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Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids (Part 1)

Differences among Opioids

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Background: **The pharmacokinetics of epidurally administered drugs has been the subject of many studies, yet drug concentration in the epidural space has never been measured. This study was undertaken to characterize the epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidurally administered opioids on the basis of measurement of drug concentration in each of these compartments after epidural administration.**

Methods: **Morphine plus alfentanil, fentanyl, or sufentanil were administered epidurally in anesthetized pigs. Microdialysis was used to sample the epidural space and the cerebrospinal fluid for measurement of opioid concentration over time. Plasma samples were obtained from the central venous plasma and the epidural venous plasma. These data were used to calculate relevant pharmacokinetic parameters, including mean residence time, elimination half-lives, areas under the concentration *versus* time curves, clearance, and volume of distribution for each opioid in each compartment.**

Results: **Some of the more important findings were that the cerebrospinal fluid and plasma pharmacokinetics of the opioids did not parallel their epidural pharmacokinetics and that their hydrophobic character governed multiple aspects of their lumbar epidural pharmacokinetics.**

Conclusions: **The findings indicate that the spinal pharmacokinetics of these drugs are complex and, in some ways, counterintuitive. Also, the bioavailability of opioids in the cerebrospinal fluid and epidural space is determined primarily by their hydrophobicity, with less hydrophobic drugs having greater bioavailability.**

THE epidural route of drug administration has been in use for approximately 100 yr, and the pharmacology of epidural drug delivery has been the subject of innumerable clinical and animal studies. However, much of what is believed about the pharmacokinetic behavior of drugs in the epidural space has been inferred from measurement of drug concentrations in plasma and, occasionally, cerebrospinal fluid (CSF).[1–3] This indirect approach to the study of epidural pharmacokinetics has been necessitated by an inability to sample the epidural space. Consequently, much of what we believe about epidural pharmacokinetics is not supported by direct experimental evidence, and its validity is therefore questionable.

To place our understanding of epidural pharmacokinetics on firmer scientific ground, we designed a study in which microdialysis techniques were used to simultaneously sample the epidural and intrathecal spaces of immature pigs after epidural administration of morphine, fentanyl, alfentanil, and sufentanil. In addition, we measured drug concentrations in femoral venous plasma, epidural venous plasma, and epidural fat. The goals of this study were to characterize the epidural, intrathecal, and plasma pharmacokinetics of epidurally administered opioids and to understand how the physicochemical properties of an opioid influence its pharmacokinetics after epidural administration.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

The experiments described below were designed to characterize the effects of both the physicochemical properties of an opioid and coadministration of epinephrine on the epidural pharmacokinetics of the drug. For the purposes of clarity, the differences among drugs with respect to their pharmacokinetics are reported in this article, and the effects of epinephrine are reported in Part 2, in this issue.

Importantly, the same animals were used to address both research questions. Therefore, the methods used are reported in detail here and are omitted from the article that follows.

Animals

All studies were approved by the University of Washington's Institutional Animal Care and Use Committee. Twenty-eight mixed-sex farm-bred pigs weighing 10.4 ± 1.3 kg were used. All animals were group housed in a room with 12-h light/dark cycles and were given water *ad libitum* and twice-daily feedings of an age-appropriate amount of pig chow.

Drugs and Drug Administration

All animals were studied on two occasions separated by 1 week. In the first experiment, the study opioids

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were administered intravenously with and without intramuscular epinephrine. In the second study, the same doses of the same opioids were administered epidurally with and without epidural epinephrine.

Each animal received only two opioids, which were administered simultaneously; one opioid was always morphine and the second opioid was fentanyl, alfentanil, or sufentanil. Each animal received the pair of study opioids twice in each experimental session, once with epinephrine (1:200,000) and once with an equal volume of saline. The order of epinephrine administration was counterbalanced, with one half of the animals receiving epinephrine first and the other half receiving it second. The injections were made approximately 4.5 h apart, and drug concentration in all samples obtained after the second injection was corrected for the concentration of residual drug from the first injection. Residual concentration was extrapolated from the concentration in the last sample point from the first injection on the basis of the terminal elimination half-life calculated from the pharmacokinetics data obtained from the first injection.

Intravenous Studies

The intravenous opioid studies were designed to determine whether epinephrine affects the plasma pharmacokinetics of epidurally administered opioids *via* a systemic effect of absorbed epinephrine.

On the first study day, the animals were brought to the laboratory, anesthetized by mask inhalation of isoflurane (2–4%) in oxygen, paralyzed with intramuscular succinylcholine (100 mg), and intubated orally. Anesthesia was maintained with 1% isoflurane, and the animals were ventilated mechanically to maintain end-tidal CO_2 at 38–40 mmHg (Datex Airway Gas Analyzer Type GAO; Datex, Helsinki, Finland). A triple-lumen central venous catheter was placed percutaneously in the internal jugular vein, and a normal saline infusion was administered continuously at 4 $ml \cdot kg^{-1} \cdot h^{-1}$ *via* the distal lumen. Temperature was maintained between 37° and 38°C with a heat lamp servo-controlled by a rectal thermistor.

After a baseline blood sample (3 ml) had been collected, the animal was given an intramuscular injection of either 0.1 ml/kg plain saline or the same volume of saline containing 1:200,000 epinephrine. Intramuscular epinephrine injection was intended to mimic epidural epinephrine injection. The intramuscular route was chosen to obviate the risk of epidural hematoma or accidental meningeal puncture, either of which could have invalidated both the intravenous study and the subsequent epidural study. Five minutes after injection of the intramuscular solution, the animals were given an intravenous bolus of the two study opioids: morphine sulfate (100 μg/kg) plus fentanyl (3 μg/kg) or sufentanil (5 μg/kg) or alfentanil (50 μg/kg). The bolus, in a volume of 0.1 ml/kg, was administered *via* the distal lumen over a period of 5 s and was followed immediately by a rapid 5-ml saline flush.

Central venous blood samples (3 ml) were collected at 2, 5, 10, 20, 40, 60, 80, 100, 120, and 150 min and then every 30 min until 270 min. Samples were withdrawn from the proximal lumen of the central venous catheter after 5 ml of blood had first been withdrawn to clear the "dead space" in the catheter. Blood samples were centrifuged to collect plasma, which was frozen at −20°C until assayed. After the last blood sample had been collected from this first opioid injection, the intramuscular injection was repeated with either plain saline or saline plus epinephrine. Five minutes later, the same dose of the same study drugs was again injected intravenously, and central venous blood samples (3 ml) were again collected at 2, 5, 10, 20, 40, 60, 80, 100, 120, and 150 min and then every 30 min until 270 min. After the last sample was collected from this second study, the animals were allowed to awaken and were returned to the vivarium.

