ORIGINAL RESEARCH ARTICLE

Clin. Pharmacokinet. 23 (3): 231-237, 1992
0312-5963/92/0009-0231/$03.50/0

CPK1 207

Comparative Absorption and Distribution Pharmacokinetics of Intravenous and Epidural Sufentanil for Major Abdominal Surgery

René H.T. Taverne, Traian I. Ionescu and *Sebastiaan T.M. Nuyten*
Institute for Anaesthesiology, Utrecht University Hospital, Utrecht, and Department of Clinical Research, Janssen Pharmaceutica B.V., Tilburg, The Netherlands

Summary The pharmacokinetics of absorption and distribution of a single bolus dose of sufentanil 150μg for major abdominal surgery were compared in 20 patients after random intravenous or epidural administration. Samples of plasma and cerebrospinal fluid were taken at regular intervals from time zero to 180 min after injection and at the time of tracheal extubation (3.43 to 12.66h). Sufentanil was analysed by radioimmunoassay. The area under the concentration-time curve (AUC) from zero to 1h, 2h, 3h, tracheal extubation and infinity, the absorption and distribution half-lives, maximum plasma and CSF concentrations, time to the peak concentration of sufentanil, and the fraction of sufentanil that reached the central circulation after epidural administration were assessed. Except in the first sample, plasma concentrations of sufentanil were comparable between the 2 groups. The initial transfer of sufentanil from the epidural space to the systemic circulation appeared to be very rapid. Explanations for this phenomenon are given. In only 3 patients could an uptake of sufentanil from the systemic circulation into the CSF be demonstrated. The transfer of sufentanil from the epidural space into the CSF is slower than the transfer into the plasma and it varied interindividually.

When sufentanil was first introduced in clinical anaesthesia in the 1970s, a new potent opioid was added to the arsenal of synthetic analgesics. In many publications the use of sufentanil via the intravenous route for perioperative analgesia was recommended (Bovill et al. 1984; Davis et al. 1987; Monk et al. 1988). In the following years papers were published about alternative routes, e.g. epidural and intrathecal administration of sufentanil for postoperative, obstetrical or chronic pain relief (Hasenbos et al. 1988; Hudson et al. 1989; Koren et al. 1989; Leicht et al. 1990; Rosen et al. 1988; Rosseel et al. 1988; Schwartz et al. 1989). However there are few publications about the investigation and comparison of the pharmacokinetics of a single dose of intravenous, epidural or intrathecal sufentanil, used to treat acute perioperative pain.

The purpose of this pilot study is to compare some pharmacokinetic parameters of a single intravenous and epidural sufentanil injection for major abdominal surgery.

Material and Methods

The study was approved by the local Hospital Ethical Committee. Informed consent was obtained from 20 patients scheduled for elective major abdominal surgery (abdominal aortoiliac desobliterative surgery, abdominal tumour extirpation), ASA 1 to 3, with no neurological,

cardiac or hepatic disorders. The patients were randomly divided into 2 groups of 10 patients, 1 group receiving intravenous sufentanil (IVS), the other receiving sufentanil epidurally (ES). No patient received opioids before the study. Premedication consisted of promethazine 25mg or midazolam 5mg administered 30 to 40 min before surgery.

On arrival in the operating theatre an intravenous drip and a radial artery cannula were inserted and the ECG lead V5 was monitored continuously. In all patients an intrathecal catheter (Portex, 18G) was introduced at the level L3 to L4 (tip 2cm cranially) for cerebrospinal fluid (CSF) sampling. An epidural catheter (Portex, 18G) at the level T12 to L1 was inserted in the patients in the epidural group. Depending on the operation, additional haemodynamic monitoring devices (central venous pressure, pulmonary artery occlusion catheter) were used.

