil have been taken as evidence that these opioids act secondarily to systemic uptake rather than to the spinal medulla. This view seems inconsistent with reports that epidural fentanyl is superior after thoracotomy when administered at the thoracic rather than the lumbar level (3). Moreover, for both morphine and sufentanil the cerebrospinal fluid (CSF) concentrations are higher after epidural as compared with intravenous or intramuscular administration and for both drugs a concentration gradient is maintained between the thoracic and lumbar CSF after epidural administration (4–7). The concentration gradient within the CSF is, however, more pronounced after sufentanil than after morphine. Thus, the efficacy of epidural sufentanil in particular would depend on the extent to which it is administered in the vicinity of spinal opioid receptors involved in surgical nociceptive processing. An accurate choice of site of epidural administration in relation to the surgical incision also offers the option of combining opioids with bupivacine. The efficacy is further enhanced since fewer doses of opioid and bupivacine are required to maintain analgesia (8).

After thoracotomy, opioid analgesia is necessary for several days (9). Sufentanil analgesia is effective but short acting (10) and epidural sufentanil must therefore be repeated frequently or be given by continuous infusion. Before this approach is considered safe, it must be studied under steady state conditions both from a pharmacodynamic and pharmacokinetic point of view. Most experience with epidural sufentanil comes from bolus dose studies and only to a lesser extent from studies under steady state conditions. This applies to pharmacokinetic studies in particular.

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Address correspondence and reprint requests to Gunnar Nordberg, MD, PhD, Department of Anesthesia and Intensive Care, Sahlgrenska University Hospital.

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The aim of this study is to evaluate the pharmacokinetics in plasma and CSF of an epidural infusion of sufentanil given for postoperative pain relief in patients undergoing thoracotomy. The pharmacokinetics were studied in relation to different epidural sites of administration and the combination of sufentanil and bupivacaine. The analgesic, adverse, and ventilatory effects were evaluated as well, and the results from these studies are published elsewhere (11).

Methods

The study was approved by our ethics committee. Informed consent was obtained from every patient.

Thirty-five patients undergoing elective lateral thoracotomy and two patients undergoing elective thoracoscopy were included in the study. Apart from data relevant to this study, additional data on the patients and the study procedures are reported separately (11). All patients had pulmonary tumors except one patient with an intrathoracic goiter and another with an esophageal diverticulum. The surgical incision was in the fifth intercostal space for all thoracotomy patients except in the patient with an esophageal diverticulum, where the incision was in the seventh intercostal space. All patients were free from opioids prior to entering the study.

All patients were premedicated with oral flunitrazepam 1.5–2 mg. The patients were randomized into three groups. Eleven patients received sufentanil 1 μg/mL infusion in an epidural catheter in a lumbar interspace (L2-3 or L3-4) (Group Ls), 12 patients received sufentanil 1 μg/mL infusion in an epidural catheter in a midthoracic interspace (T5-6 or T6-7) (Group Ts), and 14 patients received an infusion of sufentanil 1 μg/mL in bupivacaine 0.1% in an epidural catheter also placed in a midthoracic interspace (Group Tsb). The epidural catheters were placed by one of three senior anesthesiologists not taking any further part in the anesthetic procedure or the postoperative assessments. The study was further blinded for the observer by placement of another catheter on the skin outside the spine. Thus, if the patient was given a thoracic epidural catheter, a second catheter not connected to any infusion was placed on the skin at the lumbar level and *vice versa*. Drapes covered both catheters and the thoracic and the lumbar positions of the catheters could not be identified. A bolus dose of 25 μg sufentanil in 0.5% bupivacaine 2.5 mL was administered through the epidural catheter. At the discretion of the anesthesiologist not knowing the specific epidural regimen, i.e., one of the authors (VH), the epidural infusion was started simultaneously with the epidural bolus dose at 4–10 mL/h and maintained throughout surgery. A radial artery catheter was inserted for blood sampling. The anesthesia was induced and maintained with propofol and less than 50% N_2O in oxygen. Orotracheal intubation was performed after muscle relaxation with pancuronium bromide 0.1 mg/kg. Apart from epidural sufentanil, no other opioids were given.