Epidural Studies

One week after the intravenous studies were performed, the animals were again anesthetized as described above under Intravenous Studies. Femoral arterial and venous cannulae were inserted *via* cutdown for blood sampling, blood pressure monitoring, and maintenance fluid administration. The femoral venous catheter was a 20-cm-long triple-lumen catheter (model AK-15703; Arrow International, Reading, PA) that extended a sufficient distance into the inferior vena cava to lie between the kidneys and the diaphragm. A second femoral arterial catheter was placed for calibrating spinal cord blood flow measurements made with fluorescent microspheres (see Spinal Cord Blood Flow section below). Custom-made microdialysis probes[4,5] were placed in the lumbar (L5) and thoracic (T12) epidural space and the lumbar (L5) intrathecal space as described previously.[4] Epidural drugs were administered *via* an epidural catheter (Perifix; B. Braun, Bethlehem, PA) affixed to the epidural microdialysis catheter. The right or left epidural vein was exposed through an approximately 5-mm laminotomy at L3 and was cannulated with a 24-gauge venous cannula (Angiocath; Becton Dickinson, Franklin Lakes, NJ). The catheter was fixed in place and the laminotomy closed with cyanoacrylate glue.

For each animal, the same opioids, doses, and order of the epinephrine-containing injection were used for the epidural study as for the intravenous study. Freshly opened epinephrine or an equal volume of saline was added to the solution containing the study opioids to produce a final epinephrine concentration of 1:200,000. All epidurally injected opioids contained radiotracer amounts of ^{14}C-labeled morphine (specific activity, 47 mCi/mmol; radiochemical purity, 98.7%; NEN, Boston, MA) plus either ^{3}H-labeled fentanyl (specific activ-

ity, 10.2 Ci/mmol; radiochemical purity, 98.5%; Janssen Pharmaceutica, Belgium), ^{3}H-labeled alfentanil (specific activity, 21.6 Ci/mmol; radiochemical purity, 99%; Janssen Pharmaceutica, Belgium), or ^{3}H-labeled sufentanil (specific activity, 21 Ci/mmol; radiochemical purity, 98.2%; Janssen Pharmaceutica, Belgium). The study drugs were diluted in normal saline to a final volume of 0.1 ml/kg and were injected by hand through the epidural catheter over a period of 60 s, after which the epidural catheter was flushed with 0.1 ml normal saline.

Dialysate samples were collected at 5-min intervals for the first 60 min and then at 10-min intervals until 240 min. Femoral venous and epidural venous blood samples were collected at 2, 5, 10, 20, 40, 60, 80, 100, and 120 min and then every 30 min for 240 min. After the last samples from the first epidural injection had been collected, the second injection either with or without epinephrine was made as described above, and samples were collected in the same manner for 240 min.

At the end of the epidural study, the microdialysis catheters were removed and calibrated *in vitro* by dialyzing a normal saline solution containing a known concentration of the study opioids. The fraction of opioid concentration recovered from this solution at steady state was used to correct the dialysate samples for recovery. Recovery averaged 11 ± 4% for morphine, 8 ± 1% for alfentanil, 19 ± 5% for fentanyl, and 13 ± 10% for sufentanil.

Opioids in Epidural Fat

At the end of the experiment, pieces of epidural fat were removed from sites adjacent to the dialysis probes. The samples were weighed and stored frozen at −20°C until assay for drug concentration as described below in the Drug Assays section. Because of a laboratory error, samples from the morphine/sufentanil studies were not analyzed.

Spinal Cord Blood Flow

Spinal cord blood flow was measured with a classic microsphere technique to determine whether epidural epinephrine significantly altered spinal cord perfusion. The details of the fluorescent microsphere technique used to measure blood flow have been published previously by this laboratory.[6] Briefly, the heart was exposed *via* a left thoracotomy and the left atrium cannulated with a 20-gauge catheter (Abbocath; Abbott Hospitals, Inc., North Chicago, IL). At the designated time, fluorescent microspheres (Molecular Probes, Eugene, OR) were injected rapidly into the left atrium. Simultaneously, right and left femoral arterial blood was withdrawn at 10 ml/min *via* a syringe pump (model 22; Harvard Instruments, Holliston, MA). The number of microspheres in these blood samples was then used to convert the number of microspheres in tissue to blood flow per minute. Blood flow was measured immediately before each epidural drug injection and again 15 and 60 min later with different fluorescence-labeled microspheres.

At the end of the experiment, three spinal cord sections (L5, T12, C6) were removed and the tissue samples allowed to autolyse for 2 weeks at room temperature, followed by sequential digestion in potassium hydroxide and Triton X-100 (Sigma, St. Louis, MO). The microspheres were then lysed with 2-ethoxyethylacetate to release their fluorescent dye, which was then measured spectrophotometrically (LS 50B; Perkin Elmer, Bucks, UK) to determine the number of microspheres present per gram of tissue.

Drug Assays

Dialysate Samples. Radiolabeled opioid concentration in dialysate samples was determined by radiotracer methods as described previously.[4] Briefly, 5 ml of hydrofluor scintillation cocktail (National Diagnostics, Atlanta, GA) was added to each sample, and the sample was counted on a Packard Tri-carb 2000 liquid scintillation counter (Packard Instrument Corporation, Meriden, CT) for 10 min or until the SD of disintegrations per minute was < 2%. All samples were corrected for background disintegrations per minute.

Plasma Samples. The gas chromatography–mass spectrometry methods used to quantify morphine, fentanyl, alfentanil, and sufentanil in plasma have been reported previously from our analytical laboratory.[7,8] The limit of detection was 0.5 ng/ml for morphine, 0.05 ng/ml for alfentanil, 0.05 ng/ml for fentanyl, and 0.002 ng/ml for sufentanil. The interday coefficient of variation was 4.3% for morphine, 3.8% for alfentanil, 6.6% for fentanyl, and 11.5% for sufentanil.

Fat Samples. Fat samples were defrosted and allowed to autolyse at room temperature for 4–6 days. After autolysis, 3–4 ml Solvable tissue solubilizer (Packard Bioscience, Meriden, CT) was added to each sample, and the samples were incubated at 60°C for 12–24 h as needed to liquefy the sample. Four to 6 ml of Formula-989 liquid scintillation cocktail (Packard Bioscience) was added to each sample, and the samples were counted in a Packard Tri-carb 2000 liquid scintillation counter as described above for dialysate samples.

Pharmacokinetic Analysis

Noncompartmental statistical moments analysis was used to determine the area under the concentration–time curve (AUC), mean residence time (MRT), volume of distribution, and clearance. The analyses were performed with PK Solutions 2.0 software (Summit Research Services, Montrose, CO). Terminal elimination half-lives and the initial volume of the central compartment were obtained by stripping the concentration–time plots and fitting an exponential curve using PK Solutions software.

