

## LABORATORY INVESTIGATIONS

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# Comparative Spinal Distribution and Clearance Kinetics of Intrathecally Administered Morphine, Fentanyl, Alfentanil, and Sufentanil

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**Background:** Despite widespread use, little is known about the comparative pharmacokinetics of intrathecally administered opioids. The present study was designed to characterize the rate and extent of opioid distribution within cerebrospinal fluid, spinal cord, epidural space, and systemic circulation after intrathecal injection.

**Methods:** Equal doses of morphine and alfentanil, fentanyl, or sufentanil were administered intrathecally (L3) to anesthetized pigs. Microdialysis probes were used to sample cerebrospinal fluid at L2, T11, T7, T3, and the epidural space at L2 every 5–10 min for 4 h. At the end of the experiment, spinal cord and epidural fat tissue were sampled, and each probe's recovery was determined *in vitro*. Using SAAM II pharmacokinetic modeling software (SAAM Institute, University of Washington, Seattle, WA), the data were fit to a 16-compartment model that was

divided into four spinal levels, each of which consisted of a catenary arrangement of four compartments representing the spinal cord, cerebrospinal fluid, epidural space, and epidural fat.

**Results:** Model simulations revealed that the integral exposure (area under the curve divided by dose) of the spinal cord (*i.e.*, effect compartment) to the opioids was highest for morphine because of its low spinal cord distribution volume and slow clearance into plasma. The integral exposure of the spinal cord to the other opioids was relatively low, but for different reasons: alfentanil has a high clearance from spinal cord into plasma, fentanyl distributes rapidly into the epidural space and fat, and sufentanil has a high spinal cord volume of distribution.

**Conclusions:** The four opioids studied demonstrate markedly different pharmacokinetic behavior, which correlates well with their pharmacodynamic behavior. (Key words: Epidural space; pharmacokinetics; pig; spinal cord.)

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SINCE its introduction into clinical practice nearly 20 yr ago,<sup>1</sup> spinal opioid administration has become commonplace in anesthetic practice. Morphine was the first opioid used for spinal administration and is arguably the most common spinal opioid in use today. Although morphine produces long-lasting, potent analgesia after spinal administration, it also produces important dose-limiting side effects, including sedation and potentially fatal respiratory depression. These side effects result from morphine's redistribution to brain by rostral spread in spinal cerebrospinal fluid (CSF).

Because of morphine's dose-limiting side effects, numerous other opioids have been used intrathecally, including heroin,<sup>2</sup> meperidine,<sup>3</sup> methadone,<sup>4</sup> hydromorphone,<sup>5</sup> fentanyl,<sup>6,7</sup> alfentanil,<sup>8</sup> and sufentanil.<sup>9</sup> These opioids have been advocated by one or more investigators in the hope that they would provide analgesia comparable to morphine without significant side effects. Unfortunately, this "trial and error" approach has not identified any opioid with these clinical characteristics. The fact that opioids with such widely different physicochemical properties and clinical pharmacology have

been tested intrathecally underscores the fact that we lack the information necessary to mount a rational directed search for the optimal spinal opioid. The information that is missing is a thorough understanding of the processes governing the distribution of intrathecally administered drugs.

Although no opioid has emerged as an ideal choice for intrathecal administration, there are nonetheless marked clinical differences among opioids after intrathecal administration. Perhaps the clearest differences among opioids are in their durations of action, their propensity for rostral spread, and the magnitude by which an opioid's analgesic potency differs between intravenous administration and intrathecal administration.

It is likely that pharmacokinetic differences are largely responsible for these important differences in the clinical pharmacology of opioids administered intrathecally. Unfortunately, intrathecal opioid pharmacokinetics are poorly understood because of the difficulty in repeatedly sampling drug concentration in all of the relevant compartments (e.g., CSF, spinal cord, plasma, epidural space, epidural fat).

Thus, the purpose of this study was to develop an animal model of intrathecal drug delivery that allowed collection of the data necessary to model intrathecal opioid pharmacokinetics. To achieve this goal, we developed a pig model in which microdialysis techniques were used to simultaneously and continuously sample the freely diffusible opioid concentration in the extracellular fluid space of the CSF and the epidural space after intrathecal administration of morphine, alfentanil, sufentanil, and fentanyl. Microdialysis sampling has the distinct advantage that it does not remove CSF or epidural space contents and thus does not alter the system under study. The dialysate concentration-time data were used for compartmental modeling, which allowed a detailed elaboration of the rate and extent of opioid movement from the CSF into the spinal cord, the epidural space, the epidural fat, and the systemic circulation. This pharmacokinetic analysis provided useful insights into the pharmacokinetics of intrathecal drug administration, which, in turn, govern the pharmacodynamics of spinal opioid analgesia.

## Materials and Methods

### *Microdialysis Experiments*

Studies were approved by the University of Washington Animal Care and Use Committee. American Associa-

tion for Laboratory Animal Care guidelines were followed throughout the experiments.

**Preparation of Microdialysis Probes.** Microdialysis probes were prepared from cellulose microdialysis fibers (Spectrum Medical Industries, Houston, TX) with a 215- $\mu\text{m}$  ID, a 235- $\mu\text{m}$  OD, and a molecular weight cutoff of 6,000 d. Epoxy cement was used to coat all but the center 2 cm of the fiber, thus creating a 2-cm dialysis window. Epoxy was spread evenly over the fiber by running a 2-cm length of polyethylene-10 tubing over the fiber while the epoxy was still wet. Polyethylene-10 tubing has an ID of 280  $\mu\text{m}$ ; thus, the dialysis probe had a final OD of 280  $\mu\text{m}$ . To facilitate placement of the dialysis probes within the CSF, a 90- $\mu\text{m}$  diameter wire was inserted into the lumen of the dialysis probe and bent at the center of the dialysis window, thereby creating a microdialysis loop. A 0.5-mm cone-shaped length of silicone caulk was placed approximately 0.5 mm from the dialysis window. To prevent CSF leak, this elastic cone was wedged into the meningeal hole through which the probes were inserted into the CSF. All probes were allowed to "cure" for at least 12 h before implantation and were used within 48 h of preparation.

**Surgical Preparation.** Farm-bred pigs ( $n = 20$ ) weighing 7–12 kg were used. Each animal was anesthetized by mask inhalation of halothane (1–2%) and nitrous oxide (70%) in oxygen, paralyzed with intramuscular succinylcholine, orotracheally intubated, and mechanically ventilated. End-tidal carbon dioxide was continuously monitored (Datex model AS/3 airway gas analyzer, Helsinki, Finland), and arterial blood gasses were measured to verify the accuracy of expired carbon dioxide measurements. Ventilation was adjusted as indicated by end-tidal carbon dioxide measurements to maintain normocapnia (38–42 mmHg). Body temperature was maintained at 37–38°C using a servo-controlled heat lamp and a rectal thermister.

The left femoral artery was cannulated for blood pressure measurement and blood sampling. The left femoral vein was cannulated for infusion of Ringer's lactate (4 ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup>) as a maintenance fluid. Pancuronium (5–10 mg intravenously) was administered only during the surgical procedure to prevent electrocautery from depolarizing the spinal nerves, thereby causing involuntary movement.

The vertebral spines from L5 to C7 were exposed bilaterally through a midline incision. To access the epidural and intrathecal spaces, the ligamentum flavum was exposed at the L4–L5, T13–L1, T9–T10, T5–T6, and T1–T2 levels, and a small (approximately 3-mm) hole

was made through the ligament. An iris scissor was used to cut a small (1-mm) hole through the meninges, and a microdialysis probe was inserted through the hole and into the CSF at the T13-L1, T9-T10, T5-T6, and T1-T2 levels. These probes were inserted in a caudal direction for a distance of approximately 2 cm. In addition, a dialysis probe was placed in the epidural space through the incision at L4-L5 and was directed cephalad. To permit intrathecal drug injection, an epidural catheter (Buron Medical Inc., Bethlehem, PA) was placed in the intrathecal space at L4-L5 and directed cephalad a distance of approximately 2 cm. Consequently, the intrathecal injection catheter inserted at L4-L5 came to lie beneath the L3 spinous processes. Similarly, the tip of the epidural dialysis probe and the most caudad intrathecal dialysis probe (T13-L1 insertion site) were both located very near the injection site at the level of the L2 spinous process. Importantly, all intrathecal probes were separated from one another by a constant distance of four vertebral bodies.