Postoperatively, the patients were observed in a high dependency area for the first 24 h and thereafter at either one of two surgical wards. Blood pressure, heart rate, respiratory rate, and sedation were monitored at regular intervals. Pain intensity at rest (VAS-R) and during function (VAS-F) was evaluated using a 10-cm visual analog scale (VAS) with end points labeled "no pain" and "worst possible pain." The epidural infusion (0–20 mL/h) was titrated depending on the analgesic effect or the occurrence of side effects. VAS-F scores less than 4 were considered as satisfactory analgesia.

Blood samples (5–10 mL) were collected on the day of surgery, i.e., at 30, 60, 120, 300, and 600 min after the sufentanil administration was started. Postoperatively, blood samples (5–10 mL) and CSF (2 mL) samples were collected daily. During epidural infusion, CSF samples were collected with separate punctures, using a 25-gauge Yale® spinal needle (Becton Dickinson, Cockeysville, MD). When the epidural infusion was to be discontinued, a catheter (external diameter 0.85 mm and deadspace 150 μL) was inserted through a 18-gauge Touhy-Flowers® needle (Hemex; Hythe, Kent, England) into the subarachnoid space at the lumbar interspace L3-4 or L4-5. Blood and CSF samples were collected through the catheter shortly before and 1, 3, 6, 9, 12, and 24 h after discontinuation of the epidural infusion. Before each CSF sample, 200 μL of CSF was discarded to compensate for the dead space in the system. Plasma and CSF samples were stored at 20°C until analyzed.

Sufentanil concentrations were determined by radioimmunoassay (RIA) after extraction as described in detail elsewhere (12). The lower limit of quantification was 0.020 ng/mL, providing that 1-mL volumes of plasma or CSF could be extracted. Intra- and interassay coefficients of variation over a sufentanil concentration range of 0.056–9.75 ng/mL were 5.1%–8.5% and 8.5%–10.5%, respectively.

Based on bolus dose studies (6), steady-state concentrations were assumed to be attained in plasma ($C_{ss\text{-}plasma}$) and CSF ($C_{ss\text{-}CSF}$) after 1 day of infusion. Clearance (CL) from plasma was calculated during steady state as the epidural infusion rate to plasma concentration ratio. The elimination half-lives of sufentanil in plasma and lumbar CSF were calculated during the terminal phase by lin-log least square regression analysis. Some patients delivered an insufficient number of samples and/or there was no linear change in the semilogarithmic plot. Half-lives could therefore not be calculated in these patients. The volume of distribution of sufentanil in plasma was

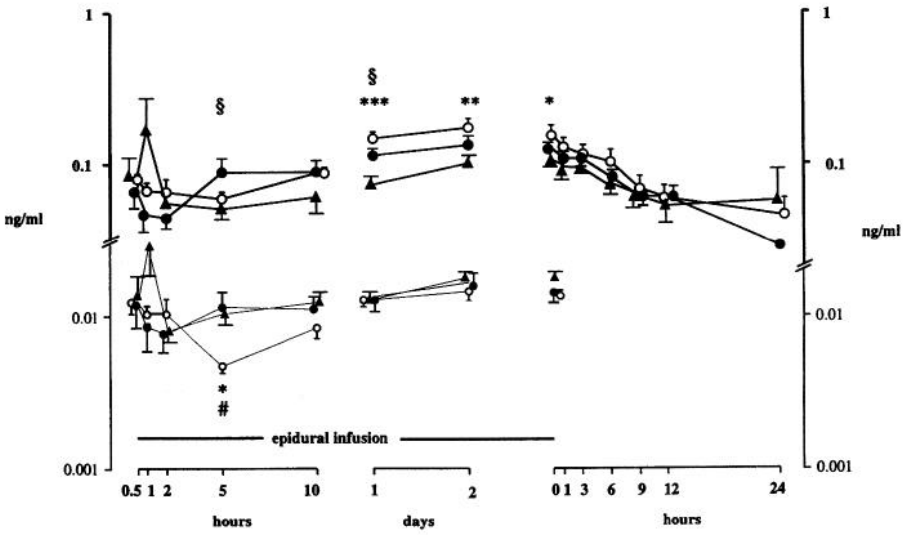

Figure 1. Shown are the plasma concentrations of sufentanil (mean ± SEM) during epidural infusion as well as after its discontinuation. The infusion was administrated at the lumbar (Ls, —○—) or thoracic level (Ts, —●—) or combined with bupivacaine (Tsb, —▲—). Shown are also the plasma concentrations when adjusted for differences in epidural infusion rates: Ls, —○—); Ts, —•—); and Tsb, —▲—). Significant differences *between Ls and Tsb, #between Ls and Ts, and §between Ts and Tsb, where $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $\#P < 0.05$, and $\S P < 0.05$.