Table 1. Epidural and Intrathecal Pharmacokinetic Parameters

Sampling Site, Parameter	Opioid			
	Morphine	Alfentanil	Fentanyl	Sufentanil
Lumbar epidural				
AUC/dose, nmol · min^{-1} · ml^{-1}	9.8 ± 5.9 (F,S)	10.8 ± 4.9 (F,S)	1.3 ± 1.0 (M,A)	2.9 ± 2.0 (M,A)
MRT, min	36.1 ± 12.8 (F,S)	58.6 ± 48.5(S)	88 ± 65 (M,S)	148 ± 76 (M,A,F)
Clearance, ml/min	0.15 ± 0.12 (F,S)	0.10 ± 0.05 (F,S)	1.2 ± 0.9 (M,A)	0.8 ± 0.8 (M,A)
Volume of central compartment, ml	3.9 ± 3.0 (F,S)	2.5 ± 2.0 (F,S)	38 ± 44 (M,A)	38 ± 58 (M,A)
Volume of distribution, ml	12.6 ± 11.5 (F,S)	14.7 ± 9.6 (F,S)	244 ± 240 (M,A,S)	139 ± 103 (M,F)
Term elim. $t_{1/2}$, min	51.5 ± 12.7 (A,F,S)	100.4 ± 46.5 (M,S)	126 ± 40 (M,S)	165 ± 67 (M,A,F)
Lumbar intrathecal				
AUC/dose, nmol · min^{-1} · ml^{-1}	1.7 ± 1.6 (A,F,S)	0.84 ± 0.67 (M)	0.19 ± 0.14 (M)	0.41 ± 0.21 (M)
MRT, min	102 ± 59	71 ± 29	67 ± 40	93 ± 30
Term elim. $t_{1/2}$, min	80 ± 40	110 ± 89	97 ± 36	100 ± 35
Thoracic epidural				
AUC/dose, nmol · min^{-1} · ml^{-1}	4.3 ± 4.1 (F,S)	4.85 ± 3.41 (F,S)	0.19 ± 0.14 (M,A)	0.30 ± 0.25 (M,A)
MRT, min	49 ± 35	97 ± 96	76 ± 43	103 ± 46
Term elim. $t_{1/2}$, min	60 ± 26 (A,S)	139 ± 124 (M)	107 ± 21	128 ± 35 (M)

A,F,S, or M indicates which opioids are significantly different from that opioid.

A = alfentanil; AUC = area under concentration–time curve; F = fentanyl; M = morphine; MRT = mean residence time; S = sufentanil; Term Elim. $t_{1/2}$ = terminal elimination half-life.

Because much of statistical moments analysis rests on measurement of AUC, it is important that the portion of the AUC derived from the actual data (*i.e.*, $AUC_{(0\text{-}t)}$) covers a large percentage of the AUC derived from extrapolation to infinity (*i.e.*, $AUC_{(0\text{-infinity})}$). That was the case in this study. Specifically, in the epidural space, the percentage of the $AUC_{(0\text{-infinity})}$ covered by the actual data averaged 98 ± 3% for morphine, 93 ± 8% for alfentanil, 92 ± 8% for fentanyl, and 89 ± 7% for sufentanil. In the intrathecal space, the percentage of the $AUC_{(0\text{-infinity})}$ covered by the actual data averaged 93 ± 6% for morphine, 95 ± 7% for alfentanil, 95 ± 5% for fentanyl, and 89 ± 6% for sufentanil.

For drug concentration measured in plasma after epidural opioid administration, the percentage of the $AUC_{(0\text{-infinity})}$ covered by the actual data averaged 87 ± 10% for morphine, 92 ± 9% for alfentanil, 88 ± 7% for fentanyl, and 80 ± 12% for sufentanil. For drug concentration measured in plasma after intravenous opioid administration, the percentage of the $AUC_{(0\text{-infinity})}$ covered by the actual data averaged 91 ± 0.05% for morphine, 93 ± 7% for alfentanil, 91 ± 4% for fentanyl, and 95 ± 4% for sufentanil.

Statistical Analysis

It was decided prospectively to analyze the effect of epinephrine on pharmacokinetic parameters within drugs and within sampling sites (*e.g.*, lumbar epidural, intrathecal, epidural venous plasma) only. These analyses were performed by use of the Student paired *t* test.

It was also decided prospectively to compare pharmacokinetic parameters among opioids for the plain (*i.e.*, non–epinephrine-containing) solution only and to make these comparisons within compartments only as well. This statistical analysis was done using ANOVA. The decision not to analyze all possible pairwise comparisons among both plain and epinephrine-containing opioid injections at each sampling site was made to preserve statistical power.

The only analysis performed that was not identified prospectively was a within-drug comparison of terminal elimination half-lives between the lumbar epidural and lumbar intrathecal sampling sites. This analysis was performed because it helped to shed light on the rate-limiting step controlling drug residence in the intrathecal space (*i.e.*, transfer from the epidural space *vs.* clearance from the intrathecal space).

For any pharmacokinetic parameter that showed a statistically significant difference between at least two opioids (table 1), ANOVA was used to determine whether there was a significant correlation between that pharmacokinetic parameter and the molecular weight or octanol:$buffer_{7.4}$ distribution coefficient of the opioids. The octanol:$buffer_{7.4}$ distribution coefficients were obtained from the literature.[9]

For all analyses, differences were considered statistically significant at a value of $P < 0.05$.

Results

Epidural and Intrathecal Space Pharmacokinetics

Lumbar Epidural Space. Figure 1 shows the dose-normalized extracellular fluid space concentration–time plots for all four opioids at the lumbar epidural site of injection. Table 1 presents the corresponding pharmacokinetic parameters.

In general, the pharmacokinetic parameters for morphine and alfentanil were similar and differed significantly from those for fentanyl and sufentanil, which were generally comparable. For example, the dose-nor-

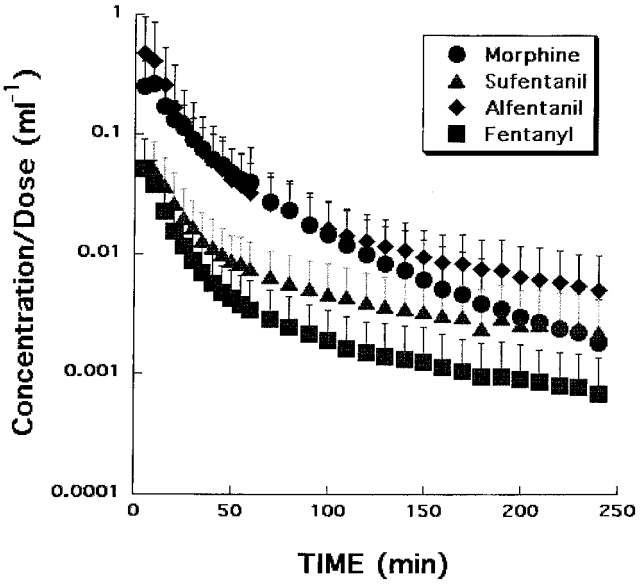

Fig. 1. Dose-normalized concentrations of morphine, alfentanil, fentanyl, and sufentanil in the extracellular fluid of the lumbar epidural space.