The insertion points through the spinal meninges and the ligamentum flavum were secured with cyanoacrylate glue to restore the integrity of the intrathecal and the epidural spaces. Integrity was verified by the absence of visible CSF leak at the beginning and the end of each experiment.

**Dialysis Protocol.** Mock CSF (NaCl 140 mEq, NaHCO<sub>3</sub> 25 mEq, KCl 2.9 mEq, MgCl<sub>2</sub> 0.4 mEq, urea 3.5 mEq, glucose 4.0 mEq, and CaCl<sub>2</sub> 2.0 mEq; pH 7.38–7.42; 295 mOsm) was oxygenated and pH-adjusted by bubbling with 95% O<sub>2</sub>/5% CO<sub>2</sub>. It was then pumped through the five dialysis probes at 10  $\mu$ l/min.

At time zero, equal doses (0.013  $\mu$ mol) of morphine and either fentanyl (n = 6), alfentanil (n = 8), or sufentanil (n = 6) and their corresponding radiotracers (<sup>14</sup>C-morphine: specific activity = 47 mCi/mmol, radiochemical purity = 98.7% [NEN, Boston, MA]; <sup>3</sup>H-fentanyl: specific activity = 10.2 Ci/mmol, radiochemical purity = 98.5% [Janssen Pharmaceutica, Beerse, Belgium]; <sup>3</sup>H-alfentanil: specific activity = 21.6 Ci/mmol, radiochemical purity = 99% [Janssen Pharmaceutica]; <sup>3</sup>H-sufentanil: specific activity = 21 Ci/mmol, radiochemical purity = 98.2% [Janssen Pharmaceutica]) were injected intrathecally at the L4-L5 level. The drugs were injected over a period of 2 min (by hand) in a volume of 100  $\mu$ l. Thereafter, CSF and epidural space microdialysis samples were collected continuously as 5-min (50  $\mu$ l) aliquots during the first hour and as 10-min aliquots thereafter until 240 min. At 4 h, the experiment was terminated, the animal was killed by intravenous injection of saturated KCl, and

the dialysis probes were removed. The explanted probes were placed into a vial of normal saline containing the study opioids and their corresponding radiotracers. This solution was then dialyzed for 20 min, and the drug concentration in the dialysate was compared with the known concentration in the vial. In this way, we corrected each dialysis probe for its recovery efficiency.

After the dialysis probes were removed, tissue samples of spinal cord (approximately 1 cm in length; average weight = 0.58 g) and epidural fat (average weight = 0.08 g) were removed from the area adjacent to the dialysis probes. Tissue specimens were briefly rinsed in ice water, patted dry, weighed, and solubilized (Solvable Tissue and Gel Solubilizer, Packard Instruments, Downer's Grove, IL) at 50°C.

**Radioactivity Assay.** Hydrofluor (National Diagnostics, Mannville, NJ) scintillation fluid (5 ml) was added to all dialysate samples and Formula 989 (Packard Instruments, Downer's Grove, IL) scintillation fluid (10–20 ml) was added to all tissue samples. All samples were counted in a liquid scintillation counter (Tri-Carb 2000; Packard Instruments) for 15 min or until the SD of disintegrations per minute was  $\leq$  2%. Background counts from mock CSF pumped through the probes before injection of any radioactivity were subtracted from total disintegrations per minute of samples collected during the postinjection period. Extracellular concentrations of <sup>14</sup>C- and <sup>3</sup>H-labeled opioids were calculated from the dialysate concentrations corrected for the probe recovery.

#### *Pharmacokinetic Modeling*

Pharmacokinetic modeling was performed on the dialysate concentration-time data. Only data from pigs free of experimental complications were used. In the alfentanil, fentanyl, and sufentanil groups, respectively, three, two, and two pigs were excluded because the injection catheter was placed in the subdural space instead of the subarachnoid space. Subdural placement was evidenced by the fact that drug concentrations were far greater in the epidural space than the intrathecal space. This left five pigs in the alfentanil group, four in the sufentanil group, and four pigs in the fentanyl group. Because morphine was coadministered as a reference drug in each experiment, morphine dialysate data were available in all 13 remaining pigs.

**Model Development.** A pharmacokinetic model for the spinal distribution of intrathecally administered opioids was developed that specifically accounts for the distribution of the four opioids under study between the



central nervous system did not contribute to the drug concentration in the adjacent spinal cord measured by microdialysis.<sup>14</sup>

Symmetrical permeability for bidirectional transfer across diffusional barriers was also assumed; thus, transfer clearances between compartments were set equal. This, in effect, allowed us to reduce the number of rate constants for estimation. For example,

$$V_{\text{cord}} \cdot k_{\text{ci}} = V_{\text{csf}} \cdot k_{\text{ic}}$$

where  $V_{\text{cord}}$  is the apparent volume of distribution of the spinal cord,  $V_{\text{csf}}$  is the apparent volume of distribution of the CSF,  $k_{\text{ic}}$  is the rate of transfer from CSF into spinal cord, and  $k_{\text{ci}}$  is the rate of transfer from cord back into CSF. Accordingly,  $k_{\text{ci}}$  can be computed from  $k_{\text{ic}}$ ,  $V_{\text{csf}}$ , and  $V_{\text{cord}}$  as follows, thereby reducing four parameters to three parameters that require estimation:

$$k_{\text{ci}} = k_{\text{ic}} \cdot [V_{\text{csf}}/V_{\text{cord}}]$$

Overall, the number of primary parameters that required estimation was reduced to 10, which included the volume terms  $V_{\text{csf}}$ ,  $V_{\text{cord}}$ , and  $V_{\text{epi}}$  (the apparent volume of distribution within the epidural space) as well as the transfer rate constants  $k_{\text{ic}}$ ,  $k_{\text{ie}}$  (transfer rate constant for drug movement from the intrathecal space into, respectively, the spinal cord and the epidural space),  $k_{\text{plc}}$  (transfer rate constant for drug movement from the spinal cord into the plasma),  $k_{\text{plepi}}$  (transfer rate constant for drug movement from the epidural space into the plasma),  $k_{\text{ef}}$  (transfer rate constant for drug movement from the epidural space into the epidural fat),  $k_{\text{fe}}$  (transfer rate constant for drug movement from the epidural fat to the epidural space), and  $k_{\text{ros}}$  (transfer rate constant for rostral drug distribution). The remaining parameters,  $k_{\text{ci}}$ ,  $k_{\text{ci}}$  (rate constant for drug transfer from, respectively, the spinal cord and the epidural space into the intrathecal space), and  $V_{\text{fat}}$  (apparent volume of distribution within epidural fat) were estimated from the primary parameters based on the symmetrical clearance assumption as illustrated previously.

**Model Adjustments.** The dialysate concentration-time data (corrected for recovery) were fitted to the 16-compartment model. The intrathecal dose was assumed to distribute instantaneously in the L2–L3 CSF compartment. Several further adjustments specific to the individual opioid were made. In the case of morphine, sequestration in epidural fat was found to be negligible; hence, the fat compartment was deleted from the model fit for morphine. In two of the fentanyl pigs, fentanyl concentrations were undetectable at levels T11, T7, and

T3; their model fits did not converge. Therefore, the iterative two-stage method<sup>15</sup> was used to provide extra information on the pharmacokinetic behavior of fentanyl. This method uses the sample mean parameter values and their SDs as Bayesian priors. In this case, these Bayesian priors were obtained from the two fentanyl pigs that were successfully fitted individually. In refitting the data, Bayesian priors were applied only to the parameters that were hard to estimate ( $k_{\text{plc}}$ ,  $k_{\text{ros}}$ ).

