

Pharmacokinetics of Human Cerebral Opioid Extraction

A Comparative Study on Sufentanil, Fentanyl, and Alfentanil in a Patient after Severe Head Injury

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Background: The pharmacodynamic differences in time to onset and dissipation of effect of sufentanil, fentanyl, and alfentanil probably result from different rates of blood-brain equilibration. The authors investigated this hypothesis in humans.

Methods: After simultaneous central venous bolus application of sufentanil (10 µg), fentanyl (100 µg), and alfentanil (1,000 µg), arterial and jugular bulb blood samples were drawn simultaneously at 20, 30, 45, 60, 75, 90, 105, 120, 140, 160, 180, 210, 240, 300, 360, and 420 s from 19 patients during the postacute stage of head injury with normal intracranial pressure, cerebral perfusion pressure, and cerebral oxygen metabolism during normocapnia.

Results: Peak brain concentration, indicated by equilibrium between arterial and jugular bulb opioid concentrations, was achieved for alfentanil at 45 s, for sufentanil at 5 min, and for fentanyl at 6 min. The corresponding median time intervals (fifth and ninety-fifth percentiles) to reach 50% of peak brain concentration were 15 (14-18), 25 (18-38) and 35 (25-45) s, respectively. Uptake was highest 20 s after bolus and decreased continuously for fentanyl and sufentanil, whereas alfentanil uptake was biphasic. The ratio of the relative amounts of sufentanil, fentanyl, and alfentanil retained in the brain at peak brain concentration was 1×:×6×:×90.

Conclusions: The differences in the time lag between changes in serum concentrations and drug effect after bolus application of nearly equipotent doses of sufentanil, fentanyl, and alfentanil originate from the different times required to reach blood-brain equilibration, mainly depending on different levels and

different time profiles of arterial blood concentrations caused by the different tissue distribution volumes. (Key words: Blood-brain equilibrium; opioid serum concentration.)

FENTANYL and its newer congeners alfentanil and sufentanil are currently the most commonly used opioid analgesics in clinical anesthesia. In contrast to older opioids such as morphine, they have a more rapid onset and a shorter duration of effect, and their opioid effects appear to parallel more closely their serum concentrations if used in low doses.^{1,2} As shown by spectral-edge electroencephalographic analysis of drug effect, however, alfentanil clearly differs from fentanyl and sufentanil because it reaches its peak effect site concentration much earlier, and its duration of effect is shorter.^{2,3} Compared with fentanyl, alfentanil has a smaller distribution volume at steady state, a lower total body clearance, and a shorter terminal elimination half-life. Like fentanyl and sufentanil, alfentanil is sufficiently fat-soluble to enter the central nervous system with ease.⁴ According to the literature, the differences in their delays in equilibration of drug concentrations and their drug effects might result from several factors.

Alfentanil might be less bound on its first pass from the site of injection to the brain, and therefore a larger concentration gradient might drive alfentanil faster from the blood into the brain.⁵⁻⁷ Alfentanil is a weak base with a pKa of 6.5, which means that it predominantly exists in an unionized form at body pH. In contrast, fentanyl (pKa 8.4) and sufentanil (pKa 8.1) are approximately 90% ionized. Therefore, more alfentanil exists in the diffusible, uncharged form.⁸ Compared with fentanyl and sufentanil, alfentanil probably undergoes less non-specific binding in the central nervous system. In rat brain, it is 22 times less soluble than fentanyl.⁹ This leaves a larger proportion of the drug available for specific binding to opioid receptors, and occupancy of

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Received from the Department of Anesthesiology, University Hospital Regensburg, Regensburg, Germany. Submitted for publication November 30, 1998. Accepted for publication December 21, 1999. Support was provided solely from institutional and/or departmental sources.

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these receptors occurs more rapidly. In conscious sheep, the half-lives of equilibrium between blood and brain were 0.8 and 6.3 min for alfentanil and meperidine, respectively. Upton et al.¹⁰ found that large differences in the cerebral distribution volumes of the opioids accounted for the different delays in their peak brain concentrations relative to blood. These differences in brain distribution volume seem to be the main factor for the different hystereses of alfentanil, fentanyl, and sufentanil. The aim of our study was to evaluate in humans this hypothesis, chiefly derived from animal studies, by measuring alfentanil, fentanyl, and sufentanil serum concentrations progressively in arterial and jugular bulb blood after a simultaneous bolus injection of these opioids.