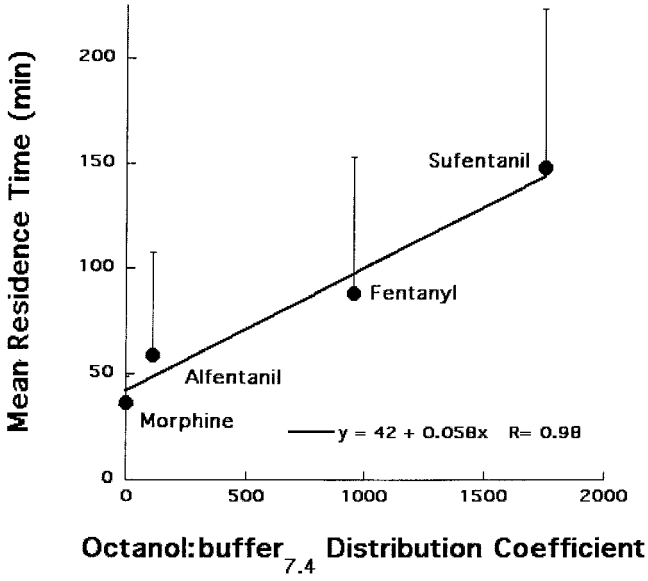

Fig. 2. Relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and their mean residence times in the extracellular fluid of the lumbar epidural space (P < 0.0001).

malized AUC did not differ between morphine and alfentanil, but the dose-normalized AUCs of both opioids were severalfold greater than the dose-normalized AUCs of both fentanyl and sufentanil. The MRT of morphine did not differ significantly from that of alfentanil, but it was significantly shorter than the MRT of both fentanyl and sufentanil. The MRT of alfentanil was shorter than that of fentanyl and sufentanil, but the difference reached statistical significance only for sufentanil.

Clearance, volume of the central compartment, and volume of distribution did not differ between morphine and alfentanil but were all significantly lower than those of fentanyl and sufentanil. None of these parameters differed significantly between fentanyl and sufentanil.

The terminal elimination half-life of morphine was significantly shorter than that of any of the other opioids, whereas that of sufentanil was the longest of the four opioids. The terminal elimination half-life of alfentanil was shorter than that of fentanyl, but the difference did not reach statistical significance.

Importantly, there was a significant linear correlation between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and both their MRTs and terminal elimination half-lives (figs. 2 and 3).

Thoracic Epidural Space. Figure 4 shows the dose-normalized extracellular fluid space concentration–time plots for all four opioids at the thoracic epidural site of injection. Table 1 presents the corresponding pharmacokinetic parameters.

As in the lumbar epidural space, the dose-normalized AUCs of morphine and alfentanil were comparable and significantly greater than those of fentanyl and sufentanil. Also, the terminal elimination half-life was significantly shorter for morphine than for the other opioids; half-lives for the other opioids did not differ significantly from one another. Interestingly, as in the lumbar epidural space, there was a significant correlation between the terminal elimination half-life of the opioids and their physicochemical properties. However, in the thoracic epidural space, the correlation was between the terminal elimination half-life and the square root of the molecular weight of the opioids (fig. 5).

Unlike at the opioid injection site in the lumbar epidural space, MRT did not differ significantly among the

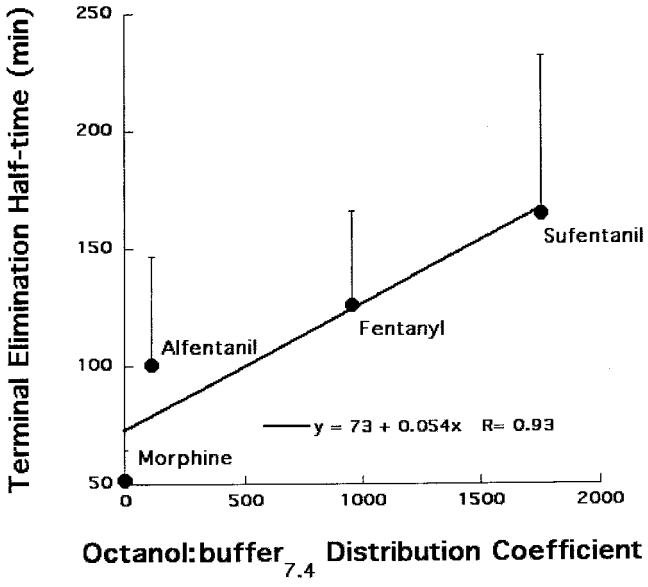

Fig. 3. Relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and their terminal elimination half-times in the extracellular fluid of the lumbar epidural space (P < 0.0001).

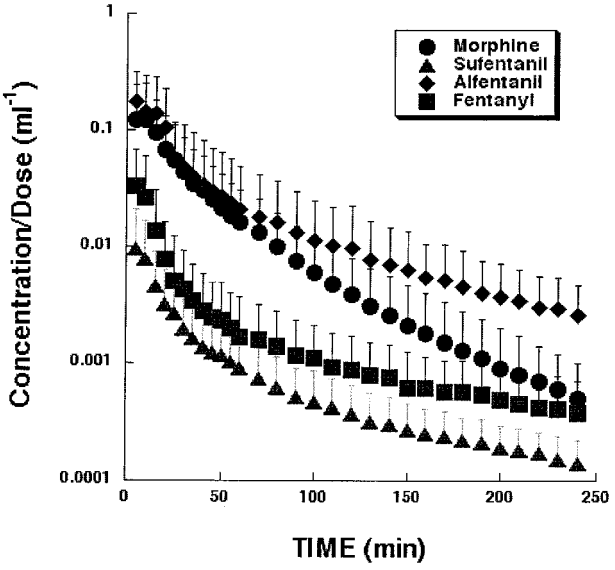

Fig. 4. Dose-normalized concentrations of morphine, alfentanil, fentanyl, and sufentanil in the extracellular fluid of the thoracic epidural space.

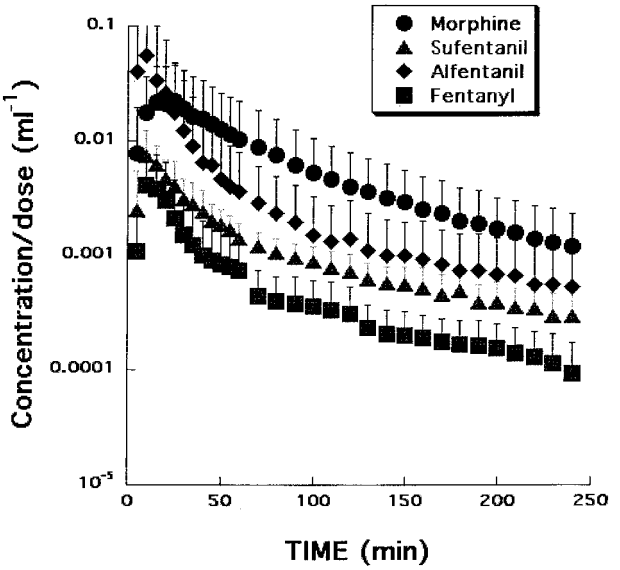

Fig. 6. Dose-normalized concentrations of morphine, alfentanil, fentanyl, and sufentanil in the cerebrospinal fluid of the lumbar intrathecal space opposite the lumbar epidural site of administration.

opioids in the thoracic epidural space (although statistical power was limited: $\beta = 0.49$).