The opioid amounts in the spinal cord tissue at 240 min, calculated by multiplying the measured tissue concentrations by the weight of the tissue section taken at the end of the experiment, were not included in the data set during the fitting process. However, the ratios of opioid amounts observed across the spinal cord tissue levels, L2–3/T11, T11/T7, and T7/T3, were compared to these ratios based on predicted opioid amounts in the spinal cord tissue at the four levels (predicted cord concentration at 240 min multiplied by the estimated  $V_{\text{cord}}$ ). If the observed and predicted ratios of opioid amounts between spinal cord tissue levels did not agree sufficiently, the observed opioid amounts in the cord tissue were used as a guide in setting the parameter guess estimates in the fitting process.

**Analysis of Model Parameters.** The distribution of model parameter estimates for the individual pigs seemed to deviate from normality. Box plots were used to represent the distribution of each parameter estimate in an opioid group. Two opioids were considered to differ significantly for a particular pharmacokinetic parameter if the 25–75th percentile box plots of the two opioids did not overlap. Residual graphs were produced within each opioid group based on either the mean, median, or geometric mean of the parameter estimates. The population statistic that produced the most homogeneous distribution of the residuals was selected to represent the pharmacokinetic population model for a particular opioid.

To examine the consequences of the observed differences in pharmacokinetic parameters across opioids, the concentration- or amount-time profiles for each opioid in the various tissue compartments were simulated based on the median values or the geometric mean values of its pharmacokinetic parameters.

## Results

### *Opioid Concentration-Time Course*

Figure 2 shows a comparison of the average concentration-time course of the four opioids at the intrathecal

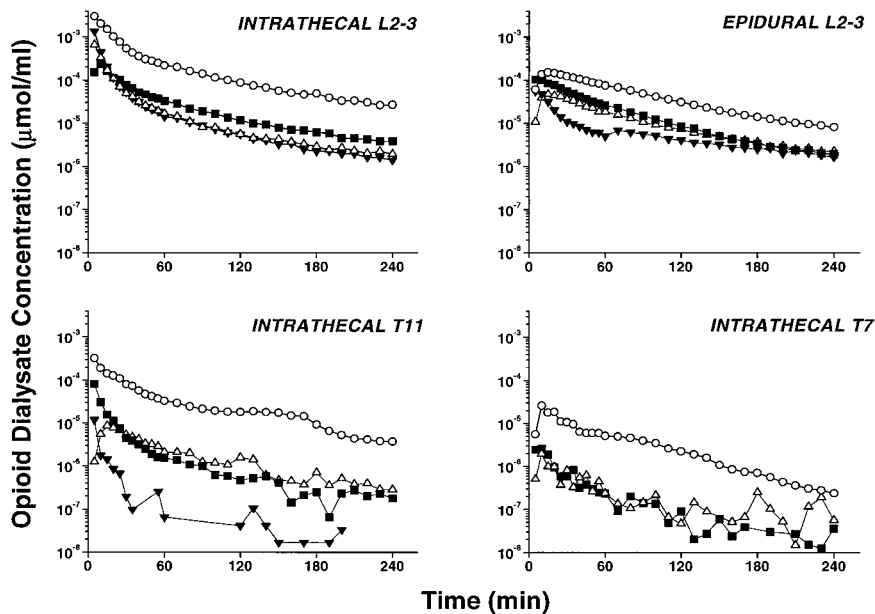


Fig. 2. The average concentration–time course of morphine (open circles;  $n = 13$ ), alfentanil (filled squares;  $n = 5$ ), fentanyl (filled inverted triangles;  $n = 4$ ), and sufentanil (open triangles;  $n = 4$ ) at each sampling site. Sampling site at T3 is not included in this figure because at this level only two pigs in the morphine group and one pig in the alfentanil group had detectable concentrations of opioid.

sites (L2–L3, T11, and T7) and at the L2–L3 epidural site. The concentration–time profile at level T3 is not included in figure 2 because opioid concentration was undetectable at this most rostral level in the majority of pigs (11 of 13 in the morphine group, 4 of 4 in the fentanyl group, 4 of 4 in the sufentanil group, and 4 of 5 in the alfentanil group). Figure 2 shows that the dialysate concentration was consistently the highest for morphine among the four opioids at all four sampling sites. Nearly instantaneous increase and rapid decrease of CSF concentration was observed for all opioids at the L2–L3 and T11 sampling sites. Another notable feature is the fast increase and biphasic decrease of fentanyl concentration compared with the other three opioids in the epidural space. At the more rostral levels of intrathecal sampling (T11, T7), fentanyl concentrations were statistically significantly lower than the other opioid concentrations. This suggests that for fentanyl, the rostral distribution *via* CSF occurred to the least extent. In general, the concentrations of alfentanil and sufentanil were intermediate of the morphine and fentanyl concentrations. Figure 3 shows that as the concentration is measured at a greater distance from the injection site (L2–L3), the peak concentration occurs later, and the absolute concentration decreases.

#### Pharmacokinetic Modeling

**Pharmacokinetic Modeling Fits.** Dialysate concentration–time data for each opioid in the individual pigs were fitted to the 16-compartment model depicted in

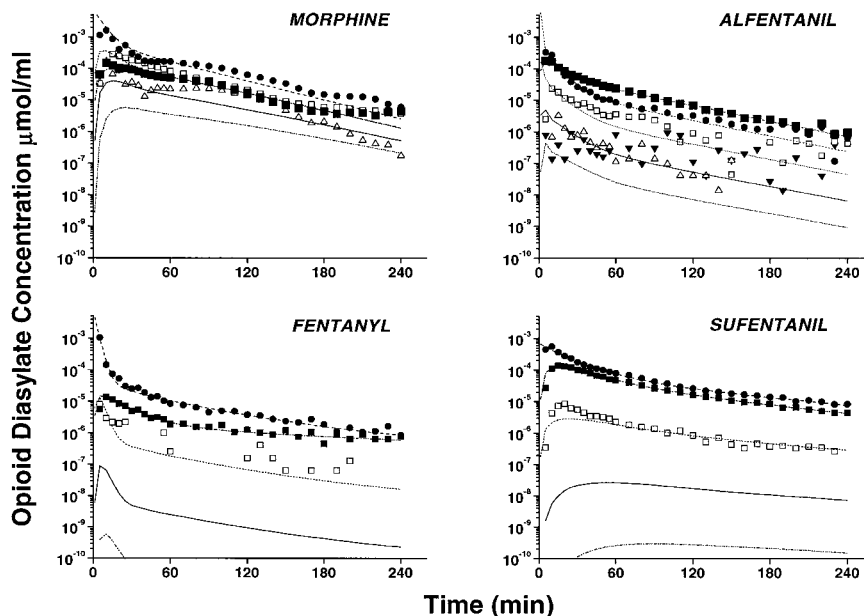
figure 1. In the case of morphine, the model could be reduced to a 12-compartment model because no significant sequestering of morphine occurred in the epidural fat compartment.

Figure 3 shows a representative fit of the model to data from individual pigs for each opioid. As this figure shows, the model generally fitted the data well. Further evidence of the model validity can be seen in figure 4, which shows a correlation plot of spinal cord amounts of each opioid predicted by the model (calculated by multiplying the estimated apparent volume of distribution of the cord by the predicted concentration at 240 min) and the actual amount measured at 240 min. At levels L2–L3 and T11, the points cluster along the line of identity, which increased our confidence in the predicted value for the apparent volume of distribution of the cord. Only at the more rostral level, T7, does the model's prediction deviate substantially from the actual measured opioid concentrations. At this level, the model predicts lower amounts than were actually found (see Discussion for explanation). This plot also increases our confidence in the estimate for the rate constants for opioid movement from spinal cord into systemic circulation ( $k_{plc}$ ), which is an inferred and spatially averaged kinetic estimate.