Materials and Methods

Patient Selection

After approval by our local ethics committee and with informed consent from their next of kin, 19 patients suffering from severe head injury were enrolled in the study. Depending on the patient's critical illness, invasive hemodynamic monitoring including an arterial and central venous catheter was performed. To determine the ratio of cerebral oxygen delivery to demand, a fiberoptic catheter (U 440, Oximetrix, Abbott Critical Care System, Abbott Laboratory, North Chicago, IL) was placed in the jugular bulb. Based on a computed tomographic scan the side of predominant lesion, or in case of diffuse or bilaterally equivalent lesions the side of the largest jugular foramen, was selected for jugularvenous monitoring.¹¹ Catheter position was verified by radiograph in anteroposterior and lateral projections or by computed tomographic scan. Pharmacokinetic investigations were done in the postacute stage, after monitoring of cerebral oxygen metabolism was no longer indicated and just before the jugular bulb catheter was removed. Patients were included in the study if parameters indicating cerebral perfusion and metabolism as well as the intracranial pressure were within normal ranges and CO₂ reactivity was preserved. Patients were excluded if one of the following conditions existed: arterial-to-jugularvenous oxygen content difference less than 4 or more than 8 ml O₂/100 ml blood (indicating uncoupling between cerebral metabolism and cerebral blood flow),¹² a modified lactate oxygen index more than 0.08 (indicating cerebral ischemia),¹³ or normocapnic intracranial pressure more than 15 mmHg.

Study Protocol and Pharmacokinetic Analysis

After simultaneous central venous bolus application of 0.01 mg sufentanil, 0.1 mg fentanyl, and 1.0 mg alfentanil (injected volume 5 ml), arterial and jugular bulb blood samples were drawn simultaneously from an arterial line and the jugular bulb catheter, respectively. The drugs were administered concurrently to reduce variability and to simplify sample collections. The opioid bolus was injected central venously within 2 s with a 10 ml saline flush. Blood sampling was performed over a 7-min period: before drug application and then at 20, 30, 45, 60, 75, 90, 105, 120, 140, 160, 180, 210, 240, 300, 360, and 420 s after bolus injection. Blood samples of 1.5 ml were drawn and promptly centrifuged. The serum samples were separated and frozen at -70°C until analyzed.

The area under the curve of the opioid concentrations over time in arterial and jugular bulb blood was calculated by the linear trapezoidal rule to the last data point. The peak brain concentration was assumed to correspond to the point of intersection between arterial and jugular bulb drug concentrations. The time course to peak brain concentration was calculated by dividing the amount of drug extracted from the arterial blood (e.g., arterial-jugular bulb concentration integrated over time) through the cumulative absorption at the time of arterial and jugular bulb intersection. Because cerebral blood flow was not quantitated, the net flux and net drug mass are expressed per unit of blood flow. Net drug flux was calculated as $J_{net}/flow = (C_{art} - C_{ven})$, in which C_{art} and C_{ven} are the drug concentrations in arterial and jugular bulb blood respectively. The net drug mass per flow results from integrating $J_{net}/flow$ with respect to time starting from the time before drug application: $M_{net}/flow = \int (C_{art} - C_{ven}) dt$.¹⁴ Even if tissue flow is not measured, $M_{net}/flow$ has been shown to be a valid measure of uptake and elution, provided that tissue blood flow remains constant.¹⁴ The cerebral opioid extraction ratio is calculated from the areas under the arterial and jugular bulb blood concentration-time curves from time 0 to the point of intersection between both concentration-time curves as follows: $ER = AUC_{art-ven}/AUC_{art}$. All data were calculated for each individual patient and then averaged.

Analytic Methods

Reagents and Materials. Sufentanil free base and alfentanil free base were obtained from Janssen (Beerse, Belgium). 3-Methylfentanyl hydrochloride (M6255), fentanyl citrate (F5886), and fentanyl-d₅ citrate (F2520) were purchased from Sigma (Deisenhofen, Germany).

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Table 1. Analytic Details Concerning the Limits of Quantification, Linearity of the Tested Assay, and Recovery Rates of the Various Opioids

Substance	Retention Time (min)	Limit of Quantification (extract in 15 μ l toluene)	Tested Assay Linearity (stock solutions/15 μ l toluene)	Recovery Rate (n = 30)
Fentanyl-d ₅	9.55			
Fentanyl	9.55	50 pg	36 pg–21.9 ng	122 \pm 23% (1000 pg)
Sufentanil	9.95	30 pg	26 pg–77.7 ng	99.5 \pm 19% (500 pg)
Alfentanil	10.80	100 pg	100 pg–145 ng	61.4 \pm 25% (20.0 ng)
3-Methylfentanyl	9.97			

The internal standard fentanyl-d₅ was used to quantify sufentanil, fentanyl, and alfentanil. 3-Methylfentanyl served as a marker for identification of chromatographic or detection problems. The recovery rate \pm coefficient of variation (%) in relation to Fentanyl-d₅ was measured from spiked opioid levels extracted from 1.0 ml serum.

Toluene and hexane came from Fluka (Deisenhofen, Germany), both high-performance liquid chromatography grade. The 2-M NaOH was prepared from sodium hydroxide pellets from Merck (Darmstadt, Germany), and 0.1-M HCl (titrisol) also came from Merck. Dimethyldichlorosilane for silanization of the conical glass tubes was obtained from Fluka.