Lumbar Intrathecal Space. Figure 6 shows the dose-normalized concentration–time plots for all four opioids in the lumbar intrathecal space opposite the epidural site of injection. Table 1 presents the corresponding pharmacokinetic parameters.

Dose-normalized AUC was significantly greater for morphine than for the other three opioids, which did not differ from one another. Neither MRT nor terminal elimination half-lives differed significantly among the opioids, although statistical power was limited ($\beta = 0.42$ and $\beta = 0.23$, respectively).

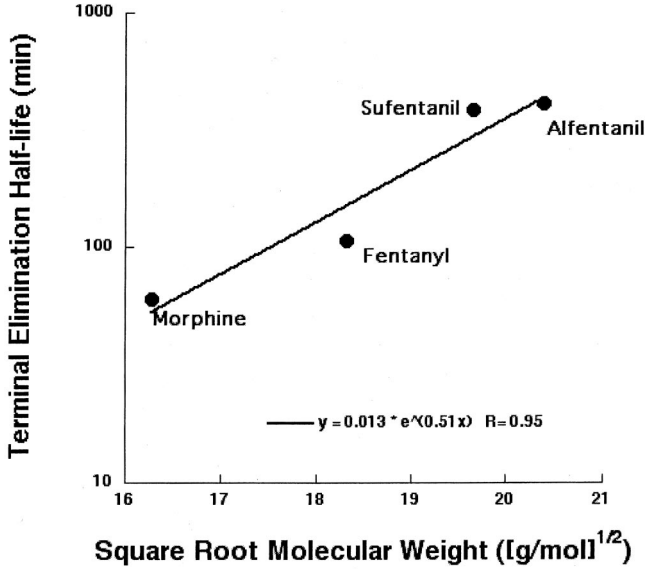

Fig. 5. Relationship between the molecular weights of the opioids and the log of their terminal elimination half-lives in the extracellular fluid of the thoracic epidural space ($P < 0.014$).

Interestingly, there was no significant difference between the epidural and the intrathecal terminal elimination half-lives of alfentanil, fentanyl, and sufentanil (table 1). However, the intrathecal terminal elimination half-life of morphine was significantly longer than the lumbar epidural elimination half-life of the drug (table 1).

Plasma Pharmacokinetics

Epidural Opioid Administration and Central Venous Sampling. Figure 7 shows the dose-normalized concentration–time plots in central venous plasma for morphine, alfentanil, and sufentanil administered into the lumbar epidural space. There are no data for fentanyl because too few of the samples had measurable concentrations. Table 2 presents the derived pharmacokinetic parameters.

The dose-normalized AUC and peak concentration of alfentanil were significantly greater than those of morphine and sufentanil, which did not differ significantly from one another. However, MRT was shorter for alfentanil than for the other two opioids.

Epidural Opioid Administration and Epidural Venous Sampling. Figure 8 shows the dose-normalized concentration–time plots in epidural venous blood for all four opioids after epidural administration. Table 2 presents the derived pharmacokinetic parameters.

The peak plasma concentration of morphine, alfentanil, and sufentanil in epidural venous blood was at least an order of magnitude greater than peak concentration in central venous blood (recall that fentanyl concentration was not reliably measurable in central venous blood after epidural administration). The MRT of sufentanil was significantly greater than that of the other opioids,

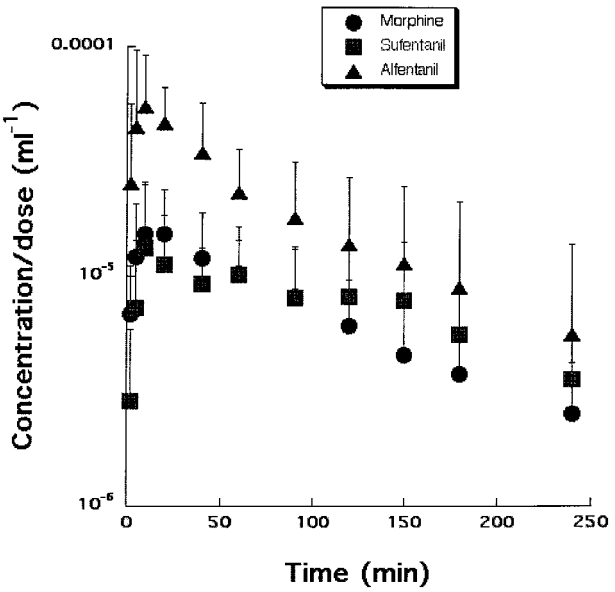

Fig. 7. Dose-normalized concentration–time plots for morphine, alfentanil, and sufentanil in central venous plasma after administration into the lumbar epidural space. There are no data for fentanyl because too few of the concentrations were within the measurable range.

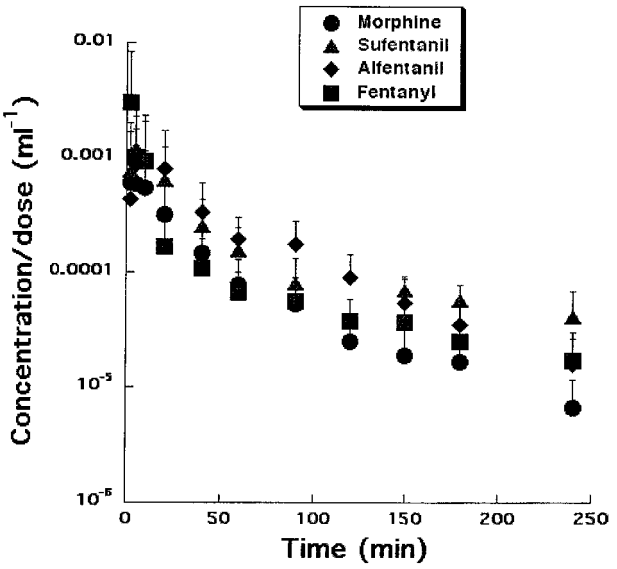

Fig. 8. Dose-normalized concentration–time plots for morphine, alfentanil, fentanyl, and sufentanil in the epidural venous plasma after lumbar epidural administration.

which did not differ from one another. In addition, there was a significant linear relationship between MRT in epidural venous plasma and the octanol:buffer$_{7.4}$ distribution coefficient of the opioids (fig. 9).

IV Opioid Administration/Central Venous Sampling. Figure 10 shows the dose-normalized central venous plasma concentration–time plots for all four opioids administered intravenously. Table 2 shows the derived pharmacokinetic parameters.

