Br J clin Pharmac 1994; **38**: 369–372

Pharmacokinetics and effects on intracranial pressure of sufentanil in head trauma patients

J. SCHOLZ[1], H. BAUSE[1], M. SCHULZ[2], U. KLOTZ[3], D. R. KRISHNA[3], S. POHL[1] & J. SCHULTE AM ESCH[1]
[1]Department of Anaesthesiology, University of Hamburg, University Hospital Eppendorf, D-20246 Hamburg,
[2]Drug Information Centre, Federal Union of German Associations of Pharmacists (ABDA), D-65760 Eschborn and
[3]Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, D-70376 Stuttgart, Germany

Ten patients with head trauma received an intravenous bolus of sufentanil (2 μg kg^{-1}) followed at 30 min by infusion of sufentanil (median 150 μg h^{-1}) and midazolam (median 9.0 mg h^{-1}) over 48 h. Median (range) values of pharmacokinetic parameters for sufentanil were: $t_{1/2,z}$ = 16 (7–49) h; CL = 1215 (519–2550) ml min^{-1}; CL_R = 7 (2–38) ml min^{-1}; V_{ss} = 10.0 (6.8–24.2) l kg^{-1}. Decreases in intracranial pressure (ICP) (from 16.1 ± 1.7 to 10.8 ± 1.3 mm Hg; $P < 0.05$) and mean arterial blood pressure (MAP) (from 85.5 ± 3.9 to 80.2 ± 4.9 mm Hg; $P < 0.05$) were observed within 15 min of the bolus injection of sufentanil and remained unchanged thereafter. Thus, cerebral perfusion pressure (CPP = MAP-ICP) was stable.

Keywords sufentanil pharmacokinetics intracranial pressure midazolam opioid

Introduction

The pharmacokinetics of sufentanil in intensive care patients have not been documented in detail [1]. Although opioids are often administered to patients with severe head trauma, the effects of such drugs on cerebral haemodynamics and intracranial pressure (ICP) are controversial. Sufentanil has been reported to increase cerebral blood flow (CBF) and ICP in man and dogs [2–4]. In contrast, other studies in humans, rats and dogs indicate that sufentanil administration is associated with either no change or a decrease in CBF and ICP [5–8].

The aims of the present study were to describe the steady state pharmacokinetics of sufentanil and to assess its effects on ICP in patients with elevated ICP following brain injury.

This work was presented in part at the thirty-fourth Spring Meeting of the German Society of Pharmacology and Toxicology, Mainz, Germany, March 1993.

Methods

After obtaining institutional ethics review board approval and informed consent from family members, 10 brain-injured patients (three women and seven men; Glasgow Coma Scale < 6) were studied within 5 days of admission to the intensive care unit (ICU). Included in the study were patients with severe head trauma who presented diffuse bihemispheric brain oedema on computed tomography scan. Patients suffering from pulmonary, cardiovascular, hepatic or renal failure were excluded. The median (range) age, weight and height of the patients were 34 (10–76) years, 80 (45–90) kg and 1.77 (1.54–1.90) m, respectively. Mechanical ventilation (FiO_2: 0.3–0.45) was adjusted to maintain arterial carbon dioxide tensions of 28–30 mm Hg. Continuous infusions of fentanyl and midazolam were used for analgesia and sedation prior to the investigation. The only co-medications were low dose heparin and 2 μg dopamine kg^{-1} min^{-1}. The patients received parenteral nutrition. Monitoring included invasive mean arterial blood pressure (MAP) and right atrial pressure (RAP), heart rate (HR), arterial O_2 saturation (SaO_2) and blood gases. ICP was measured using an epidural probe (Epidyn; Braun, Melsungen, Germany). Cerebral perfusion pressure (CPP) was calculated from MAP-ICP.

Following baseline measurements, a bolus of 2 μg kg^{-1} sufentanil was injected intravenously. After 30

Correspondence: Priv.-Doz. Dr Jens Scholz, Universitäts-Krankenhaus Eppendorf, Abteilung für Anästhesiologie, Martinistrasse 52, D-20246 Hamburg, Germany

min sufentanil citrate (150 (25–200) μg base h^{-1}) and midazolam (9.0 (3.6–13.5) mg h^{-1}) were infused intravenously in individually adjusted doses for 48 h.