Standards were prepared in toluene ether by solution of the free bases (sufentanil and alfentanil) or by dilution of the commercially available standard solutions (fentanyl-d₅ citrate, fentanyl citrate, and 3-methylfentanyl hydrochloride).

Drug Extraction. Opioid extraction was performed by the method described by Gandolfi.¹⁵ Serum, 0.1–1.0 ml, were filled in glass screw-cap tubes and mixed with 50 μ l fentanyl-d₅ standard solution (2,000 pg) in toluene and then alkalized with 0.5 ml 2-M NaOH. The first extraction was achieved by shaking the sample with 8 ml of hexane:toluene (19:1) for 20 min using centrifugation (1,180g for 3 min). Reextraction of the opiates out of the organic layer into aqueous solvent was done by adding 2 ml 0.1-M HCl to the organic phase in new tubes. The samples were shaken again for 20 min. The organic layer was withdrawn, the water phase alkalized with 0.5 ml 2-M NaOH, and the extraction with fresh 19:1 hexane:toluene repeated. Finally, the organic layer was transferred into a silanized conical tube and evaporated under N₂ at 37°C. Before the tube was dried completely, it was shaken using a whirl mixer for a few seconds. After evaporation to dryness, the sample was redissolved in 15 μ l toluene containing 6.0 ng 3-methylfentanyl and transferred into 100- μ l microvials.

For analysis we used a Hewlett-Packard 5890 gas chromatograph (Waldbronn, Germany) equipped with a split-splitless injection system (splitless mode) and a

mass-selective detector. Chromatographic separation was achieved by combination with a 10-M, 0.25 mm inner diameter deactivated fused silica retention gap from Alltech (Deerfield, IL) with a DB1 (15-M, 0.25 mm inner diameter, 0.1- μ m film thickness; J&W Scientific, Folsom, CA). A sample volume of 2 μ l was injected at a 265°C injector temperature. The oven was held at 95°C during the first 1.5 min and heated linearly to 260°C at 20°C/min afterward. Finally, the temperature was kept at 260°C for 5 min. The MS-transfer line (the interface between gas chromatograph and mass spectrometer) was heated to 300°C. Helium (4.6) at a head pressure of 60 kPa was used as the carrier gas. The internal standard fentanyl-d₅ was used to quantify fentanyl, alfentanil, and sufentanil. 3-Methylfentanyl served as a marker to identify possible chromatographic interferences or detection problems.¹⁶ Details concerning the detected mass, the limits of quantification, the linearity of the tested assay, and the recovery rates of the various opioids are shown in table 1. All measured opioid concentrations were well above the corresponding limits of quantification. All serum opioid concentrations lie within the range of linearity of the tested assay.

Mathematic and Statistical Analysis

For data analysis, the Kolmogorov-Smirnov modification of the Lillefor test was used to check for normal distribution of arterial and jugularvenous serum opioid concentrations at the various sampling times.^{17,18} Because these criteria were not fulfilled, data are presented as median values with corresponding 5% and 95% percentiles. All derived data from serum concentrations were calculated in each individual patient and then averaged.

Table 2. Patient Demographic and Physiologic Characteristics

Patient No.	Age (yr)	Sex	BSA (m ²)	pH	Hct	Albumin [g/l]	Pa _{CO₂} (mmHg)	Study Day Postinjury	Concomitant Sedative	GCS Score
1	38	F	1.9	7.40	29.0	31.4	39.8	10	Clonidine	14
2	80	F	1.9	7.35	30.0	24.0	38.5	8	Clonidine	15
3	16	M	2.3	7.42	26.9	38.6	36.9	7	None	15
4	39	F	1.9	7.40	31.5	36.5	38.9	11	Clonidine	13
5	46	F	1.9	7.47	25.0	27.0	39.5	9	Clonidine	14
6	58	M	2.2	7.45	33.0	32.0	39.6	14	None	13
7	45	M	1.9	7.40	31.7	28.9	38.9	8	None	15
8	61	F	1.9	7.45	24.0	34.0	38.8	9	None	12
9	55	M	1.9	7.43	30.0	34.0	40.6	10	Clonidine	15
10	52	M	2.3	7.48	34.6	36.0	40.1	10	Clonidine	15
11	46	M	1.9	7.44	25.8	24.9	39.6	12	None	14
12	18	M	1.7	7.37	29.5	25.9	39.2	8	None	15
13	76	M	1.8	7.42	29.0	30.0	40.1	9	None	14
14	19	F	1.9	7.45	32.7	36.7	39.5	11	Clonidine	15
15	32	F	1.6	7.35	29.0	31.1	38.6	12	Clonidine	13
16	36	F	1.7	7.45	32.8	30.8	40.2	9	Clonidine	13
17	36	M	1.8	7.45	27.3	33.4	39.5	15	None	14
18	16	M	1.7	7.41	27.5	27.9	37.9	12	None	15
19	63	F	1.7	7.38	33.0	28.0	38.4	10	None	14

BSA = body surface area, Hct = hematocrit, GCS = Glasgow Coma Scale. All data refer to the day of investigation.