Overall, the model demonstrates that alfentanil and fentanyl are cleared much more rapidly from the CSF than morphine and sufentanil, as indicated by the rapid initial decrease in their CSF concentration at L2–L3, T11, T7, and T3 (fig. 3). As in figure 2, the model demon-

## INTRATHECAL OPIOID KINETICS

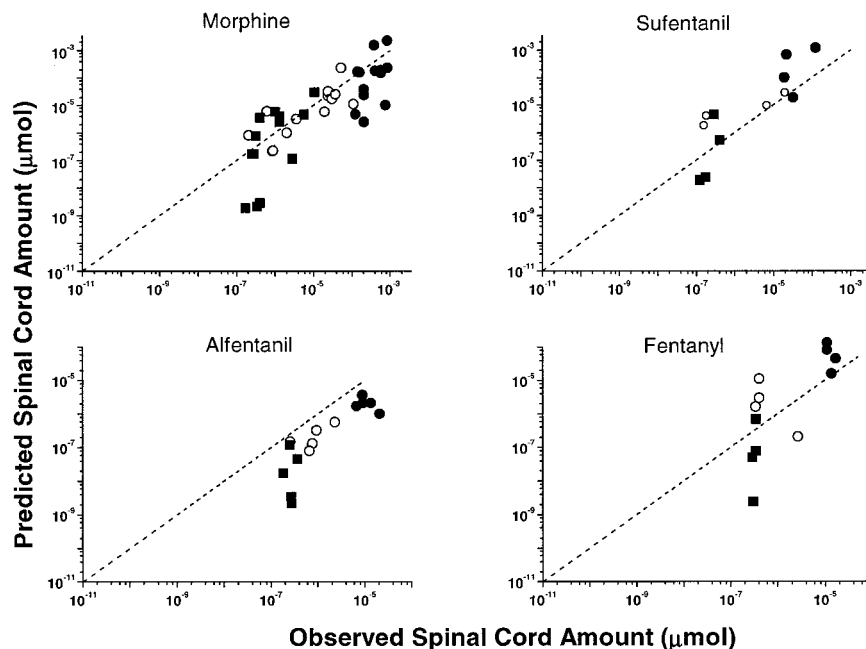
Fig. 3. Representative fits of the pharmacokinetic model to the concentration-time data for each of the four opioids in each individual pig. The scattered symbols are filled squares for epidural L2-L3, filled circles for intrathecal L2-L3, open squares for intrathecal T11, open triangles for intrathecal T7, and filled inverted triangles for intrathecal T3. The predicted concentration-time profiles are drawn as single filled circles with a dashed line for epidural L2-L3, dashed line alone for intrathecal L2-L3, filled circles alone for intrathecal T11, straight line for intrathecal T7, and double filled circles with a dashed line for intrathecal T3 through the observed concentration points at each sampling site.



strates that fentanyl exhibits two distinct exponential phases of elimination from the epidural space. This suggests compartmentation within the epidural space, which conceivably represents the distribution kinetics between the fluid and fat compartments of the epidural space. The model also predicts that fentanyl and sufentanil undergo limited rostral spread, as indicated by their low CSF concentrations at T7 and T3.

**Pharmacokinetic Parameter Estimates.** Residual analysis of the population models based on the mean, median, or geometric mean of the parameter estimates was performed to find out which parameter distribution performed the best in representing the data for each opioid. For this purpose, residual graphs were produced to look for homogeneous distribution around the statistic. Figure 5 displays the log (measured/predicted) resid-

Fig. 4. Scatter graph of the observed spinal cord tissue amounts plotted against the predicted spinal cord amounts at 240 min after intrathecal administration. The symbols represent different sampling sites: (filled circles) L2-L3; (open circles) T11; (filled squares) T7. The dashed line is the line of identity.



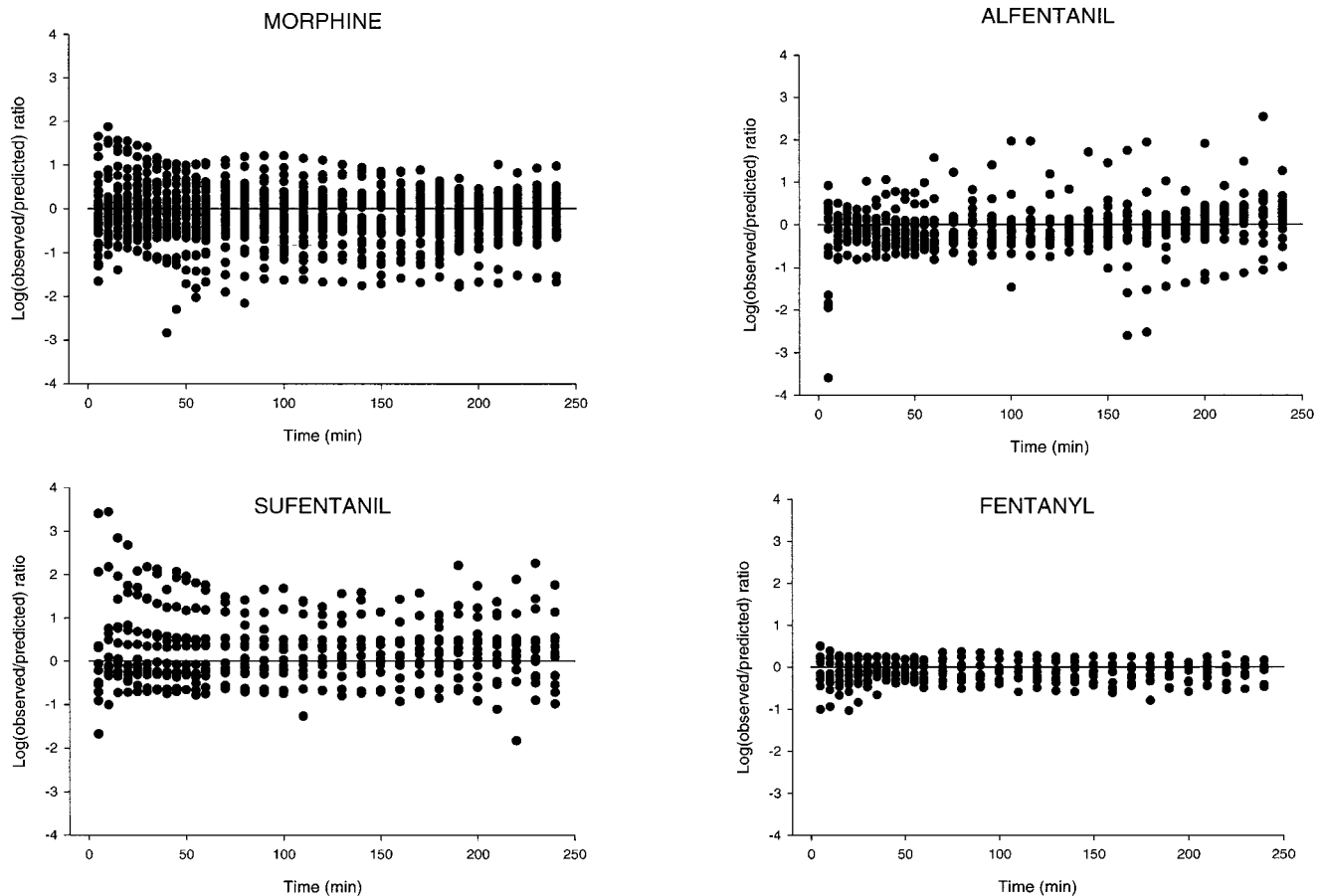


Fig. 5. Residual graphs for each opioid. The log ratio was calculated of each observed concentration divided by its predicted concentration using either the median parameters for morphine and sufentanil or the geometric mean of the parameter for alfentanil and fentanyl in the pharmacokinetic model.

ual graphs of the models chosen for each of the opioids: the median for morphine and sufentanil and the geometric mean for alfentanil and fentanyl. Table 1 lists the median pharmacokinetic parameter estimates for morphine and sufentanil and the geometric mean of the pharmacokinetic parameter estimates for alfentanil and fentanyl. The within-group distributions of the pharmacokinetic parameter estimates are displayed in the box plots in figures 6 and 7.