General anaesthesia was induced with midazolam 0.1 mg/kg and vecuronium 0.1 to 0.15 mg/kg. Orotracheal intubation was performed and controlled ventilation was adjusted to maintain an end-tidal CO_2 concentration between 3.5 to 4%. Anaesthesia was continued with N_2O/O_2 1 : 1 and increments of midazolam and vecuronium.

Sufentanil 150μg (Janssen Pharmaceutica, 1ml = 50μg) was administered intravenously or epidurally 5 to 10 min before the skin incision. Arterial blood and CSF were sampled at time intervals of 0, 2, 15, 30, 45, 60, 90, 120, 150, 180 min after sufentanil administration and at the time of tracheal extubation. This last sampling period varied in the IVS group from 3.43 to 8.5h and in the ES group from 3.91 to 12.66h. Blood was collected in plastic tubes containing lithium heparin and centrifuged at 1000g for 10 min. The supernatant plasma and CSF samples were frozen at −40°C until analysed. Sufentanil in the plasma and CSF were measured by radioimmunoassay (RIA) using a commercial kit supplied by Janssen Pharmaceutica. The detection limit of the assay was 0.02 μg/L for plasma and 0.05 μg/L for CSF. These limits were assessed by internal double verification. The intra- and interassay coefficients of variation were on average 5.1 and 6.2% over the range of 0.05 to 4ng per test tube. All patients were catheterised to measure the urinary production. Glucosel/saline or Hartmann solution 0.010 to 0.015 L/kg/h was administered throughout the operation. Blood loss was accurately assessed and replaced by blood and fresh frozen plasma. All infusion fluids were warmed to 36°C. Blood gas measurements were taken at regularly intervals and acid/base balance was maintained. Body temperature was maintained by a warmed mattress.

Table I. Mean (± SD) patient demographic data

Parameter	Intravenous (n = 10)	Epidural (n = 10)
Gender	6F, 4M	4F, 6M
Age (y)	58 ± 13.9	63 ± 8.7
Weight (kg)	66 ± 8.8	75 ± 13.8
Height (cm)	166 ± 6.7	171 ± 7.0
Surgical procedure	AAIS (1) ATE (9)	AAIS (4) ATE (6)

Abbreviations: F = female; M = male; AAIS = abdominal aortoiliac surgery; ATE = abdominal tumour extirpation.

The area under the concentration-time curve (AUC) from time zero to 1h, 2h, 3h and tracheal extubation (TE) were calculated by trapezoidal rule (Gibaldi & Perrier 1982; Rowland & Tozer 1980) and then extrapolated to infinity ($AUC_{0-\infty}$). A curve-stripping statistical analysis of plasma and CSF concentrations using the JANA program (Dunne 1985) was used to fit the exponential terms. On this basis, a 2-compartment model with first-order input and output was used for plasma and CSF pharmacokinetic parameters. The absorption half-life ($t_{1/2\alpha}$), distribution half-life ($t_{1/2\beta}$), maximum plasma and CSF concentrations ($C_{p,max}$, $C_{csf,max}$) and the time to reach C_{max} levels ($t_{p,max}$, $t_{csf,max}$) for sufentanil were obtained from the nonlinear least squares regression program, NONLIN (Metzler et al. 1974).

The fraction of sufentanil (F) that reached the central circulation after epidural administration at 1h, 2h, 3h, TE and at $AUC_{0-\infty}$ was calculated from the formula:

$$F = (AUC_{ES} \times Dose_{IV})/(AUC_{IV} \times Dose_{ES})$$

where F is based on comparisons of mean AUC_{ES} and AUC_{IV}.

The duration of analgesia was defined as the time between the abdominal incision and the patient's request for postoperative pain relief. The maintenance of normal blood gases (values within physiological ranges) for a period of at least 30 min during postoperative spontaneous respiration was taken as the criterion for tracheal extubation.

Statistics

A student's t-test was used to compare between the 2 groups with regard to gender, age, weight, height and plasma concentrations. Significance was taken to be $p < 0.05$.