calculated from the formula

$$V_{plasma} = CL_{plasma} \times t_{1/2}/\ln 2.$$

The availability to CSF of epidural sufentanil was calculated as $f = CL_{CSF} \times C_{ss\text{-}CSF}$/epidural infusion rate where CL_{CSF} was taken from a previous study on intrathecal sufentanil (13).

To "adjust" for the variable rate of epidural infusions, the individual ratio of the plasma and CSF sufentanil concentrations to the epidural infusion rate was calculated.

Data are presented as mean ± SEM. For between groups comparisons, analysis of variance (ANOVA) with Tukey's compromise *post-hoc* test was used. Sedation was compared with regard to plasma concentration and infusion rates using the nonparametric Mann-Whitney test. For this comparison, the patients were divided into two groups—one group with a sedation score = 0 and the other with a score > 0. A significant difference with respect to infusion or plasma concentration indicated enhanced sedation. Comparisons between analgesia and plasma concentrations were similarly performed by dividing into two groups, i.e., VAS-F ≤ 4 and VAS-F > 4. $P < 0.05$ was considered statistically significant.

Results

There were no statistically significant differences between the groups regarding general characteristics of the patients, type of operation, degree of lung resection, or perioperative anesthesia data (11). During epidural infusion, pain relief was good in all groups but pain scores (VAS-F) differed to some extent between the groups in favor of Tsb patients, and satisfactory analgesia was achieved by different rates of epidural infusion (Tsb < Ts < Ls).

A sufentanil 25-μg loading dose was sufficient to circumvent the initial period with otherwise low concentrations that follows an infusion (Figure 1). There were, however, no differences between the groups during an average 3.1, 2.7, and 2.8 h of surgery and anesthesia in the Ls, Ts, and Tsb groups, respectively (11).

At Days 1 and 2 after the start of infusion, differences between the groups in plasma concentrations (Tsb < Ts < Ls) were related to differences in infusion rates (Figure 1) and unrelated to group placement. Sedation but not pain scores were related to plasma sufentanil concentrations.

After discontinuation of epidural sufentanil infusion, the plasma concentration curves declined (Figure 1) with an average elimination half-life of 9.9, 8.6, and 12 h in the Ls, Ts, and Tsb groups, respectively (Table 1). Systemic clearance was high; on Day 2 in all groups the average was 17.2 mL/min · kg. The long half-lives were related to a high volume of distribution; on Day 2 in all groups the average was 14.2 L/kg (Table 1).

In Ls patients sufentanil could be detected more frequently and the concentrations were higher than in both Ts and Tsb patients (Figure 2). In Ls patients the CSF concentrations were on average four times those in plasma. When adjusted for differences in epidural infusion rates, lumbar CSF concentrations were similar in Ls and Tsb patients on Day 2 and about 5 and 6 times higher than those in Ts patients. The availability to CSF of lumbar epidural sufentanil was: Day 1, 0.70% ± 0.25%; and Day 2, 0.44% ± 0.12% (Table 1).

After discontinuation of the epidural infusion sufentanil concentrations in CSF could be calculated in five Ls patients (Figure 3). The half-life of lumbar CSF sufentanil during the terminal phase was 7.2 ± 0.5 h (Table 1).

Table 1. Pharmacokinetic Variables of Sufentanil in Cerebrospinal Fluid (CSF) and Plasma During and After Discontinuation of an Epidural Infusion at the Lumbar Level (Ls) and Thoracic Level (Ts), and Combined with Bupivacaine at the Thoracic Level (Tsb)

	CSF			Plasma			
						Day 2	
	Day 1, f (%)	Day 2, f (%)	$t_{1/2}$ (h)	$t_{1/2}$ (h)	Day 1, CL (mL/min · kg)	CL (mL/min · kg)	V (L/kg)
Ls							
Mean	0.71	0.44	7.24	9.9	17.8	16.9	15.2
SEM	0.25	0.12	0.6	1.7	1.1	2.0	3.5
n	8	7	5	7	11	10	7
Ts							
Mean				8.6	22.9	20.0	14.8
SEM				0.7	3.5	2.6	2.4
n				7	11	12	7
Tsb							
Mean				12	22.4	14.5	12.9
SEM				2	3.0	1.3	1.2
n				8	13	12	8