Results

Patients' demographic and physiologic characteristics are presented in table 2. All patients were in the weaning phase from artificial ventilation and responsive to commands. The median Glasgow Coma Scale score was 14 (range, 12–15). Patients were studied between 7 and 15 days (median, 10) postinjury. Clonidine was applied continuously ($1.0\text{--}1.5\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) as concomitant sedative in nine patients. Parameters known to influence opioid pharmacokinetics to some degree, such as age, body surface area, serum albumin levels, erythrocyte counts, and blood pH values, were distributed normally in our patient population. Nevertheless, we found a high interindividual variation both in arterial and jugular bulb opioid concentrations over time. The median (range) peak arterial concentration was 9.1 ng/ml (3.4–18.9) for fentanyl, 1.6 ng/ml (0.9–3.3) for sufentanil, and 910 ng/ml (615–1576) for alfentanil. Figure 1 demonstrates the opioid concentrations in arterial and jugular bulb blood over time in an individual patient. The point of intersection between arterial and jugular bulb drug concentrations corresponds to the point of maximum brain concentration.

Figure 2 illustrates the median and fifth and ninety-fifth percentiles for the times to reach peak brain concentrations after simultaneous bolus application of the three opioids. The curve for alfentanil showed by far the steep-

est slope, followed by sufentanil and fentanyl. The median time intervals to maximum brain concentration were 45 s for Alfentanil, 300 s for sufentanil, and 360 s for fentanyl. The median time intervals (fifth and ninety-fifth percentiles) to 50% of peak brain concentration were 15 s (14–18), 25 s (18–38), and 35 s (25–45) for alfentanil, sufentanil, and fentanyl, respectively.

The median and fifth and ninety-fifth percentiles of net drug flux per unit of cerebral blood flow ($J_{\text{net}}/\text{flow}$), indicating the rate of cerebral drug uptake, are illustrated in figure 3. $J_{\text{net}}/\text{flow}$ started at 0 because the blood concentrations were 0, but for all three opioids we found a maximum drug flux into the brain at 20 s after bolus injection; then it became progressively smaller as arterial and jugular bulb concentrations equilibrated. For fentanyl and sufentanil the extent of drug uptake into the brain decreased continuously thereafter to the point of maximum brain concentration, which was at 360 s for fentanyl and 300 s for sufentanil. For alfentanil there was a biphasic $J_{\text{net}}/\text{flow}$ within the first 90 s. After cerebral alfentanil uptake up to 45 s there was a net alfentanil flux out of the brain into jugular bulb blood. At approximately 90 s we found a small second cerebral drug uptake (fig. 3A).

As an indicator of the extent of cerebral opioid uptake, the median (fifth and ninety-fifth percentiles) of net drug mass per unit of cerebral blood flow are illustrated in

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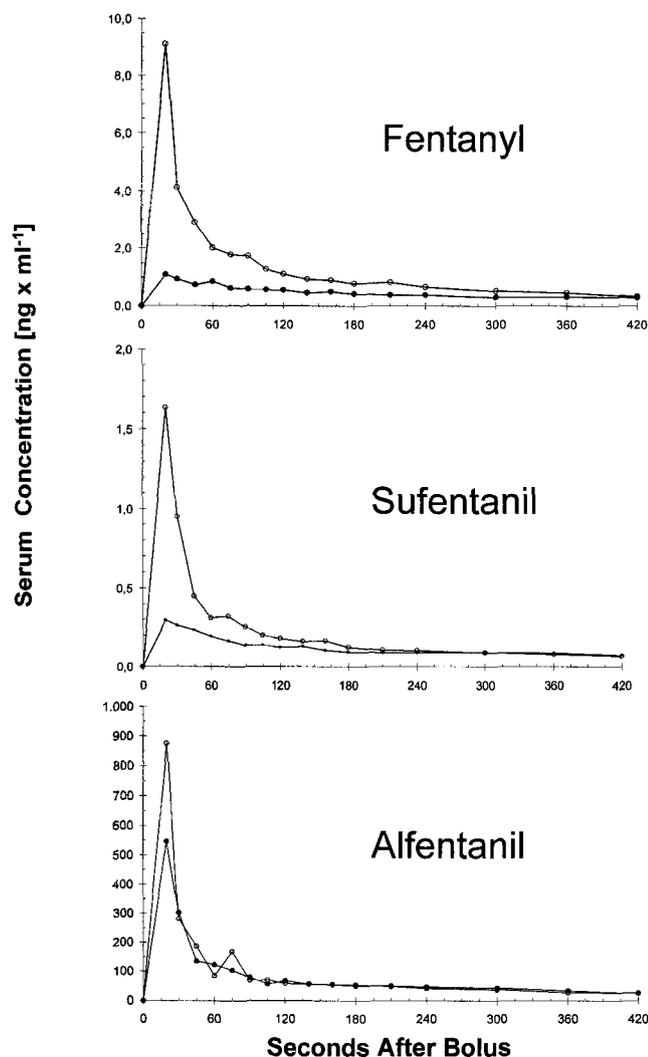


Fig. 1. Plot of corresponding arterial (○) and jugular bulb (●) fentanyl, sufentanil, and alfentanil serum concentrations over time for patient 5.

figure 4. The ratio of the amounts of sufentanil, fentanyl, and alfentanil retained in the brain at the equilibrium point is about 1×:×6×:×90.