Sample collection

Arterial blood samples (5 ml) were taken before the bolus injection of sufentanil and at 1, 3, 5, 10, 15, 20, 30 (start of infusion), 45, 60, 90 min and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h. Further samples were taken at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90 min and 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after the end of infusion. Blood samples were collected in heparinised tubes and centrifuged. Plasma and urine (0–72 h) were transferred to polypropylene tubes and stored at −70°C.

Drug assays

Plasma and urine sufentanil concentrations were measured by radioimmunoassay (r.i.a.). The assay is specific for sufentanil and has a lower limit of determination of 0.1 ng ml^{-1} [9]. Intra- and inter-assay coefficients of variation were 5.4 and 5.9%, respectively, over a range of 0.1 to 8.0 ng per assay tube. Plasma concentrations of midazolam were measured by a g.l.c. assay with electron-capture detection [10]. The assay has a lower limit of quantification of 5 ng ml^{-1}. Intra- and inter-assay coefficients of variation were 5.1 and 5.8%, respectively, over a range of 10 to 100 ng ml^{-1}.

Pharmacokinetic analysis

The individual plasma sufentanil concentrations following bolus injection (30 min), during continuous infusion (47.5 h) and post-infusion (48–72 h) were fitted simultaneously in a two compartment open model using the nonlinear least square regression programme TopFit [11]. Data points were weighted by the ratio $1/y^2$. Total clearance (CL) and the volume of distribution at steady state (V_{ss}) were calculated from the fitted data. In addition, the initial distribution following bolus injection was estimated from a separate fit over the first 30 min by the same programme. The terminal elimination half-life ($t_{1/2,z}$) was calculated from the post-infusion data (4–24 h). The mean value of four plasma drug concentrations measured within 5 min at the end of infusion were taken as the average steady state concentration. Renal clearance (CL_R) was calculated from the urinary recovery of sufentanil divided by the corresponding AUC value over the monitored 72 h. The clearance of midazolam was estimated from its infusion rate divided by the mean steady state plasma concentration at the end of infusion.

Statistical analysis

All pharmacokinetic data are expressed as median and range. MAP and ICP are expressed as mean values ± s.d. Student's *t*-test and analysis of variance (ANOVA) followed by Duncan's multiple range test were used to assess significant differences ($P < 0.05$).

Results

Representative plasma concentrations of sufentanil are shown in Figure 1 and pharmacokinetic parameters of all patients are summarized in Table 1. Following the i.v. bolus injection concentrations of sufentanil declined rapidly in a biexponential fashion (median $t_{1/2,1}$ = 0.65 min and $t_{1/2,z}$ = 19 min). The median plasma clearance was 1215 (519–2550) ml min^{-1} and renal clearance represented 0.6% of this. After the end of the sufentanil infusion a biphasic decline of plasma drug concentrations was observed with an initial distribution phase ($t_{1/2}$ = 0.23 h) and a terminal elimination half-life ($t_{1/2,z}$) between 7 and 49 h (median 16 h).

The clearance of midazolam was 256 (108–941) ml min^{-1} (C_{ss} = 595 (65–1458) ng ml^{-1}).

After i.v. bolus administration of sufentanil a significant decrease in ICP within 15 min was observed (from 16.1 ± 1.7 mm Hg to 10.8 ± 1.3 mm Hg) and thereafter values remained stable. There was no change in HR and RAP (data not shown), but at 15 min MAP was significantly decreased from 85.5 ± 3.9 mm Hg to 80.2 ± 4.9 mm Hg. Thus CPP (MAP-ICP) was 69.4 mm Hg and remained unchanged. The same results were obtained on the following 2 days.

Discussion

Pharmacokinetics

Values of the rapid and slow distribution half-lives of sufentanil following the initial i.v.-bolus and its clearance in head trauma patients were similar to those reported for normal anaesthetized patients [12, 13]. In contrast, the terminal elimination half-life (16 h) was longer than reported after bolus administration (1–12 h) [14–17] and the V_{ss} value (10 l kg^{-1}) was higher (2–9 l kg^{-1}) [14–21]. These differences may be related to differences in the underlying disease states and to the duration of plasma sampling (24 h in our study). Also, the state of ventilation and a possible interaction between sufentanil and fentanyl may be considerations [12, 13]. The large variability in the pharmacokinetics of sufentanil in ICU patients may have implications for safe and effective dosage.