Systemic clearance (CL) was calculated as the epidural infusion rate (EIR) divided by the concentration of sufentanil in plasma on Day 1 and Day 2. $t_{1/2}$ during terminal elimination was calculated by lin-log least regression analysis. V was computed as the product of systemic clearance and the slope of the concentration curve during elimination. The availability (f) to CSF from the epidural space was calculated from the formula $f \times EIR = CL(CSF) \times Css(CSF)$, where CL(CSF) was taken from a previous study (13) on intrathecal sufentanil. Css(CSF) was the concentration of sufentanil in CSF on Days 1 and 2, respectively.

Discussion

There is very little information regarding sufentanil pharmacokinetics after epidural infusion to steady state. After intravenous infusion, the target plasma concentration of sufentanil is reported to be 0.25–1 ng/mL during surgery with N_2O/O_2 and 2–8 ng/mL with O_2 alone (14). In the present study, anesthesia was satisfactory with no more than 50% nitrous oxide and propofol apart from the epidural treatment and with no reports of awareness. Obviously, with the epidural approach these patients attained plasma concentrations far below those reported to be required to obtain analgesia during major surgery with intravenous sufentanil. In case the "target" plasma concentration after epidural administration is 0.1 ng/mL, the volume of distribution of about 1000 L calculated in the study indicates that the loading dose should be 100 μg. Initially, this would result in large and potentially toxic plasma concentrations. The loading dose used in the present study was sufficient to circumvent the initially low concentrations that follows an infusion and still not excessively large. All patients could be extubated and regain spontaneous ventilation immediately after surgery. The concentrations were well below 0.25 ng/mL, which is considered to be the upper limit for adequate postoperative ventilation (14).

In plasma, there were no pharmacokinetic differences related to the various epidural regimens used in the present study, apart from those caused by the influence of variation in the rate of epidural infusion. The minimum effective plasma concentrations of sufentanil for postoperative analgesia are reported to be in the range 0.01–0.56 ng/mL, an average of 0.024 ng/mL (15), after intravenous administration. In the present study, the concentrations of sufentanil were in that range during epidural treatment. In Ls, Ts, and Tsb patients, the sufentanil concentrations were, on average, 0.17, 0.13, and 0.10 ng/mL, respectively, on Day 2. The epidural infusion rates were adjusted to give satisfactory postoperative analgesia, and those with the lowest infusion rates (Tsb patients) had the smallest plasma concentrations but yet superior analgesia compared with both Ts and Ls patients. Consistent findings have been reported by others (16,17) and obviously the plasma levels do not reflect the concentration of sufentanil at the effector site. Plasma concentrations of sufentanil after epidural analgesia in the same range as those seen after intravenous analgesia indicate that sufentanil in plasma also contributes to analgesia after epidural administration. However, since analgesia after epidural sufentanil was unrelated to the plasma concentration level, the efficacy of epidural sufentanil is more likely to be related to its activity at spinal opioid receptors. This contrasts to side effects such as sedation, which was related to plasma concentration.

The terminal elimination half-life of sufentanil in plasma was calculated to be longer in the present study after cessation of an infusion to steady state compared with that seen after bolus dose administration (6). These variations may be caused by the differences in mode of administration and total dose given as well as by underestimation by a too-short sampling procedure after bolus administration. Consistent with its high lipophilicity, the long half-life of