The dose-normalized peak concentration and AUC were significantly greater for alfentanil than for the other three opioids. Neither dose-normalized peak concentration nor AUC differed among alfentanil, fentanyl, and sufentanil. Apparent clearance was significantly lower for alfentanil than for the other opioids. Both MRT and terminal elimination half-life were longer for alfentanil

Table 2. Plasma Pharmacokinetic Parameters

Opioid Administration Site	Morphine	Alfentanil	Fentanyl	Sufentanil
Internal jugular				
Central venous				
AUC/dose, min/ml	0.0039 ± 0.0035 (A)*	0.012 ± 0.009 (M,F,S)*	0.0022 ± 0.0006 (A)*	0.0024 ± 0.0011 (A)*
MRT	77 ± 20	154 ± 188	85.9 ± 31	55.3 ± 18.6
Vd, l	53 ± 37	33 ± 53	53 ± 9	41.9 ± 15.6
Cl, ml/min	482 ± 502 (A)*	139 ± 88 (M,F,S)*	498 ± 190	552.8 ± 314.7
Terminal elim. $t_{1/2}$, min	78 ± 21	108 ± 81	68 ± 33	59.2 ± 22.0
Peak conc./dose, × 10^{-9}/ml	0.20 ± 0.19 (A)*	1.1 ± 1.1 (M,F,S)*	0.062 ± 0.02 (A)*	0.083 ± 0.04 (A)*
Time to peak conc., min	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0
Epidural				
Central venous				
AUC/dose	0.0027 ± 0.0011 (A)*	0.0054 ± 0.0048(M,S)*	UM	0.0022 ± .0009 (A)*
MRT	150.3 ± 63.2	100.5 ± 54.6	UM	192 ± 53
Terminal elim. $t_{1/2}$	114.2 ± 62.2	73.2 ± 37.3	UM	132 ± 43
Peak conc./dose, × 10^{-9}/ml	0.025 ± 0.011 (A)*	0.066 ± 0.044 (M,S)*	UM	0.019 ± 0.013 (A)*
Time to Peak Conc., min	21.5 ± 21	17.9 ± 13.1	UM	33 ± 19
Epidural venous				
AUC/dose	0.033 ± 0.021	0.043 ± 0.024	0.034 ± 0.033	0.049 ± .04
MRT	60.3 ± 43.3 (S)*	75.5 ± 20.8 (S)*	82.5 ± 41.4 (S)*	163 ± 83 (M,A,F)*
Terminal elim. $t_{1/2}$	69.6 ± 38.3	60.3 ± 31.5	149 ± 79	144 ± 50
Peak conc./dose, × 10^{-9}/ml	1.2 ± 1.3	1.2 ± 1.1	1.1 ± 1.1	1.3 ± 1.3
Time to peak conc., min	13.0 ± 14.1	12.4 ± 11.7	7.0 ± 3.2	4.8 ± 3.3

A,F,S, or M indicates which opioids are significantly different from that opioid for that parameter.

* Indicates $P < 0.05$ compaired with other opioids. A = alfentanil; AUC = area under concentration–time curve; Conc. = concentration; F = fentanyl; M = morphine; MRT = mean residence time; S = sufentanil; Terminal elim. $t_{1/2}$ = terminal elimination half life; UM = unmeasureable; Vd = volume of distribution.

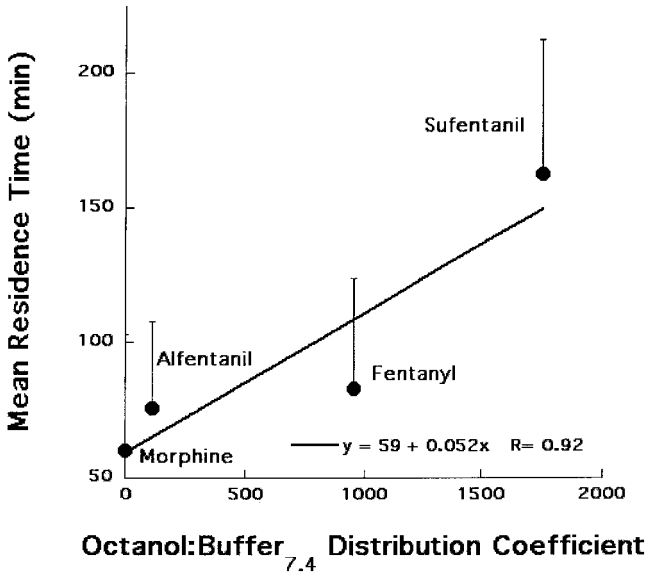

Fig. 9. Relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and their mean residence times in epidural venous plasma (P = 0.0004).

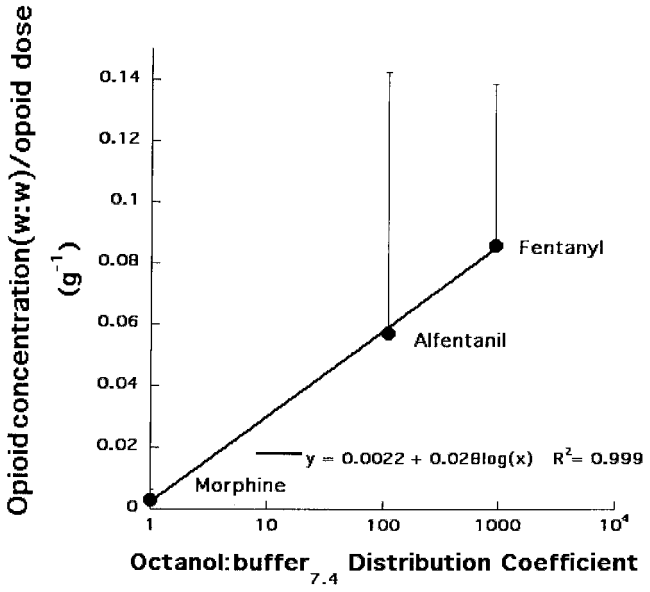

Fig. 11. Relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and their dose-normalized concentration (w:w) in fat taken from the lumbar epidural space at the conclusion of the experiment.

than the other opioids, although these parameters just missed being statistically significant (P = 0.064, power = 0.595 and P = 0.076, power = 0.563, respectively).

Opioid Accumulation in Epidural Fat. The dose-normalized morphine content in epidural fat averaged $2.7 \pm 3.4 \times 10^{-3}$/g, $0.74 \pm 0.61 \times 10^{-3}$/g, and $0.078 \pm 0.079 \times 10^{-3}$/g in samples obtained from the lumbar, thoracic, and cervical epidural spaces, respectively. At the lumbar level, the alfentanil content of epidural fat was approximately 20-fold greater than the concentration of morphine ($57.0 \pm 85.6 \times 10^{-3}$/g). In the thoracic and cervical epidural fat, dose-normalized alfentanil content was $23.6 \pm 47.8 \times 10^{-3}$/g and $0.21 \pm 0.01 \times 10^{-3}$/g, respectively. At the lumbar level, the fentanyl content of epidural fat ($85.9 \pm 53.0 \times 10^{-3}$/g) was approximately 32-fold greater than the morphine content. In the thoracic and cervical epidural fat, dose-normalized fentanyl content was $47.2 \pm 26.1 \times 10^{-3}$/g and $0.64 \pm 0.12 \times 10^{-3}$/g, respectively. Sufentanil content in epidural fat was not determined because of a laboratory error.