**Apparent Volume of Distribution.** The box plots in figure 6 show the apparent volume of distribution for the CSF, spinal cord, and epidural space for each opioid. In general,  $V_{csf}$  was the smallest, and  $V_{epiflat}$  was the largest. The latter volume is the sum of  $V_{epi}$  and  $V_{fat}$ , which allows a fair comparison of epidural distribution volume between morphine and the other opioids, because  $V_{fat}$  for morphine was considered negligible. Both  $V_{csf}$  and  $V_{cord}$  increased as the hydrophobicity of the opioid in-

Table 1. Pharmacokinetic Parameters of Intrathecal Opioids

Parameter	Morphine*	Alfentanil†	Fentanyl†	Sufentanil*
$k_{ic}$ ( $\text{min}^{-1}$ )	0.0370	0.1700	0.0339	0.0200
$k_{ci}$ ( $\text{min}^{-1}$ )	0.0143	0.0236	0.0159	0.0095
$k_{ie}$ ( $\text{min}^{-1}$ )	0.0542	0.1372	0.1078	0.0291
$k_{ei}$ ( $\text{min}^{-1}$ )	0.0021	0.0063	0.0285	0.0137
$k_{ros}$ ( $\text{min}^{-1}$ )	0.0048	0.0158	0.0022	0.0006
$k_{ef}$ ( $\text{min}^{-1}$ )	N/A	0.0108	0.1190	0.0077
$k_{fe}$ ( $\text{min}^{-1}$ )	N/A	0.0817	0.0105	0.0092
$k_{pic}$ ( $\text{min}^{-1}$ )	0.0082	0.0868	0.0080	0.0131
$k_{plepi}$ ( $\text{min}^{-1}$ )	0.0199	0.0201	0.1088	0.0323
$V_{csf}$ (ml)	2.420	1.910	11.08	47.50
$V_{cord}$ (ml)	7.890	13.76	23.58	100.7
$V_{epi}$ (ml)	44.40	41.88	45.88	112.3
$V_{fat}$ (ml)	N/A	5.536	518.0	3.170

\* Median value.

† Geometric mean.



## INTRATHECAL OPIOID KINETICS

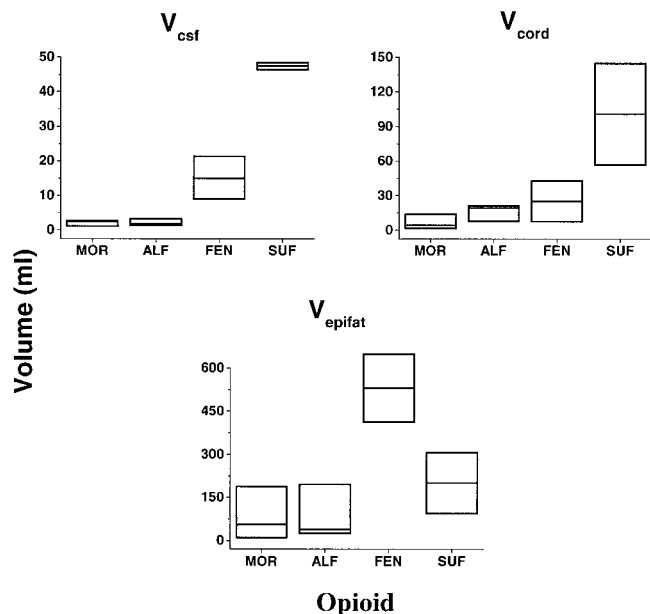


Fig. 6. Box plots of the volume of distributions (milliliters). The top line of the box represents the 75th percentile, the bottom line represents the 25th percentile, and the "middle" line represents the 50th percentile or the median. The opioids are arranged along the x-axis in the order of increasing lipophilicity. Different y-axis scales are used for the three volumes.  $V_{epifat}$  is the sum of  $V_{epi}$  and  $V_{fat}$ , which allows a fair comparison of epidural distribution volume between morphine and the other opioids, because  $V_{fat}$  for morphine was considered negligible.

creased. However,  $V_{epifat}$  showed a different trend: fentanyl had a higher  $V_{epifat}$  than sufentanil, despite its nearly 50% smaller octanol:buffer distribution coefficient.<sup>16</sup>

**Rate Constants.** Figure 7A-F shows the box plots for the rate constants derived from the model. Rostral movement within CSF ( $k_{ros}$ ) is the slowest process for all four opioids. The rate constant for CSF-to-cord transfer ( $k_{ic}$ ) of alfentanil was five to eight times higher than those of the other opioids, *i.e.*, five to eight times more rapid transfer (fig. 7A, table 1). Values for  $k_{ic}$  were reasonably comparable between the other opioids, with sufentanil being the lowest.

Alfentanil's rate constant for transfer from the CSF to the epidural space ( $k_{ie}$ ) was higher than the other opioids as well (fig. 7B, table 1). The rank order of the other three opioids was fentanyl > morphine > sufentanil.

Figure 7C shows the transfer rate constants for rostral spread ( $k_{ros}$ ) within the CSF.  $k_{ros}$  was greatest for the less hydrophobic drugs, morphine and alfentanil, and least for sufentanil, the most hydrophobic drug. It should be noted that  $k_{ros}$  values are estimated from regression fit of the data to the mass transfer compartmental model. They represent a direct measure of the transit time of the opioid molecules in each of the CSF compartments. Furthermore, the product of apparent CSF volume and the rostral rate constant ( $k_{ros}$ ) should equal rostral clearance or rostral flow of the opioids. This flow is molecule-

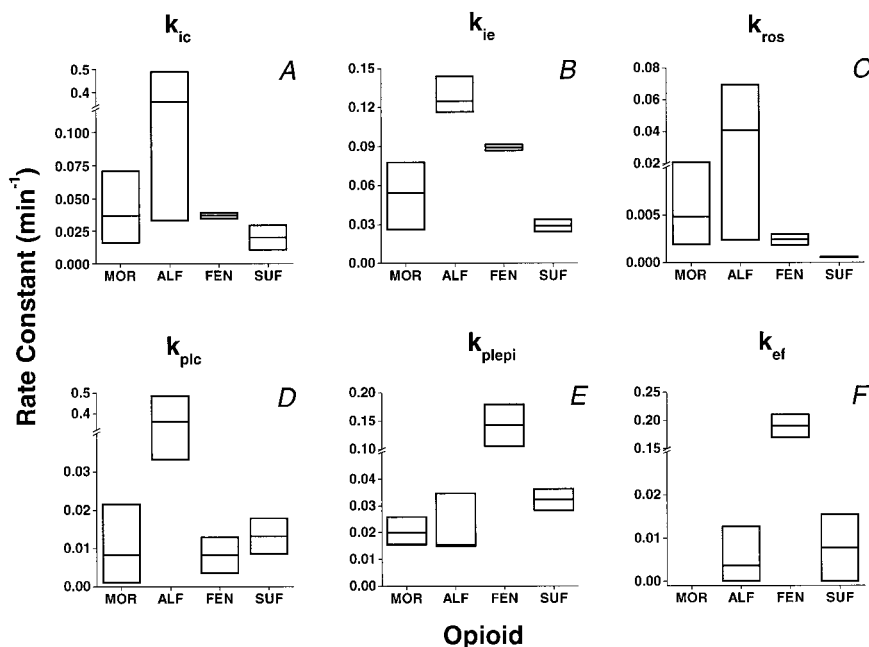


Fig. 7. (A-E) Box plots of the transfer rate constants (per minute). The top line of the box represents the 75th percentile, the bottom line represents the 25th percentile, and the "middle" line represents the 50th percentile or the median. The opioids are arranged along the x-axis in the order of increasing lipophilicity.