Discussion

To get some practical pharmacokinetic information concerning the preinduction of anesthesia or “on top” analgesia for painful manipulations in the intensive care unit, we chose to apply the opioids as a bolus in equipotent doses. The hysteresis or delay in equilibration of drug concentrations is most apparent if there is a rapid change in plasma concentrations of a large magnitude

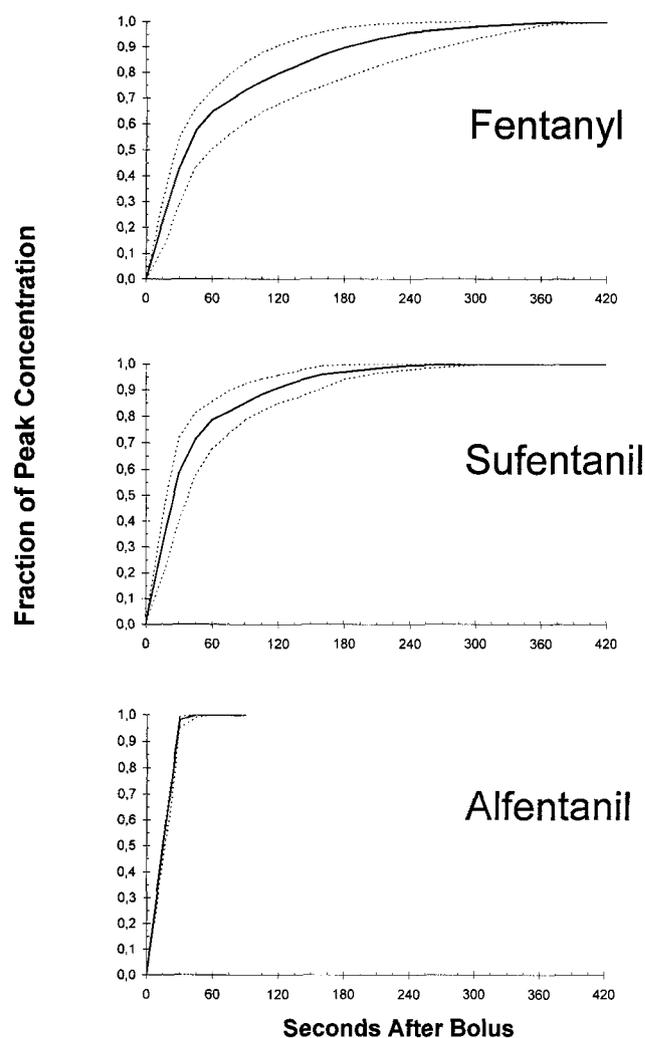


Fig. 2. Time to reach brain concentration after simultaneous bolus applications of fentanyl, sufentanil, and alfentanil. The fraction of peak brain concentration results from the amount of drug extracted from arterial blood (arterial–jugular bulb concentration, integrated over time) plotted as a fraction of the cumulative absorption. Data are presented as the median (solid lines) and fifth and ninety-fifth percentiles (dotted lines) from individual patients.

relative to the concentration at the site of action, as is true immediately after a rapidly injected intravenous dose.

As expected, we found marked differences in the corresponding opioid concentrations in arterial and jugular bulb blood from patient to patient. One reason is the application of a fixed bolus dose without regard to differences in body weight and body composition. With central venous bolus injection the peak arterial concentration is present almost immediately after completion of