Results

Table I shows the patient data. There were no significant differences in gender, age, weight, and height between the groups.

Plasma Concentrations and Pharmacokinetics

A biexponential function could be fitted to the plasma concentrations (C_p) of sufentanil for each patient after intravenous, and a bi- and triexponential curve after epidural administration (figs. 1 and 2). The C_p during the first 0.03h after sufentanil administration were higher in the IVS group

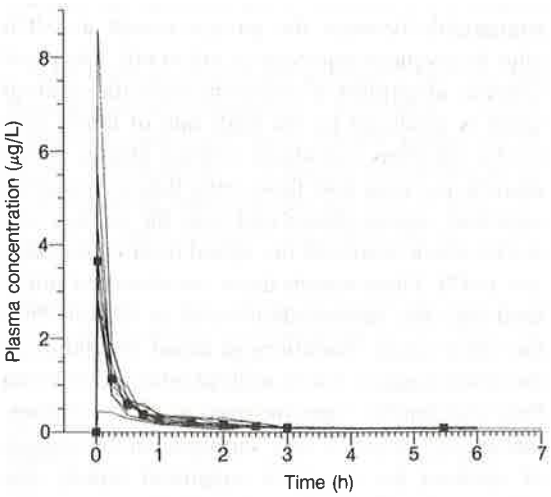

Fig. 1. Plasma concentrations of sufentanil after intravenous administration. ■ = mean value.

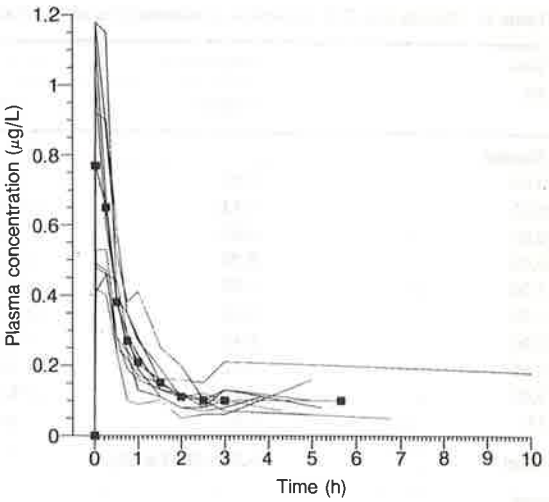

Fig. 2. Plasma concentrations of sufentanil after epidural administration. ■ = mean value.

than in the ES group (table II). Thereafter the C_p in the IVS group were comparable with those in the ES group at any given time. The sufentanil mean $C_{p,max}$ in the ES group was 0.80 ± 0.32 μg/L. The mean $t_{p,max}$ in the ES group was 0.06 ± 0.05h. The systemic $t_{1/2\alpha}$ after ES was 0.01 ± 0.01h (table III). The plasma sufentanil $t_{1/2\beta}$ after intravenous administration was 0.25 ± 0.18h and after ES it was 0.62 ± 0.18h (table III).

Table IV shows the plasma $AUC_{0\text{-}1h}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}3h}$ and $AUC_{0\text{-}TE}$ after intravenous and epidural injection. The $AUC_{0\text{-}\infty}$ was not significantly different between the groups. The fraction of sufentanil that reached the systemic circulation after epidural administration was 46% at 1h, 51% at 2h, 55% at 3h and 73% at tracheal extubation.

CSF Concentrations and Pharmacokinetics

Bi- and triexponential curves fitted the CSF concentrations of sufentanil (C_{csf}) after intravenous and epidural administration, respectively. The sufentanil concentrations in CSF after intravenous administration were below the detection limit in 7 patients at all times (table II). In the other 3 patients the C_{csf} varied, with a mean of 0.33 ± 0.42 μg/L. The $t_{csf,max}$ in the IVS group could not be evalu-

Table II. Plasma and CSF sufentanil concentrations after intravenous and epidural administration (μg/L; median and range)