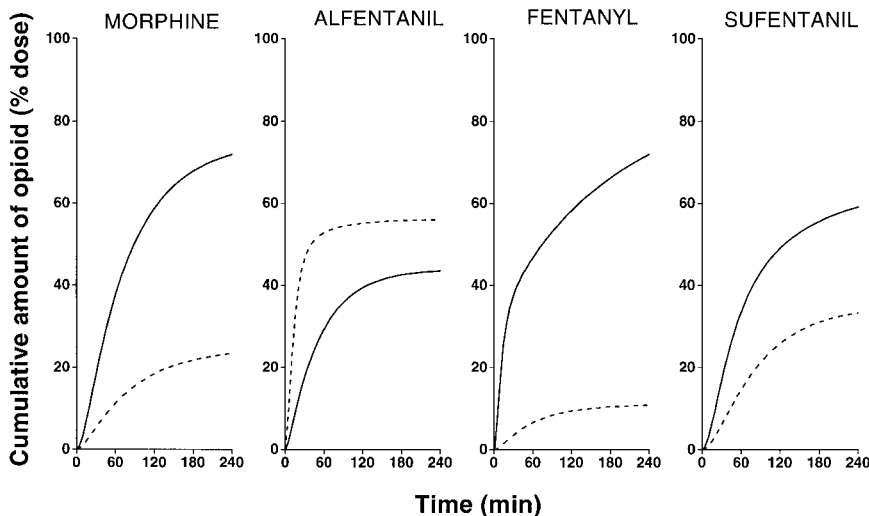


Fig. 8. Simulation of the cumulative amount of opioid (percent dose) that is cleared over time into the systemic circulation *via* the spinal cord (dotted line) or the epidural space (straight line). The amounts are the sum of the predicted amount in the L2–L3 and T11 compartments. The median for morphine and sufentanil and the geometric mean for alfentanil and fentanyl of the estimated model parameters were used to simulate the profiles for each drug.

independent because it would be the CSF bulk flow and should be similar for the four opioids. This, in fact, was the case: morphine, 0.7 ml/h; alfentanil, 1.81 ml/h; fentanyl, 1.5 ml/h; sufentanil, 1.7 ml/h. This confirms a well-recognized kinetic principle that intercompartmental transfer rate constants are governed by clearance (*i.e.*, permeability-product or flow) and distribution volume of the compartment with respect to freely diffusable drug. Viewed in this fashion, it may not be surprising that  $k_{ros}$  ranged over nearly two orders of magnitude. It simply reflects how binding or adherence of the opioid molecule to the structural surfaces that delimits the CSF space deters rostral spread of drug molecules.

Figures 7D and 7E compare the rate constants for vascular uptake of opioids from the spinal cord ( $k_{pic}$ ) and epidural space ( $k_{plepi}$ ), respectively. In the spinal cord, morphine diffused most slowly into plasma, whereas alfentanil diffused the fastest by an order of magnitude. In contrast, in the epidural space alfentanil diffuses slowly into plasma, whereas fentanyl was the most rapidly transferred of the four opioids. This differential vascular uptake from the spinal cord and the epidural space is more clearly illustrated in figure 8. This figure shows model simulations of the cumulative amount of opioid that is cleared into plasma from the spinal cord and from the epidural space. Approximately 70% of the dose of morphine and fentanyl and 60% of the dose of sufentanil was cleared into plasma from the epidural space, whereas 60% of the alfentanil dose was cleared into plasma from the spinal cord.

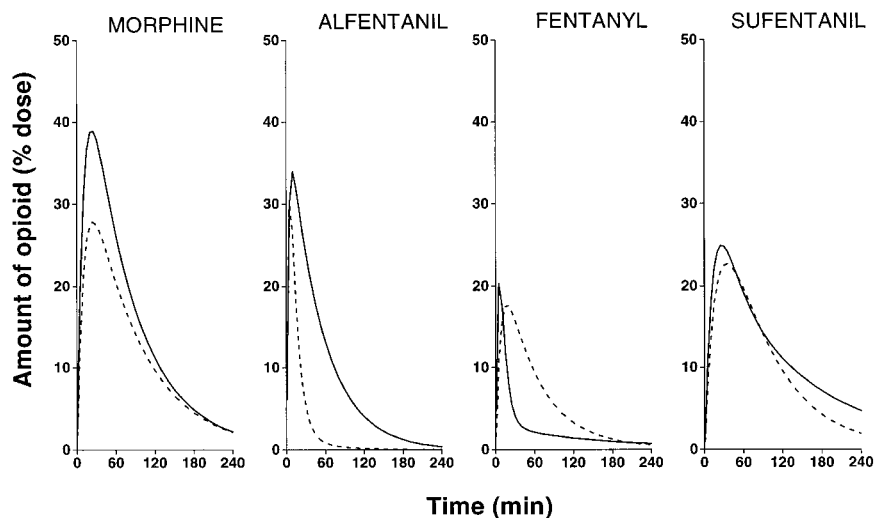
Figure 7F shows the transfer rate constants for drug movement into epidural fat ( $k_{ef}$ ).  $k_{ef}$  was too small to be

calculated for morphine, but for fentanyl  $k_{ef}$  was 15 times greater than for sufentanil, which did not differ significantly from alfentanil.

Transfer rate constants for drug movement back toward the site of administration (*i.e.*, from spinal cord to CSF [ $k_{ci}$ ], from epidural space into CSF [ $k_{ci}$ ], and from epidural fat into the epidural space [ $k_{fe}$ ]) were generally much smaller than their corresponding rate constants for movement away from the intrathecal space (table 1). Exceptions to this trend were the transfer rate constants  $k_{fe}$  and  $k_{ef}$  for sufentanil and alfentanil.  $k_{fe}$  was nearly eightfold greater than  $k_{ef}$  for alfentanil, whereas  $k_{fe}$  and  $k_{ef}$  were similar for sufentanil. These exceptions suggest that sequestration in epidural fat was not prominent for these drugs.

Figure 9 is an additional simulation that helps to clarify pharmacokinetic differences among the opioids. This figure shows the model prediction of the percent of the administered opioid dose present in either the spinal cord or epidural space during the 4 h of study. Both sufentanil and morphine enter the epidural space and the spinal cord at similar rates, and comparable amounts of sufentanil and morphine are present in these two compartments over time. Alfentanil also enters the epidural space and the spinal cord at similar rates, but these rates are much faster than for the other three opioids. The rates out of these compartments differ from each other, with alfentanil leaving the cord at least three times faster than the epidural space, which results in lower exposure of the spinal cord to alfentanil compared with the epidural space. For fentanyl, the rates into and out of the epidural space are much faster compared with the

## INTRATHECAL OPIOID KINETICS

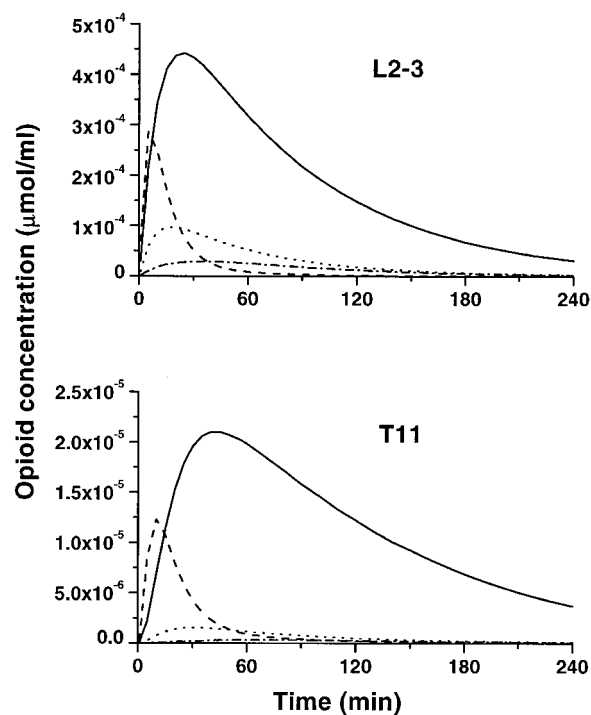


**Fig. 9.** Simulation of the amount of opioid (percent dose) in spinal cord (dotted line) and the epidural space (straight line) over time. The amounts are the sum of the predicted amount in the L2–L3 and T11 compartments. The median for morphine and sufentanil and the geometric mean for alfentanil and fentanyl of the estimated model parameters were used to simulate the profiles for each drug.

spinal cord, resulting in a higher exposure to fentanyl in the cord compared with the epidural space.

Figure 10 is a model prediction of opioid concentrations over time in the extracellular fluid space (*i.e.*, the dialyzable opioid) of the spinal cord. Opioid concentration in the extracellular fluid space is simulated, instead of the total drug concentration in the spinal cord (as in fig. 9), because it is this unbound, freely diffusible opioid that is believed to have access to the opioid receptors. Opioid nonspecifically bound and sequestered within the spinal cord is not able to reach opioid receptors. Figure 10 was generated by dividing the opioid amounts in figure 9 by each drug's median or geometric mean apparent volume of distribution within the spinal cord ( $V_{\text{cord}}$ ). This plot has several striking features. First, alfentanil reaches peak concentration within extracellular fluid space of the spinal cord earlier than any other opioid and is cleared from the cord more rapidly than the other opioids. Morphine reaches the highest concentration in the spinal cord extracellular fluid space and is cleared slowly. Fentanyl and sufentanil attain comparatively low concentrations in the spinal cord.