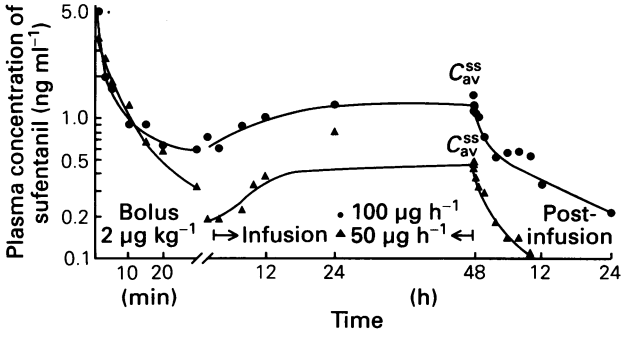

Figure 1 Plasma sufentanil concentrations following i.v. bolus/infusion of sufentanil in two patients with head trauma.

Table 1 Pharmacokinetic parameters of sufentanil (base)

Patient	Loading dose (μg)*	R_o (μg h^{-1})	Ae 0–72 h (μg)	$t_{1/2,l}$ (h)	$t_{1/2}$ (postinfusion) $t_{1/2,z}$ (h)	CL (ml min^{-1})	CL_R (ml min^{-1})	V_{ss} (l kg^{-1})
1	100	100	28	0.27	23	632	6	16.6
2	160	50	42	0.10	7	1690	25	8.7
3†	150	150	192	0.14	—	1140	38	—
4	150	100	25	0.21	10	1290	7	10.0
5	175	150	15	0.25	8	1440	4	6.8
6	150	25	25	0.25	28	931	22	21.4
7	180	§	9	0.25	16	2300	2	16.3
8	160	200	50	0.13	7	2550	16	9.4
9	90	200	20	1.10	49	711	2	24.2
10	150	200	64	0.16	19	519	4	6.9
Median	150	150	27	0.23	16	1215	7	10.0
Range	90–180	25–200	9–192	0.1–1.1	7–49	519–2550	2–38	6.8–24.2

R_o, infusion rate; *Ae*, amount excreted unchanged in urine (0–72 h); $t_{1/2,l}$ and $t_{1/2,z}$ distribution and terminal elimination half-lives after end of infusion; CL, clearance; CL_R, renal clearance; V_{ss}, apparent volume of distribution at steady state.
*Corresponding to 2 μg base kg^{-1} body weight.
†Data for patient 3 partly omitted for calculation of median because of incomplete blood sampling after end of infusion.
§Varying infusion rates (for clinical reasons).

Alazia *et al.* [1] reported lower steady state plasma sufentanil concentrations in ICU patients (0.28 ng ml^{-1}) than in the present study (1.50 ng ml^{-1}) but similar $t_{1/2,z}$ (15 ± 8 h) and V_{ss} (15 ± 6 l kg^{-1}) values (mean ± s.d., n = 8). The long terminal half-life observed in head trauma patients suggests that recovery from prolonged administration of sufentanil may be longer than would have been anticipated from previously published pharmacokinetic data based on i.v. bolus administration.

The clearance of midazolam was comparable with previous findings [22, 23], indicating no modification by sufentanil.

Pharmacodynamics

The effects of opioids on central haemodynamics remain controversial, questioning in some instances their use in patients with increased ICP or compromised intracranial compliance. As in previous studies [24, 25], a slight decrease in MAP was noted in the present study. The observed small decrease in ICP appeared to precede the change in MAP. Since CPP was stable throughout our study, the observed pharmacodynamic changes were not considered to be harmful to the patients. In earlier studies [2, 4], a decrease in MAP may have been the primary cause of a reflex increase in ICP. The latter may result from an exponential increase in cerebral blood volume resulting from vasodilatation of brain areas with intact autoregulation. This happens when CPP decreases to less than 60 mm Hg. In accordance with Weinstabl *et al.* [7], we conclude that sufentanil itself exerts no increase in ICP. Thus, concomitant haemodynamic changes should be monitored closely.

The authors thank Mrs M. Schmidt for excellent assistance.