Time (h)	Intravenous		Epidural	
	median	range	median	range
Plasma				
0.03	3.08	0.44-6.87	0.56	0.44-1.18
0.25	1.11	0.42-1.84	0.53	0.40-1.55
0.50	0.67	0.29-0.99	0.24	0.20-1.18
0.75	0.36	0.23-0.62	0.24	0.10-0.76
1.00	0.29	0.16-0.39	0.19	0.09-0.50
1.50	0.19	0.10-0.33	0.14	0.10-0.33
2.00	0.16	0.05-0.31	0.11	0.05-0.32
2.50	0.12	0.09-0.21	0.10	0.06-0.24
3.00	0.10	0.07-0.11	0.10	0.06-0.26
TE	0.07	0.05-0.11	0.09	0.06-0.17
Total	**5.96h (3.43-8.50)**		**5.00h (3.91-12.66)**	
CSF				
0.03	0.36	BDL-0.38	0.05	0.05-21
0.25	0.33	BDL-0.50	0.26	0.05-20
0.50	0.19	BDL-0.42	2.61	0.12-22
0.75	0.16	BDL-0.24	1.63	0.20-16
1.00	0.16	BDL-0.27	2.45	0.18-20
1.50	0.12	BDL-0.21	1.29	0.19-12.5
2.00	0.16	BDL-0.19	0.82	0.19-9
2.50	0.11	BDL-0.12	0.56	0.16-6.2
3.00	0.10	BDL-0.10	0.53	0.15-4.8
TE	0.07	BDL-0.10	0.26	0.05-1.29
Total	**5.96h (3.43-8.50)**		**5.00h (3.91-12.66)**	

Abbreviations: TE = tracheal extubation; BDL = below detection limit; Total = total time between intubation and extubation.

ated because it varied greatly. The $t_{1/2\beta}$ of sufentanil in these 3 patients was 0.82 ± 0.17h (table III).

The C_{csf} after ES increased gradually until the $C_{csf,max}$ of 5.04 ± 6.93 μg/L occurred at 0.72 ± 0.68h (fig. 3). After epidural administration, the $t_{1/2\alpha}$ of CSF sufentanil was 1.34 ± 1.86h and the $t_{1/2\beta}$ of CSF sufentanil was 1.04 ± 0.78h (table III).

Table V shows data (mean ± SD) for the duration of the surgical procedure, the period of analgesia, the beginning of spontaneous respiration, the blood loss, the urinary output and certain complications.

Discussion

Plasma Concentrations and Pharmacokinetics

The transfer of sufentanil from the epidural space to the systemic circulation appeared to be very rapid. The plasma concentrations seem to be comparable between the groups, except at 0.03h after intravenous injection of sufentanil. The rapid systemic absorption of sufentanil from the epidural space is produced by the high rate of blood flow in the valveless extradural venous plexus, which absorbs the drug and flows into Batson's internal vertebral venous plexus and into the venous networks which surround the spinal dura mater (Batson 1957). These vessels drain the absorbed sufentanil into the basivertebral veins or directly into the venae cavae. Variations in blood circulation in the epidural space due to individual epidural blood flow and lumbar vasoconstriction during abdominal surgery, together with variations in the amount of epidural fat, in which sufentanil rapidly dissolves and is firmly bound, probably account for interindividual C_p variations.

Table III. Plasma and CSF pharmacokinetics of 150μg sufentanil injected intravenously or epidurally for major abdominal surgery