Another informative index of spinal cord exposure to each of the opioids was generated by dividing the area under each of the curves in figure 10 (at L2–L3) by the dose of each drug. The median dose-normalized integral exposure thus obtained was 3.4 min/ml for morphine, compared with 0.56 min/ml, 0.44 min/ml, and 0.25 min/ml for fentanyl, alfentanil, and sufentanil, respectively.



**Fig. 10.** Model simulation of the opioid concentration over time in the spinal cord at the L2–L3 and T11 levels. To produce these graphs, the simulated amounts in the spinal cord plotted in figure 9 were divided by the median (morphine and sufentanil) or the geometric mean (alfentanil and fentanyl) of the apparent volumes of distribution for each of the four opioids. Morphine (straight line) achieves much higher spinal cord concentrations than alfentanil (dashed line), fentanyl (dotted line), and sufentanil (dash-dot line). The concentrations reached at level T11 are  $> 10\times$  lower compared with those at level L2–L3.

## Discussion

Opioids are administered spinally with the aim of achieving selective spinal analgesia. Whether this goal is achieved depends on the rate and extent to which opioids distribute from the CSF to opioid receptors in the spinal cord dorsal horn as opposed to competing extraspinal sites. The pharmacokinetics of this distribution, in turn, governs much of the spectrum of pharmacodynamics (dose potency, onset, and duration) observed clinically. To understand better the patterns of distribution and thus further our understanding of spinal analgesia, we investigated the distribution and clearance of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil by means of continuous sampling through microdialysis probes placed at critical sites along the spinal cord. Our modeling of the data obtained from microdialysis has yielded several interesting results, which help to explain the pharmacodynamics of these drugs.

Perhaps the most striking finding is the heretofore underappreciated fact that a large fraction of intrathecally administered drug is "lost" into the epidural space and epidural fat and is thus unavailable to target sites in the spinal cord (fig. 8). Interestingly, the rank order for the transfer rate constants from the CSF to the epidural space ( $k_{ie}$ ) was the same as the meningeal permeability coefficients determined in previous *in vitro* studies from this laboratory,<sup>17</sup> namely, alfentanil > fentanyl > morphine > sufentanil. Thus, the findings of this study serve to confirm the fact that drugs of intermediate hydrophobicity (alfentanil's octanol:buffer distribution coefficient = 129) are more permeable across the spinal meninges than are drugs of greater (fentanyl's octanol:buffer distribution coefficient = 955, and sufentanil's octanol:buffer distribution coefficient = 1,737) or lesser hydrophobicity (morphine's octanol:buffer distribution coefficient = 1).

It is important to consider the possibility that drug measured in the epidural space in this study was an artifact caused by leakage around the dialysis probes placed in the subarachnoid space. If this were the case, we would expect that drug concentrations in the epidural space would initially be the same for both morphine and one of the phenylpiperidine opioids with which morphine was always coadministered in equal doses. However, there were marked differences among the opioids in their epidural concentrations. Thus, we conclude that drug present in the epidural space reached that site by diffusion across the spinal meninges

and that the differences in the rate of transfer among the drugs represent real permeability differences.

Although drug lost into and cleared from the epidural space is clearly unavailable at spinal cord opioid receptors, there are more subtle mechanisms by which drugs are sequestered and unavailable at the target site. This is seen most clearly in the drug's apparent volume of distribution within the spinal cord. The estimated apparent volume of distribution ( $V_{\text{cord}}$ ) applies to the unbound, freely diffusible and therefore pharmacologically relevant opioid in the extracellular fluid space. This apparent volume is expected to increase as more opioid is nonspecifically bound to tissue components because drug so bound is unavailable to opioid receptors. Because lipophilicity is a determinant of the extent of this nonspecific binding, it was not surprising to find that  $V_{\text{cord}}$  paralleled the drug's octanol:buffer distribution coefficient, with morphine having the smallest median  $V_{\text{cord}}$  (7.9 ml) and sufentanil the largest (101 ml). The very high  $V_{\text{cord}}$  for sufentanil suggests that much of the sufentanil in the spinal cord partitions into the myelin and other lipids that make up most of the nonaqueous portion of the white matter.<sup>18</sup> Because the gray matter in which spinal cord opioid receptors lie is surrounded by white matter, we hypothesize that much of the sufentanil is sequestered in the white matter and relatively little reaches spinal cord opioid receptors.

One would also expect  $V_{\text{epifat}}$  to be the largest for sufentanil because of the fatty tissue present in the epidural space. However, fentanyl showed the highest  $V_{\text{epifat}}$ . The reason for this is not clear, but it is possible that at physiologic pH, fentanyl's lower nonionized fraction compared with sufentanil may lead to greater ion-trapping of fentanyl in epidural fat.

The exceptionally large  $V_{\text{csf}}$  for sufentanil was a surprise and may be explained by sufentanil's adherence to the spinal cord surface and/or the spinal meninges as well as binding to the network of cellular trabeculae running between the arachnoid and pia mater. Sufentanil's large  $V_{\text{csf}}$  compared with the other phenylpiperidine opioids cannot be explained by nonspecific binding to CSF proteins because sufentanil, alfentanil, and fentanyl are all protein bound to a similar extent.

Although the pharmacokinetic modeling is in and of itself an interesting exercise, it is useful only to the extent that it is consistent with or helps to explain pharmacodynamics, particularly the observed clinical differences among these drugs. Our spinal model seems to do that rather well.

Perhaps the two clearest differences among intrathecal

opioids are their relative intrathecal dose potencies and their durations of action. For example, an intrathecal dose of morphine can produce analgesia lasting 13–33 h,<sup>19</sup> whereas a comparable dose of intrathecal sufentanil and fentanyl produces analgesia lasting only 2–6 h.<sup>9,20</sup> This clinical observation is readily explained by the simulation in figure 10 and the integral exposure data (see Results), which demonstrate that the spinal cord's exposure to morphine over time is much greater than that of any of the other opioids.

Another critical difference among opioids is their relative potency when administered intravenously compared with intrathecally. For example, when administered intravenously, sufentanil is approximately 1,000 times more potent than morphine (weight:weight) in terms of analgesic efficacy. However, when these drugs are administered intrathecally, the dose of sufentanil that produces maximal analgesia (12.5  $\mu\text{g}$ ) is only 8–16 times less than a "typical" analgesic dose of intrathecal morphine (100–200  $\mu\text{g}$ ).<sup>21</sup> Thus, when administered intrathecally, there is a remarkable 100-fold decrease in the relative potency of sufentanil compared with morphine (weight:weight). This clinical fact is also readily explained by the modeling of our data (fig. 10), which clearly shows that the spinal cord's exposure to morphine, both in terms of peak concentration and duration of exposure, is greater than the exposure to sufentanil. Similarly, fentanyl is 100 times more potent in terms of dose than morphine when administered intravenously<sup>22</sup> but is only four times more potent when administered intrathecally.<sup>7</sup> This 25-fold decrease in the dose potency of fentanyl relative to morphine is also explained by the greater exposure of the spinal cord to morphine compared with fentanyl seen in our model (fig. 10). There are inadequate human data by which to compare the relative intrathecal potency of morphine and alfentanil; however, animal data indicate that intrathecal administration lowers the antinociceptive dose potency of alfentanil relative to morphine by 12.5-fold compared with intravenous administration.<sup>23</sup> This observation is also consistent with the model predictions in figure 10, in which the peak spinal cord concentration of alfentanil is less than that of morphine but is nonetheless much closer than are the peak concentrations of either fentanyl or sufentanil.