References

1 Alazia M, Albanese J, Martin C, de la Coussaye JE, Levron JC. Pharmacokinetics of long-term sufentanil infusion (72 hours) used for sedation in I.C.U. patients. *Anesthesiology* 1992; **77**: A364.

2 Marx W, Shah N, Long C, *et al.* Sufentanil, alfentanil, and fentanyl: impact on cerebrospinal fluid pressure in patients with brain tumours. *J Neurosurg Anesthesiol* 1989; **1**: 3–7.

3 Newberg Milde L, Milde JH, Gallagher WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. *Anesth Analg* 1990; **70**: 138–146.

4 Sperry RJ, Bailey PL, Reichman MV, Peterson JC, Petersen PB, Pace NL. Fentanyl and sufentanil increase intracranial pressure in head trauma patients. *Anesthesiology* 1992; **77**: 416–420.

5 Keykhah MM, Smith DS, Carlsson C, Safo Y, Englebach I, Harp JR. Influence of sufentanil on cerebral metabolism and circulation in the rat. *Anesthesiology* 1985; **63**: 274–277.

6 Mayer N, Weinstabl C, Podreka I, Spiss CK. Sufentanil does not increase cerebral blood flow in healthy human volunteers. *Anesthesiology* 1990; **73**: 240–243.

7 Weinstabl C, Mayer N, Richling B, Czech T, Spiss CK. Effect of sufentanil on intracranial pressure in neurosurgical patients. *Anaesthesia* 1991; **46**: 837–840.

8 Werner C, Hoffman WE, Baughman VL, Albrecht RF, Schulte am Esch J. Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. *Anesth Analg* 1991; **72**: 177–181.

9 Michiels M, Hendriks R, Heykants J. Radioimmuno-

assay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. *J Pharm Pharmac* 1983; **35**: 86–93.
10 Klotz U, Reimann IW. Chronopharmacokinetic study with prolonged infusion of midazolam. *Clin Pharmacokin* 1984; **9**: 469–474.
11 Heinzel G, Woloszczak R, Thomann P. *TopFit—Pharmacokinetic and pharmacodynamic data analysis system for the PC*. Stuttgart: Gustav Fischer, 1993.
12 Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clin Pharm* 1991; **10**: 581–593.
13 Monk JP, Beresford R, Ward A. Sufentanil. A review of its pharmacological properties and therapeutic use. *Drugs* 1988; **36**: 286–313.
14 Bovill JG, Sebel PS, Blackburn CL, Oei-Lim V, Heykants JJ. The pharmacokinetics of sufentanil in surgical patients. *Anesthesiology* 1984; **61**: 502–506.
15 Davis JP, Cook DR, Stiller RL, Davin-Robinson KA. Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. *Anesth Analg* 1987; **66**: 203–208.
16 Greeley WJ, de Bruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. *Anesth Analg* 1987; **66**: 1067–1072.
17 Hudson RJ, Bergstrom RG, Thomson IR, *et al.* Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. *Anesthesiology* 1989; **70**: 426–431.
18 Guay J, Gaudreault P, Tang A, Goulet B, Varin F. Pharmacokinetics of sufentanil in normal children. *Can J Anaesth* 1992; **39**: 14–20.
19 Matteo RS, Schwartz AE, Ornstein E, Young WL, Chang W. Pharmacokinetics of sufentanil in the elderly surgical patient. *Can J Anaesth* 1990; **37**: 852–856.
20 Davis PJ, Stiller RL, Cook DR, Brandom BW, Davin-Robinson KA. Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. *Anesth Analg* 1988; **67**: 268–271.
21 Fyman PN, Reynolds JR, Moser F, Avitable M, Casthely PA. Pharmacokinetics of sufentanil in patients undergoing renal transplantation. *Can J Anaesth* 1988; **35**: 312–315.
22 Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokin* 1989; **16**: 337–364.
23 Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite α-hydroxy midazolam in healthy volunteers. *Clin Pharmac Ther* 1992; **51**: 715–728.
24 de Lange S, Boscoe MJ, Stanley TH, *et al.* Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. *Anesthesiology* 1982; **56**: 112–118.
25 Sebel PS, Bovill JG. Cardiovascular effects of sufentanil anesthesia. *Anesth Analg* 1982; **61**: 115–119.

(Received 24 February 1994, accepted 6 June 1994)