Pt. no.	Intravenous		Epidural		
	AUC (μg/L · h)	$t_{½\beta}$ (h)	AUC (μg/L · h)	$t_{½\alpha}$ (h)	$t_{½\beta}$ (h)
Plasma					
1	1.63	0.14	0.90	0.005	0.44
2	1.60	0.19	0.64	0.01	0.49
3	1.62	0.21	0.66	0.008	0.71
4	1.38	0.20	0.65	0.01	0.68
5	1.19	0.14	1.08	0.004	0.45
6	1.47	0.14	2.27	0.004	0.94
7	1.35	0.29	0.60	0.01	0.53
8	0.72	0.76	1.09	0.005	0.74
9	1.70	0.31	2.25	0.04	0.82
10	2.36	0.15	0.71	0.003	0.35
Mean ± SD	1.50 ± 0.40	0.25 ± 0.18	1.09 ± 0.61	0.01 ± 0.01	0.62 ± 0.18
CSF					
1	BDL	BDL	3.79	0.02	0.53
2	BDL	BDL	4.60	0.06	0.85
3	1.17	1.06	3.14	0.06	0.47
4	BDL	BDL	2.01	4.29	0.24
5	0.79	0.74	20.60	0.82	1.43
6	BDL	BDL	3.07	5.40	0.57
7	BDL	BDL	1.93	2.06	0.22
8	BDL	BDL	21.27	0.42	1.96
9	BDL	BDL	51.34	0.01	1.39
10	0.64	0.66	16.86	0.26	2.72
Mean ± SD	0.33 ± 0.42	0.82 ± 0.17	12.86 ± 14.85	1.34 ± 1.86	1.04 ± 0.78

Abbreviations: TE = tracheal extubation; BDL = below detection limit in 7 patients; AUC = area under the concentration-time curve; $t_{½\beta}$ = distribution half-life; $t_{½\alpha}$ = absorption half-life.

The fraction of epidural sufentanil that reached the systemic circulation was low 1h after injection. It increased gradually up to 73% at tracheal extubation. Sufentanil is very rapidly transferred to the systemic blood, where it does not remain long. The $t_{½\beta}$ shows that sufentanil also leaves the circulating blood rapidly. However, epidural sufentanil leaves the plasma more slowly than after intravenous administration.

The $t_{p,max}$ after epidural sufentanil was shorter than that reported by Nordberg et al. (1988), who injected sufentanil 75μg epidurally in 10ml saline

Table IV. Mean (± SD) fraction of sufentanil that reached the central circulation after epidural administration

	AUC_{0-1} (μg/L · h)	AUC_{0-2} (μg/L · h)	AUC_{0-3} (μg/L · h)	AUC_{0-TE} (μg/L · h)	$AUC_{0-\infty}$ (μg/L · h)
Intravenous	1.06 ± 0.41	1.27 ± 0.43	1.39 ± 0.43	1.50 ± 0.40	1.78 ± 0.52
Epidural	0.48 ± 0.21	0.65 ± 0.28	0.76 ± 0.33	1.09 ± 0.61	1.43 ± 0.62
Fraction	46%	51%	55%	73%	

Abbreviation: AUC_x = area under the concentration-time curve over the period of *x* hours; TE = tracheal extubation.

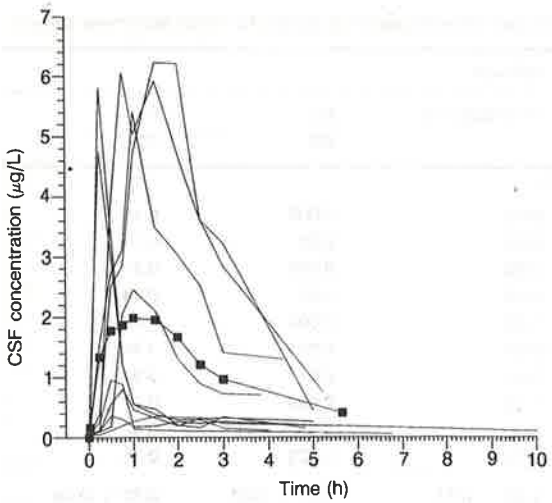

Fig. 3. CSF concentrations of sufentanil after epidural administration. ■ = mean value.

in surgical patients. This can be explained by the difference in the volume injected epidurally. We assume that when injected epidurally, a larger volume may cause a greater surface area of epidural fat to bind a highly lipophilic opioid than occurs with a smaller volume. The resorption and distribution of different volumes of analgesics injected into the epidural space are not yet thoroughly studied.