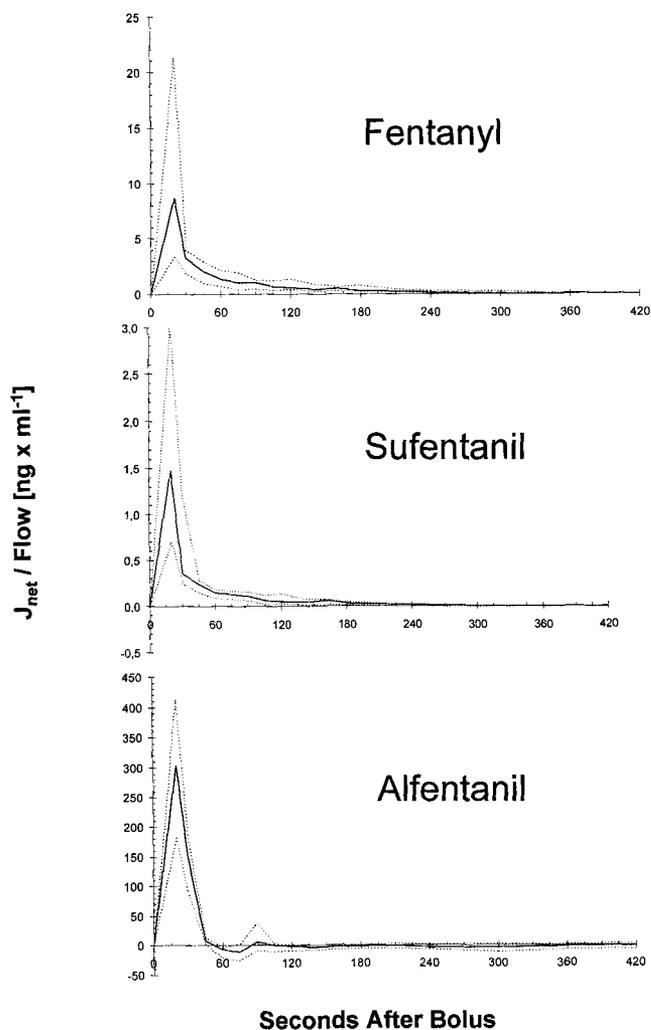


Fig. 3. Plot of net drug flux (J_{net}) per flow for fentanyl, sufentanil, and alfentanil under the assumption that cerebral blood flow is not quantitated but remains constant. Under these conditions, J_{net} corresponds to the difference in mass per unit time of drug respectively entering and leaving the brain *via* the arterial and venous blood vessels. Data are presented as the median (solid lines) and fifth and ninety-fifth percentiles (dotted lines) from individual patients

the injection. The peak arterial concentration is a function of the dose administered, cardiac output, and capacity of the lung for the drug.^{19,20} In our study we did not measure cardiac output. According to the literature, interindividual variations in cardiac output seem to play a major role in the differences in arterial and consecutively jugular bulb concentrations between patients.²⁰

Studies concerning the uptake of opioids in the human lung using the nondiffusible indicator indocyanine green have shown that the peak of arterial opioid concentrations occurs between 16 and 24 s after central venous

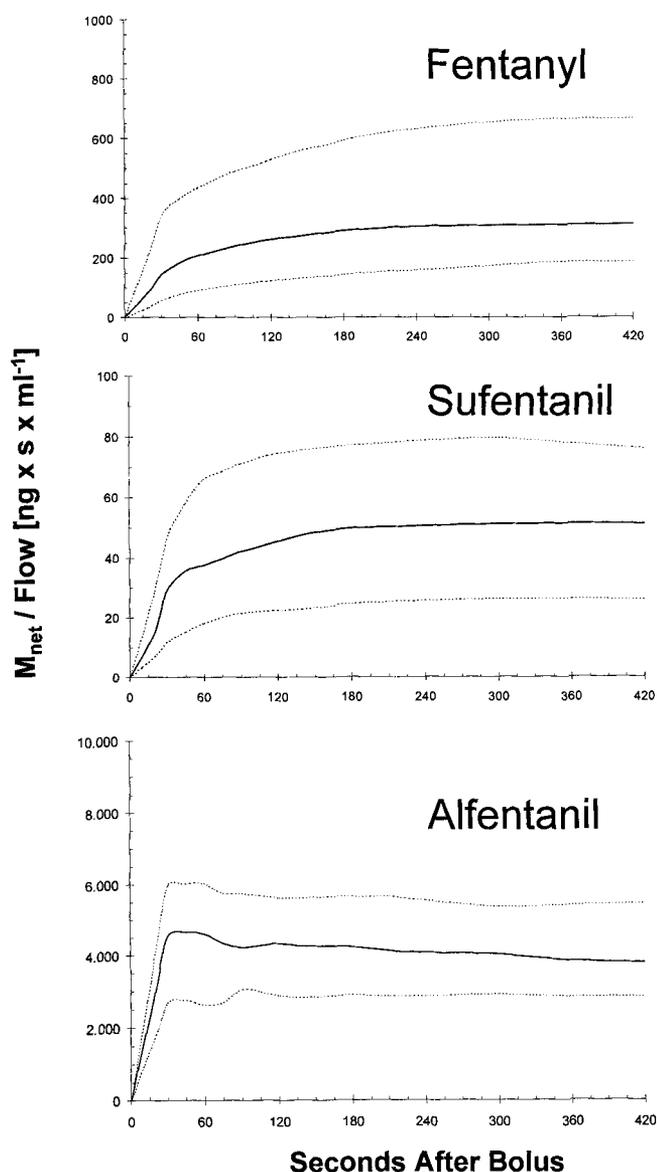


Fig. 4. Plot of net drug mass (M_{net}) per flow for fentanyl, sufentanil, and alfentanil under the assumption that cerebral blood flow is not quantitated but remains constant. Under these conditions, M_{net} corresponds to the mass of drug that has entered the brain *via* the arterial blood vessels but has not left the brain *via* the venous blood vessels. Data are presented as the median (solid lines) and fifth and ninety-fifth percentiles (dotted lines) from individual patients.