Not surprisingly, there was a strong linear relationship between the hydrophobic character of the opioids and their concentration in epidural fat (fig. 11).

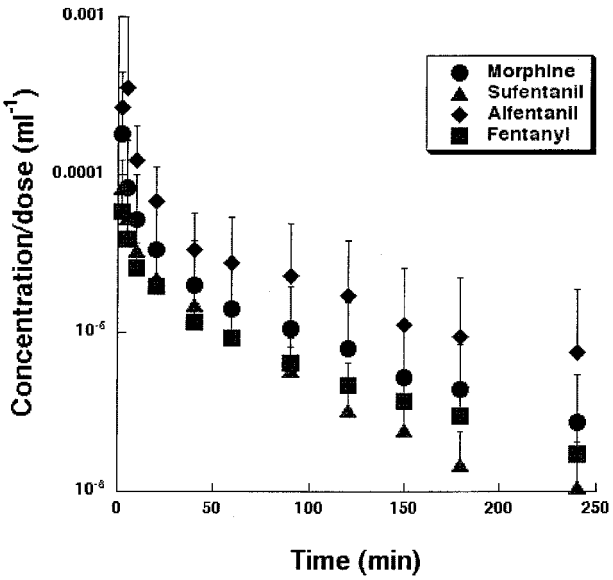

Fig. 10. Dose-normalized concentration–time plots for morphine, alfentanil, fentanyl, and sufentanil in central venous plasma after intravenous administration.

Discussion

The behavior of drugs in the epidural space has been the subject of much discussion, speculation, and description. To the best of our knowledge, however, this is the first study to actually measure drug concentration in the epidural space. Not surprisingly, our findings confirm some conventional wisdoms and cast doubt on others.

As expected, there were some marked differences among the opioids in their pharmacokinetics, and many of the pharmacokinetic differences correlated with differences in physicochemical properties among the drugs. For example, there was a significant correlation between the hydrophobicity of the opioids and MRT both in the extracellular fluid of the lumbar epidural space and in the epidural venous plasma (figs. 2 and 9). Similarly, terminal elimination half-lives in the lumbar epidural space were linearly related to hydrophobicity as well (fig. 3). A likely explanation for these findings is that

hydrophobic opioids are sequestered in lipoidal environments surrounding the epidural space to a greater degree than are more hydrophilic drugs. Slow release of sequestered opioids back into the extracellular fluid of the epidural space would result in a prolonged elimination half-life and an increased MRT. Consistent with this hypothesis is the linear relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and opioid content in epidural fat obtained at the end of the experiments (fig. 11). Further evidence that hydrophobic opioids are sequestered in periepidural tissues is the comparatively large volume of distribution and initial volume of the central compartment of fentanyl and sufentanil.

The prolonged residence time of hydrophobic opioids in the epidural space is consistent with the fact that multiple human studies have shown that epidurally administered alfentanil, sufentanil, and fentanyl produce little, if any, of their postoperative analgesic effects *via* a spinal mechanism,[10–15] *i.e.*, they have negligible access to the spinal cord because of sequestration and/or rapid vascular uptake from the epidural space.

Although hydrophobicity correlated with terminal elimination half-life in the lumbar epidural space, this was not the case in the thoracic epidural space. In the thoracic epidural space, the molecular weight of the opioids was correlated significantly with terminal elimination half-life. Why the thoracic and lumbar epidural spaces should differ in this regard is unclear. One possibility is that rate of spread from the lumbar injection site to the thoracic sampling site varies inversely with molecular weight and that terminal elimination half-life in the thoracic epidural space is more dependent on differences in the rate at which opioids spread rostrally than it is on differences in the rate at which opioids are eliminated from the thoracic epidural space. This hypothesis is consistent with the fact that diffusion rates vary inversely with molecular weight. However, this hypothesis would require that diffusion, as opposed to bulk flow during opioid injection, is the rate-limiting step governing opioid movement from the lumbar epidural space to the thoracic epidural space. The data do not clarify whether this is the case.

One of the more interesting findings with respect to differences among the opioids in their CSF pharmacokinetics is that their epidural pharmacokinetics did not predict their CSF pharmacokinetics. For example, whereas the epidural MRT and terminal elimination half-lives differed significantly among the opioids, no such differences occurred in the intrathecal space. In addition, unlike the epidural space, there was no correlation between any of the pharmacokinetic parameters and the hydrophobic character or molecular weight of the opioids. This is an important observation because it demonstrates that the epidural and intrathecal spaces are not directly linked, in a kinetic sense, such that a change in opioid pharmacokinetics in one compartment is reflected by a corresponding change in pharmacokinetics in the other compartment. This is not to suggest that drug concentration in the epidural space does not affect drug concentration in the intrathecal space, because clearly it must, given that the epidural space is the original source of all intrathecal drug. Rather, the data suggest that there is not a clear, direct, one-to-one correspondence between the pharmacokinetics of the two compartments.

The reason(s) behind this apparent dissociation of epidural and intrathecal pharmacokinetics is unclear. It may be that the opioids accumulate to varying degrees in intervening barriers (*e.g.*, dura mater, arachnoid mater, epidural fat) and that their CSF pharmacokinetics are dependent on their pharmacokinetics in these tissues as much as on their pharmacokinetics in the extracellular fluid of the epidural space. If this were the case, then one might well expect the link between epidural and intrathecal pharmacokinetics to be masked by the impact of these intervening tissues.

Another interesting aspect of the intrathecal pharmacokinetics of these opioids is that the terminal elimination half-lives of alfentanil, fentanyl, and sufentanil did not differ significantly between the epidural and intrathecal spaces. This suggests that diffusion through the multiple meningeal barriers is the rate-limiting process controlling the terminal elimination half-lives of these opioids. However, the intrathecal terminal elimination half-life of morphine was significantly longer than its epidural terminal elimination half-life. This would suggest that slow clearance from the intrathecal space is the rate-limiting step controlling the concentration of morphine in the CSF. Slow clearance of morphine from the aqueous CSF is consistent with its relatively hydrophilic character and an earlier intrathecal opioid study from our laboratory.[4]

A final, and clinically relevant, aspect of the intrathecal pharmacokinetics of these drugs is the very large dose-normalized AUC of morphine compared with the other opioids. As in the epidural space, the AUC of morphine exceeds that of fentanyl and sufentanil by severalfold. In addition, the dose-normalized AUC of morphine in the intrathecal space also exceeds that of alfentanil by severalfold. This contrasts sharply with the epidural space AUCs for morphine and alfentanil, which did not differ. Why this is the case is unclear, but it underscores that the bioavailability of morphine in the intrathecal space is far greater than that of the other more hydrophobic opioids.