CSF Concentrations and Pharmacokinetics

The transfer of sufentanil from the systemic circulation into the CSF and the pharmacokinetics were impossible to calculate in 7 patients.

The CSF absorption of sufentanil after epidural injection was rapid in most cases, but great individual variations were recorded in the transfer of sufentanil from the epidural space. This could be expected to take longer in patients with a large volume of epidural fat and to be very short in patients in whom sufentanil was injected around epidural arachnoid granulations through which a large amount of the dose could rapidly reach the CSF. The amount of epidural sufentanil absorbed through arachnoid granulations after epidural administration is variable. Some of the arachnoid granulations protrude into the dura or even lie in the epidural space. Thus, part of the sufentanil dose can easily diffuse into the CSF during the process of administration. The distribution of sufentanil from the CSF differed individually, due to the following factors:

1. The absorption rate of sufentanil by the spinal cord, where it is tightly bound to the opioid receptors, is variable. An unknown amount of sufentanil may cross the extracellular space of the spinal cord to bind nonspecifically to proteins and lipids, since there is free communication between the CSF and the interstitial space in the spinal cord (Cousins &

Table V. Mean (± SD) clinical data of intravenous and epidural sufentanil anaesthesia for major abdominal surgery

Parameter	Epidural	Intravenous	Difference
Duration of surgery (min)	216 ± 86.2	149 ± 33.4	–*
Analgesia (min)	438 ± 147.9	294 ± 129.1	–**
Spontaneous respiration (min after administration)	275 ± 102.9	232 ± 43.8	NS
Blood loss (ml)	1434 ± 867.6	1246 ± 1004	NS
Urine production (ml)	687 ± 566.9	436 ± 275.9	NS
Complications	1 central anticholinergic syndrome 1 arterial hypertension 1 postoperative atrial fibrillation	5 arterial hypotension 2 arterial hypertension 1 tachycardia 3 nausea 1 postoperative bleeding	

Statistically significant difference between the groups: * = $p < 0.007$; ** = $p < 0.003$.

Bridenbaugh 1988). Free sufentanil in the CSF, transferred to the Virchow-Robin spaces in the spinal cord, is probably slowly taken up into the systemic circulation.

2. Systemic transfer. Sufentanil behaves as a free form in the protein-free CSF, regardless of the route of administration. The shorter presence of sufentanil in the CSF than that of morphine indicates that the CSF does not act as a reservoir, as is the case with intrathecal morphine (Ionescu et al. 1989).

In conclusion, the passage of sufentanil into the systemic circulation after epidural injection appears to be rapid. A longer plasma $t_{1/2\beta}$ of the drug after epidural injection than after intravenous injection appears to be caused by slow plasma transfer from the epidural and arachnoid spaces. Following intravenous injection, the sufentanil concentrations in CSF were below the detection limit in most cases. The absorption of sufentanil into the CSF after epidural administration is slow. The distribution of sufentanil in the CSF varies interindividually.

Clinical Implications

A single intravenous bolus of sufentanil for producing surgical analgesia seems to be less sufficient than a single epidural bolus. Plasma concentrations of sufentanil decrease rapidly because of its extravascular distribution where it binds firmly to the nonspecific receptors. A small amount of sufentanil penetrates the central nervous system to interact with the opioid receptors and exert its analgesic effect. The lumbar CSF concentrations are likely to induce and maintain a stable spinal surgical analgesia. The initial C_p could produce supraspinal analgesia for only a short period of time after intravenous injection. In contrast, a single epidural sufentanil bolus seems to be sufficient to produce stable surgical analgesia because of its rapid and constant plasma and CSF absorption and distribution. The epidural space acts as a reservoir. Intermittent or continuous intravenous administration of sufentanil, techniques that are frequently used in clinical anaesthesia, are not able to provide a steady, long and profound analgesia for major surgery (Philbin et al. 1990), because of the same pharmacokinetic occurrence. Thus, further pharmacodynamic and pharmacokinetic studies of epidural and spinal sufentanil appear to be warranted.