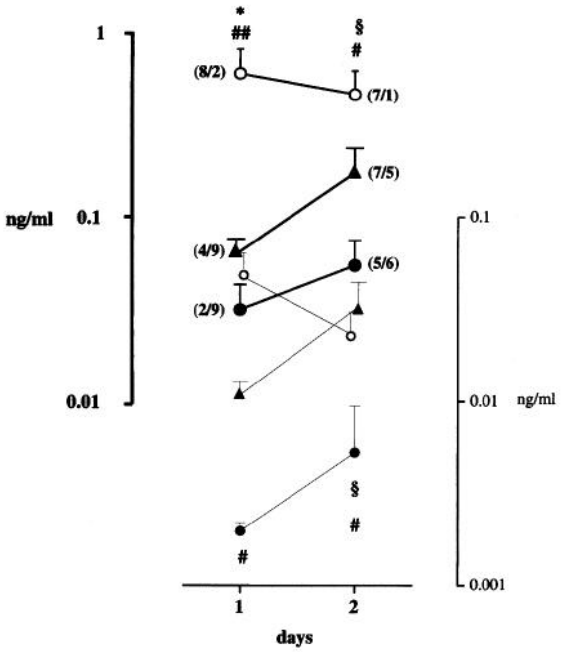

Figure 2. Shown are the cerebrospinal fluid (CSF) concentrations of sufentanil (mean ± SEM) during epidural infusion. The infusion was administrated at the lumbar (Ls, —○—) or thoracic level (Ts, —●—) or combined with bupivacaine (Tsb, —▲—). Shown also are CSF concentrations when adjusted for differences in epidural infusion rates: Ls, —○—); Ts, —•—); and Tsb, —▲—). In parentheses are shown the number of patients in whom sufentanil was either detected or not detected. Significant differences #between Ls and Ts and §between Ts and Tsb, where #$P < 0.05$ and §$P < 0.05$.

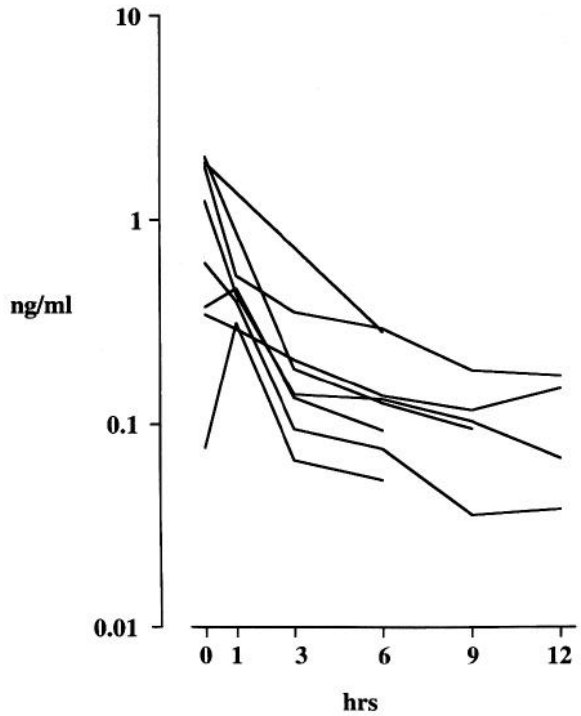

Figure 3. Shown are individual concentrations of sufentanil in lumbar cerebrospinal fluid (CSF). An epidural infusion of sufentanil was given for 2 days at the lumbar region, and the CSF was sampled shortly before and again subsequent to the discontinuation of the infusion.

sufentanil was related to a very large distribution volume. This is comparable with data found on sufentanil after large-dose intravenous administration and long sampling procedures; the elimination half-life and distribution volume were reported to be, on average, 12.1 h and 8.7 L/kg, respectively (18). Based on the terminal half-life of sufentanil calculated in the present study, it takes almost two days from the start of an infusion until steady state is reached in plasma. For safety reasons, monitoring of vital functions must be of a corresponding duration.

After epidural administration, the availability of sufentanil to CSF was calculated to be 2.7% after a bolus dose of sufentanil (4), which is to be compared with, on average, 0.7% and 0.44% after epidural infusion. The low availability derived after epidural infusion may be related to an underestimation of CSF clearance of sufentanil. The value of CSF clearance of sufentanil was from a 10-hour study during and shortly after surgery (13). In the present study, however, the availability to CSF was calculated one and two days after surgery. Recovery of a perioperative reduction in metabolism and blood flow could explain a difference in CSF clearance peri- and postsurgery and one to two days later. These figures on availability most likely reflect direct passage of sufentanil across the dura into the CSF. The availability after epidural administration seems very low, but most likely it is still higher than after intravenous or intramuscular administration (7). Lacking the option of direct passage across the dura and with a small diffusible fraction (protein bound to 93%) (19), considerably lower CSF concentrations will be seen after intravenous sufentanil than after epidural administration (7).