bolus application.^{9,10,21} Based on these data, it must be considered that the maximum opioid concentration measured in individual patients in our study may not be equivalent to the true peak concentration, occurring before or after the 20 s interval chosen by us. After bolus injection, however, the time interval during which the

arterial concentrations are above 80% of the individual maximum value is about 6 s. Therefore, we should have measured at least 80% of the peak concentration at 20 s after bolus application.

The more lipid-soluble the drug, the more rapidly it should penetrate membranes and the more rapid should be its uptake into tissues if there is some diffusion barrier to the less soluble drug.⁸ Therefore, sufentanil should have the fastest brain uptake, followed by fentanyl and finally alfentanil.^{8,22} Beyond a certain limit of lipid solubility, however, which is close to the solubility of morphine, there seems no longer to be any hindrance to the diffusion of a drug out of the blood through the blood-brain barrier.⁸ The difference between arterial and venous drug concentrations before the point of equilibrium in figure 1 indicates that a transcerebral gradient exists and that, if no cerebral elimination occurs, the drug moves from the blood to the brain despite already decreasing blood concentrations.

Concerning the different rates of blood-brain equilibration after bolus injection of the opioids, our data confirm the computer-simulated total brain concentration curves for fentanyl and alfentanil in humans based on steady state blood-brain partition coefficients in rats, in which the maximum brain concentration of fentanyl should be reached approximately 10 min after injection and that of alfentanil in less than 1 min.⁹ The different time intervals to blood-brain equilibrium found in our study also are reflected in the dynamics of the drug effects. Scott *et al.*¹ used power spectral analysis of the electroencephalogram and computation of the spectral edge to measure the effect of opioids on the brain. For alfentanil the electroencephalographic spectral edge was shown to change almost in parallel with the arterial serum concentration; the electroencephalographic changes induced by fentanyl were delayed and prolonged compared with the time course of the serum concentration. For sufentanil the time interval between bolus injection and blood-brain opioid equilibrium is on the same order of magnitude as that for fentanyl and corresponds to the delay in equilibration between peak plasma concentration and maximal drug effect, which was 6.6 ± 1.7 min for fentanyl and 6.2 ± 2.8 min for sufentanil.² Based on these pharmacodynamic data reported by Scott *et al.*¹, a pharmacokinetic-pharmacodynamic computer simulation for bolus injection from Shafer and Varvel²³ found peak brain concentrations for fentanyl at 3.6 min, for sufentanil at 5.6 min, and for alfentanil at 1.4 min. After bolus injection, the brain effect site concentration peaks much earlier for alfen-

tanil compared with fentanyl and sufentanil, at a time at which plasma alfentanil concentration is still close to its maximum. This results from alfentanil's markedly lower distribution volume in brain tissue, which leads to a more rapid blood-brain equilibration.

As demonstrated in the J_{net}/flow plots in figure 3, the rates of cerebral fentanyl and sufentanil uptake after bolus injection after the initial peak were declining continuously up to the maximum brain concentration. In contrast, alfentanil uptake by the brain was very rapid and seemed to be biphasic. As shown here in figure 4, however, the second wave of alfentanil uptake adds little to the total extent of cerebral drug uptake.

The characteristics of cerebral alfentanil uptake and elution demonstrate highly dynamic brain tissue saturation kinetics (fig. 3). The closeness of the correlation between plasma and tissue concentrations depends on the rate of equilibration of the free unionized drug concentrations across membranes and on the number of binding sites in plasma and tissues. The initial distribution volume for alfentanil is approximately five to seven times smaller than for fentanyl.²⁴ An alfentanil bolus dose 10 times larger than a fentanyl dose should achieve initial serum concentrations that are at least 50 times higher than initial fentanyl serum concentrations. The recirculatory peak in arterial alfentanil concentrations is most probably a result of its comparatively very small apparent distribution volume in body tissue.^{7,23} As a result of the low affinity of tissues and organs for alfentanil, the bolus dose remains unevenly distributed in plasma during the first few minutes. This recirculatory peak caused the alternate cerebral alfentanil extraction and release.