Obviously, greater morphine concentration in the CSF is not proof of greater concentrations at opioid receptors in the spinal cord dorsal horn, which is the intended target site. However, in an earlier intrathecal opioid study from this laboratory using this same model, we

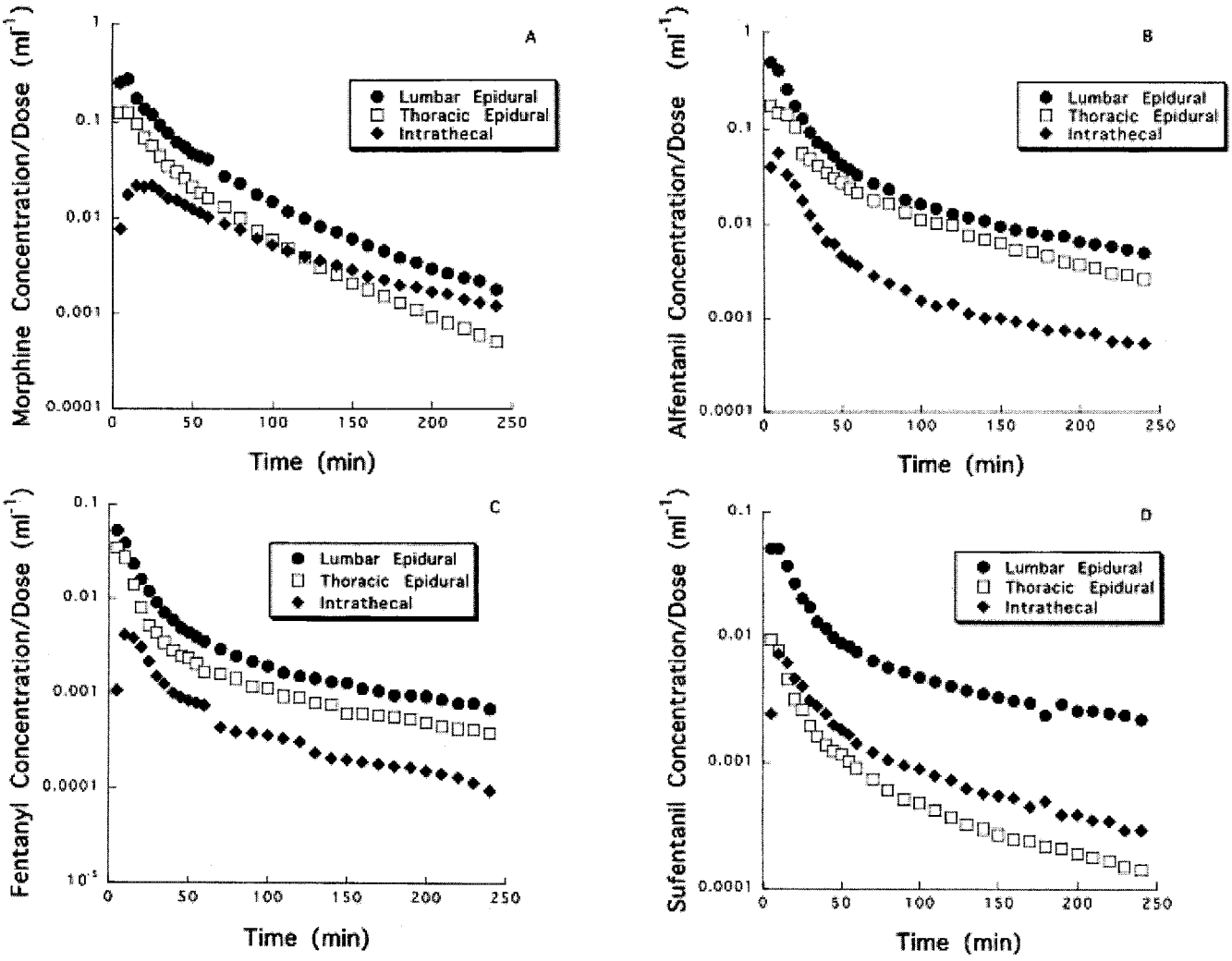

Fig. 12. Dose-normalized concentration–time plots for morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in the lumbar epidural, thoracic epidural, and intrathecal spaces.

demonstrated that the dose-normalized concentration of morphine in CSF was significantly greater than that of alfentanil, fentanyl, and sufentanil and that this was predictive of significantly greater morphine content in the spinal cord.[4] Thus, together, the present study and our earlier work suggest that after epidural administration, morphine has much greater bioavailability in the spinal cord than alfentanil, fentanyl, and sufentanil. This view is entirely consistent with the clinical observation that epidurally administered morphine clearly produces postoperative analgesia *via* a spinal mechanism, whereas alfentanil and sufentanil do not and fentanyl does so to a very limited degree at best.

As noted in Materials and Methods, we did not make statistical comparisons across opioids and compartments to preserve statistical power. However, inspection of the data does reveal some interesting apparent differences among the opioids in their relative behaviors in the different compartments, *i.e.*, sampling sites. To facilitate comparisons, figure 12 plots the concentration–time data for the plain solution of each opioid in the lumbar epidural, thoracic epidural, and lumbar intrathecal spaces on a single graph.

Figure 12, *A* clearly demonstrates the marked difference in the intrathecal terminal elimination half-life of morphine compared with its lumbar epidural terminal elimination half-life. For alfentanil and fentanyl, the lumbar epidural and intrathecal curves are nearly parallel (fig. 12, *B* and *C*). For sufentanil, the terminal portions of the epidural and intrathecal curves trend toward divergence (fig. 12, *D*), although the difference in elimination half-lives did not quite reach statistical significance ($P = 0.058$).

Another striking feature is that for morphine, alfentanil, and fentanyl (fig. 12, *A–C*), the lumbar epidural and thoracic epidural curves are reasonably close to one another (recognize that these are logarithmic plots). However, this is not the case for sufentanil, for which the thoracic epidural curve is markedly less than the lumbar epidural curve (fig. 12, *D*), thereby demonstrat-

ing relatively poor rostral spread of sufentanil compared with the other opioids.

Comparison of the lumbar epidural and lumbar intrathecal curves demonstrates that the two are much closer to one another for morphine than for any of the other opioids, which is consistent with relatively greater amounts of morphine than of the other three opioids reaching the intrathecal space.

In summary, this is the first study to simultaneously measure drug concentration in the epidural, intrathecal, and plasma compartments over time after epidural drug administration. The most salient findings are that the kinetics of drug movements among these compartments are complex, and the epidural and intrathecal spaces cannot be viewed simply as two well-stirred compartments separated by a single kinetic barrier. Consequently, it is not possible to infer drug behavior in one compartment by measuring its concentration in another. In addition, much of the pharmacokinetic behavior of epidurally administered opioids within the epidural space is governed by the hydrophobic character of the drug, with hydrophobic drugs having less bioavailability in the epidural and intrathecal space than more hydrophilic molecules.

One final point follows. We recognize that some readers would have preferred that we perform a compartmental analysis of these data. However, we plan to take the data from the present study and integrate them with our earlier study of intrathecally administered opioid pharmacokinetics[4] to produce a comprehensive compartmental model of spinal opioid pharmacokinetics. This integrated model will be published in the future as a separate article.

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