Sufentanil is rapidly distributed away from CSF and does not accumulate in CSF to homogeneous high concentration levels. This was illustrated by the concentration differences between Ls and Ts patients, showing that a gradient is still maintained throughout the CSF two days after the start of the epidural infusion. This observation suggests that epidural sufentanil infusion analgesia would be optimal when administered segmentally and tailored to the surgical incision. Likewise, the initial rapid decay in CSF concentrations after discontinuation of the epidural infusion in several Ls patients (Figure 3) indicates that sufentanil does not linger in CSF. Interestingly, despite lower epidural infusion rates, the Tsb patients exhibited higher CSF concentrations than the Ts patients. This might indicate an enhanced availability to CSF caused by the bupivacaine administration, but this hypothesis must be substantiated in further studies.

This study shows that during epidural infusion of sufentanil analgesia is obtained without accumulation

to excessively high concentrations, which is explained by its rapid clearance. The sufentanil concentrations are still higher in CSF than in plasma, and they are not homogeneously distributed within the CSF despite two days of epidural infusion. The terminal elimination is longer than that reported previously, and steady state conditions are not reached until about two days after the start or change of an infusion. Monitoring of these patients should therefore be organized accordingly.

References

1. Glynn C, Mather L, Cousins M, et al. Spinal narcotics and respiratory depression. Lancet 1979;2:356–7.
2. Chrubasik J, Chrubasik S, Martin E. The ideal epidural opioid—fact or fantasy. Eur J Anaesthesiol 1993;10:79–100.
3. Salomäki T, Laitinen J, Nuutinen L. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 1991;75:790–5.
4. Nordberg G, Borg L, Hedner T, et al. CSF and plasma pharmacokinetics of intramuscular morphine. Eur J Clin Pharmacol 1985;27:677–81.
5. Nordberg G, Hansdottir V, Kvist L, et al. Pharmacokinetics of different epidural sites of morphine administration. Eur J Pharmacol 1987;33:499–504.
6. Hansdóttir V, Woestenborghs R, Nordberg G. The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. Anesth Analg 1995;80: 724–9.
7. Taverne RH, Ionescu TI, Nuyten ST. Comparative absorption and distribution pharmacokinetics of intravenous and epidural sufentanil for major abdominal surgery. Clin Pharmacokinet 1992;23:231–7.
8. Mourisse J, Hasenbos MA, Gielen MJ, et al. Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain. Acta Anaesthesiol Scand 1992;36:70–4.
9. Kavanagh B, Katz J, Sandler A. Pain control after thoracic surgery. Anesthesiology 1994;81:737–59.
10. Auwera DVd, Verborgh C, Camu F. Analgesic and cardiorespiratory effects of sufentanil and morphine in humans. Anesth Analg 1987;66:999–1003.
11. Hansdóttir V, Bake B, Nordberg G. The analgesic efficacy and adverse effects of continuous epidural sufentanil and bupivacaine infusion after thoracoctomy. Anesth Analg 1996;83: 394–400.
12. Woestenborghs R, Timmerman P, Cornelissen M-L, et al. Assay methods for sufentanil in plasma: radioimmunoassay versus gas chromatography-mass spectrometry. Anesthesiology 1994; 80:666–70.
13. Hansdóttir V, Hedner T, Woestenborghs R, et al. The CSF and plasma pharmacokinetics of sufentanil after intrathecal administration. Anesthesiology 1991;74:264–9.
14. Shafer S, Varvel J. Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 1991;74:53–63.
15. Lehmann K, Gerhard A, Horrichs-Haermeyer G, et al. Postoperative patient-controlled analgesia with sufentanil: analgesic efficacy and minimum effective concentrations. Acta Anaesthesiol Scand 1991;35:221–6.
16. Deleted in proof.
17. Harbers JB, Hasenbos MA, Gort C, et al. Ventilatory function and continuous high thoracic epidural administration of bupivacaine with sufentanil intravenously or epidurally: a double-blind comparison. Reg Anesth 1991;16:65–71.
18. Hudson R, Bergström R, Thomson I, et al. Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. Anesthesiology 1989;70:426–31.
19. Meuldermans W, Hurkmans R, Heykants J. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn Ther 1982;257:4–19.