The cerebral extraction of sufentanil and fentanyl is monophasic. These differences in blood-brain equilibration may be caused by different extents of uptake by pulmonary and other tissues and different affinities to brain tissue.⁹ Taeger *et al.*⁵ demonstrated in surgical patients that 70.9% of the injected fentanyl was sequestered by the lung on the first passage of the opioid-containing blood through the pulmonary capillaries. For sufentanil, Boer *et al.*⁶ found a first-pass retention of 61.1%, whereas the mean peak extraction was 93.7%. Alfentanil showed a peak extraction of 67.4% and a much lower first-pass uptake of 10.1%. The smaller pulmonary uptake results in comparatively much higher arterial concentrations, against which the brain equilibrates. For drugs with extensive uptake like sufentanil and fentanyl, the lungs act as a temporary capacitor, reducing the peak concentration but delaying the de-

crease of arterial concentration after intravenous bolus application. The differences in blood-brain equilibration may result from different arterial concentration profiles. The smaller pulmonary uptake results in relatively higher initial arterial concentrations against which the brain equilibrates. Arterial alfentanil blood concentrations decrease much quicker than those of either fentanyl or sufentanil. Therefore, already within our short observation period they would decrease below the brain tissue concentration; *i.e.*, alfentanil release occurs.

According to figure 4, the amount of alfentanil that is present in the brain at the equilibrium point is 15 times greater than that of fentanyl and 90 times greater than that of sufentanil. The number of molecules transported over the membrane (drug flux) until equilibration differed significantly—thus the loading of the total of specific and unspecific binding sites.

To calculate the extent of drug uptake and elution by the mass balance principle, the afferent arterial and efferent venous blood samples must be representative of blood entering and leaving the region. It is known that the jugular bulb contains nearly exclusively cerebral venous blood if cerebral blood flow is normal.²⁵ The presence of normal global cerebral oxygen metabolism and intracranial pressure, cerebral perfusion pressure, and partial pressure of arterial carbon dioxide (P_{aCO_2}) values at the time of the study, as shown in table 1, suggests that cerebral blood flow was within the normal range in the population studied.^{26,27}

Concerning the effect of opioids on cerebral blood flow, animal studies as well as clinical studies are somewhat contradictory.²⁸⁻³³ In summary, based on the premise of unchanged P_{aCO_2} and preserved cerebral autoregulation, as was the case in our patient population, clinically used doses of opioids have minimal to modest depressive effects on cerebral blood flow and cerebral oxygen consumption. During the study some patients received continuous low-dose clonidine ($1.0-1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) as concomitant sedative. The direct effects of clonidine-associated α_2 -receptor stimulation on cerebral circulation are known to be very small with regard to both sympathetic and humoral influence.^{34,35} In human volunteers clonidine, $5 \mu\text{g}/\text{kg}$ orally, decreases mean cerebral blood flow velocity; therefore a slightly decreased cerebral blood flow should be anticipated.³⁶ In severely head-injured patients, clonidine bolus application had no clinically relevant influence on local cerebral circulation.^{37,38} With respect to the low doses used in our study and the mode of continuous application, clonidine should have had no significantly influence cerebral blood flow.

By administering the three drugs simultaneously there might have been some competition of the opioids for the same binding sites in blood. In human plasma approximately 84.4% of fentanyl, 92.5% of sufentanil, and 92.1% of alfentanil are bound.⁷ Basic drugs like these opioids are said to be far more extensively bound to α_1 -acid glycoprotein than to albumin. In newborn, infants, children and adults the free fraction of sufentanil was correlated strongly with the α_1 -acid glycoprotein plasma concentration; it was weakly correlated with plasma albumin concentration.³⁹ In contrast to sufentanil and alfentanil, fentanyl binding to α_1 -acid glycoprotein seems to be of minor importance but mainly depends on albumin, total protein, and apolipoprotein B concentrations.⁴⁰ Based on these data, competitive interactions in protein binding might have occurred between sufentanil and alfentanil. According to Meuldermans *et al.*,⁷ however, the rates of plasma protein binding of the three opioids were independent of their concentrations over the whole therapeutic range. In our opioid "cocktail" we applied a bolus containing 1.0 mg of alfentanil, which is considered to be in the lower part of the therapeutic range. Thus, even peak alfentanil serum concentrations in our patients were within this therapeutic range defined by Meuldermans *et al.*⁷ We therefore conclude that, despite the simultaneous alfentanil and sufentanil application, enough α_1 -acid glycoprotein binding sites should have been left for unchanged binding of sufentanil and at least alfentanil.

Conclusion

In conclusion, the underlying physiologic phenomenon that accounts for the different time lags between changes in serum concentrations after bolus application and drug effect of nearly equipotent doses of sufentanil, fentanyl, and alfentanil is the different time periods to blood-brain equilibration, which are caused mainly by the different tissue distribution volumes. Consequently, arterial alfentanil blood concentrations against which the brain equilibrates are relatively higher and change much more quickly than those of either fentanyl or sufentanil. In contrast to the monophasic cerebral uptake of sufentanil and fentanyl, alfentanil uptake by the brain is biphasic, caused by the recirculatory peak in arterial blood combined with the very rapid blood-brain equilibration kinetics.

The authors thank the Department of Anesthesiology and General Intensive Care (B), University Hospital Vienna, Austria for the opportunity to perform the analysis of serum opioid concentrations in their laboratory.

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