References

Batson OV. The vertebral vein system. American Journal of Roentgenology 78: 195-212, 1957

Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. Anesthesiology 61: 502-506, 1984

Cousins MJ, Bridenbaugh PO. Neural blockade in clinical anaesthesia and management of pain, 2nd ed., pp. 215-220, J.P. Lippincott Company, Philadelphia, 1988

Davis N, Cook DR, Stiller RL, Davin-Robinson KA. Pharmacodynamics of high dose sufentanil in infants and children undergoing cardiac surgery. Anaesthesia and Analgesia 66: 203-208, 1987

Dunne A. JANA: a new iterative poly-exponential curve stripping program. Computer Methods and Programs in Biomedicine 20: 269-275, 1985

Gibaldi M, Perrier D. Pharmacokinetics, Drugs and the pharmaceutical sciences, Vol. 15, 2nd ed., Marcel Dekker Inc., New York, 1982

Hasenbos MA, Gielen MJ, Bos J, Tielbeek E, Stanton-Hicks MD. High thoracic epidural sufentanil for post-thoracotomy pain: influence of epinephrine as an adjuvant – a double blind study. Anesthesiology 69: 1017-1022, 1988

Hudson RJ, Bergstrom RG, Thomson IR, Sabourin MA, Rosenbloom M. Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. Anesthesiology 70: 426-431, 1989

Ionescu TI, Taverne RHT, Drost RH, Roelofs JMM, Winckers EKA. Epidural morphine anaesthesia for abdominal aortic surgery: pharmacokinetics. Regional Anaesthesia 14: 109-114, 1989

Koren G, Sandler AN, Klein J, Whiting WC, Lau LC. Relationship between the pharmacokinetics and the analgesic and respiratory pharmacodynamics of epidural sufentanil. Clinical Pharmacology and Therapeutics 46: 458-62, 1989

Leicht CH, Kelleher AJ, Robinson DE, Dickerson SE. Prolongation of postoperative epidural sufentanil analgesia with epinephrine. Anaesthesia and Analgesia 70: 323-325, 1990

Metzler CM, Elfring GL, McEwen AJ. A User's manual for NONLIN and associated programs, Upjohn Company, Kalamazoo, 1974

Monk JP, Beresford R, Ward A. Sufentanil: a review of its pharmacological properties and therapeutic use. Drugs 36: 286-313, 1988

Nordberg G, Hedner T, Mellstrand T. Sufentanil pharmacokinetics in plasma and CSF following epidural administration. Clinical Pharmacology and Therapeutics 43: 138, 1988

Philbin DM, Roscow CE, Schneider RC, Koski G, D'Ambra MN. Fentanyl and sufentanyl anesthesia revisited: how much is enough? Anesthesiology 73: 5-11, 1990

Rosen MA, Dailey PA, Hughes SC, Leicht CH, Shnider SM. Epidural sufentanil for postoperative analgesia after cesarean section. Anesthesiology 68: 448-54, 1988

Rosseel PM, v.d. Broek WG, Boer EC, Prakash D. Epidural sufentanil for intra- and postoperative analgesia in thoracic surgery: a comparative study with intravenous sufentanil. Acta Anaesthesiologica Scandinavica 32: 193-198, 1988

Rowland M, Tozer TN. Clinical Pharmacokinetics, concepts and applications, Lea and Febiger, Philadelphia, 1980

Schwartz AE, Matteo RS, Ornstein E, Young WL, Thornhill M. Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. British Journal of Anaesthesia 63: 385-388, 1989

Correspondence and reprints: Dr *René H.T. Taverne*, Institute of Anesthesiology, Utrecht University Hospital, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.