The dramatic difference in relative dose potency between the systemic and intrathecal routes of administration suggests marked differences in the processes governing access to opioid receptors after systemic delivery (e.g., passage of the blood–brain barrier) or intrathecal

delivery (e.g., diffusion through the substance of the spinal cord). Another piece of evidence that the processes governing systemic and spinal opioid bioavailability are different is the fact that the relationship between hydrophobic character and relative potency is exactly opposite after systemic and intrathecal administration. With systemic delivery, the dose potency of opioids increases as hydrophobic character increases. However, with intrathecal administration, opioid dose potency actually decreases as hydrophobic character increases. This suggests that drugs of lesser hydrophobicity have greater spinal bioavailability than drugs of greater hydrophobicity. Our modeling data suggest that this is caused in large part by the fact that  $V_{\text{CSF}}$  and  $V_{\text{cord}}$  increase (i.e., spinal cord and CSF concentrations of freely diffusible, pharmacologically available opioid decreases) as hydrophobic character increases.

However, greater hydrophilic character is not without its downside. Morphine, the most hydrophilic opioid, reached the highest concentrations at all rostral CSF sampling sites, indicating that it underwent the greatest rostral spread. Conversely, fentanyl and sufentanil underwent little rostral spread and, in fact, were undetectable above the T11 CSF sampling site. This finding is consistent with the well-appreciated clinical phenomenon of delayed respiratory depression observed with morphine but not with the phenylpiperidine opioids.

Importantly, the fact that opioid concentration was found to decrease with distance from the site of injection in the CSF and the spinal cord is consistent with the observations of Shafer *et al.*,<sup>24</sup> who studied the CSF pharmacokinetics and pharmacodynamics of intrathecal neostigmine in humans. They used a diffusion model to demonstrate that the distance from the injection site to the sampling site and to the spinal effect site influences both the pharmacokinetics and pharmacodynamics of the injected drug.

Measurements of opioid concentrations in the spinal cord tissue obtained at the end of our experiments suggest an alternate route for rostral distribution that was ignored in our model. Figure 4 compares the observed amount of each opioid in the spinal cord at 240 min to the amount of opioid predicted by the model at 240 min. If the amount of opioid in the spinal cord at the end of the experiment were correctly predicted by the model, the symbols representing a particular cord level in figure 4 are expected to cluster, and the clusters should lie along the line of identity with minimum overlap. Figure 4 shows that, for the most part, this is the case for morphine. However, the predicted amounts at

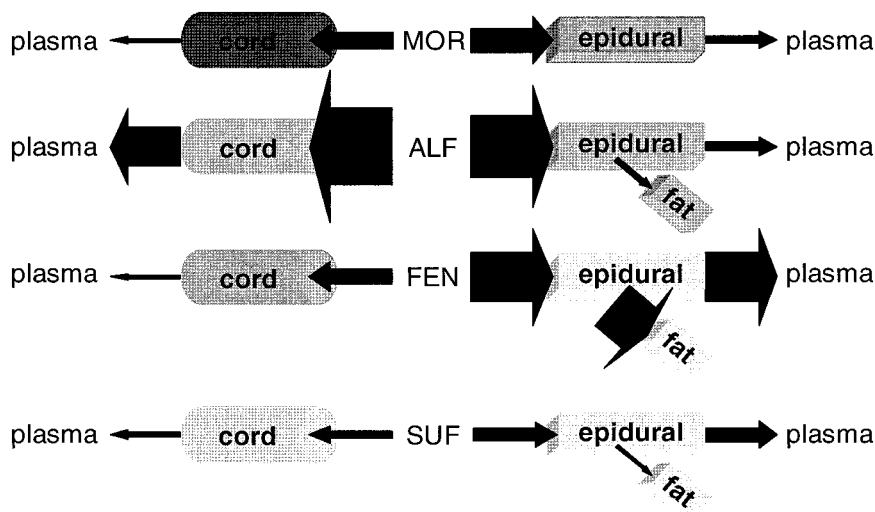


Fig. 11. Schematic comparison of the median (morphine and sufentanil) or geometric mean (alfentanil and fentanyl) transfer and elimination rate constants. The thickness of the arrow is proportional to the rate constant estimate, *i.e.*, the thicker the arrow, the higher the rate of transfer or elimination. The intensity of the shading of the compartments increases with increasing integral exposure of the spinal cord to the freely diffusible drug in the spinal cord extracellular fluid space.

the more rostral level, T7, decrease below the line of identity in some of the animals, indicating that the observed amount of morphine was higher than the predicted amount at these levels. The deviation at these most rostral sites is likely explained by morphine redistribution into the spinal cord from the systemic circulation. Systemic redistribution to cord is presumably constant at all levels, but at more caudal levels near the site of injection, the amount of drug reaching the cord in this manner is negligible relative to the amount that simply diffuses into the cord from the CSF. Apparently, alfentanil undergoes significant redistribution into the spinal cord from the systemic circulation at all spinal levels. This can be explained by the fact that alfentanil has a concentration gradient across the blood-spinal cord barrier that favors redistribution. Specifically, alfentanil has a small systemic volume of distribution (0.75 l/kg)<sup>25</sup> relative to other opioids, giving rise to relatively high plasma concentrations. In addition, alfentanil is cleared rapidly from the spinal cord, giving rise to low spinal cord concentrations (fig. 10).

Pharmacokinetic characteristics of the "ideal" opioid for intrathecal use would include rapid distribution from the CSF to the cord combined with slow clearance from the cord to plasma (*i.e.*, high integral exposure of the spinal cord to the opioid) and moderate rostral CSF distribution. Unfortunately, none of the opioids investigated in this study has the physicochemical properties to achieve this. In fact, physicochemical properties, which produce favorable properties, seem to be responsible for unfavorable properties as well. For example, morphine's relatively low hydrophobicity seems to be responsible for the fact that it has the greatest integral exposure

within the cord. Unfortunately, this low hydrophobicity likely also accounts for the fact that morphine displays the greatest rostral spread. Alfentanil, a drug of intermediate hydrophobicity (octanol:buffer distribution coefficient = 129) distributes very rapidly from the CSF into the spinal cord and would be expected to have the most rapid onset of analgesia. However, this same property seems to result in the most rapid clearance from the spinal cord, and thus its duration of action would be expected to be very short. In fact, animal models demonstrate that alfentanil does, in fact, produce rapid onset of very short-lived analgesia.<sup>26</sup> The most lipid-soluble drugs, fentanyl and sufentanil, undergo the most limited rostral spread, but their very high volumes of distribution in the spinal cord, epidural space, and epidural fat result in very low integral exposure within the extracellular fluid space of the spinal cord. Thus, it may not be possible to design a drug with physicochemical properties that result in an "ideal" constellation of pharmacokinetic properties.

However, with the information from the pharmacokinetic analysis we can now rationally develop pharmaceutical strategies to modify particular distribution processes to achieve optimal pharmacodynamics. For example, alfentanil rapidly redistributes into the cord but is similarly very rapidly cleared into plasma. Our model predicts that addition of a vasoconstrictor, such as epinephrine, to intrathecal alfentanil would decrease vascular uptake ( $k_{plc}$ ) and slow alfentanil's disappearance from the spinal cord without significantly changing the rostral distribution. Coadministration of a vasoconstrictor to spinal sufentanil would not offer any improvement because it does not resolve the partitioning of

sufentanil into the myelin and other lipids that comprise spinal cord white mater. In the case of fentanyl, vasoconstriction would be modestly beneficial to the cord's integral exposure, but to a much lesser extent compared with alfentanil because most of the dose of fentanyl is lost into the epidural space.

In conclusion, we measured spinal cord opioid concentration over time in CSF plasma and epidural space after intrathecal drug injection and used these data to develop a model of intrathecal opioid redistribution. We found that integral exposure of the spinal cord to morphine is high relative to alfentanil, fentanyl, and sufentanil after intrathecal administration. This high integral exposure to morphine is attributed to its limited volume of distribution in the spinal cord and slow clearance into the systemic circulation. The relatively low spinal cord exposure to the other three opioids occurs for different reasons. Alfentanil is cleared rapidly from the spinal cord into the systemic circulation. Fentanyl is routed largely into the epidural space, followed by sequestration in epidural fat. Given its very high lipophilicity, sufentanil has limited free drug availability within the spinal cord, despite its long residence time and sequestration in spinal cord tissue. Figure 11 offers a visual representation of these findings.

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