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Epidural, Cerebrospinal Fluid, and Plasma Pharmacokinetics of Epidural Opioids (Part 2)

Effect of Epinephrine

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Background: **The ability of epinephrine to improve the efficacy of epidurally administered drugs is assumed to result from local vasoconstriction and a consequent decrease in drug clearance. However, because drug concentration in the epidural space has never been measured, our understanding of the effect of epinephrine on epidural pharmacokinetics is incomplete. This study was designed to characterize the effect of epinephrine on the epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidurally administered opioids.**

Methods: **Morphine plus alfentanil, fentanyl, or sufentanil was administered epidurally with and without epinephrine (1:200,000) to pigs. Opioid concentration was subsequently measured in the epidural space, central venous plasma, and epidural venous plasma, and these data were used to calculate relevant pharmacokinetic parameters.**

Results: **The pharmacokinetic effects of epinephrine varied by opioid and by sampling site. For example, in the lumbar epidural space, epinephrine increased the mean residence time of morphine but decreased that of fentanyl and sufentanil. Epinephrine had no effect on the terminal elimination half-life of morphine in the epidural space, but it decreased that of fentanyl and sufentanil. In contrast, in the lumbar intrathecal space, epinephrine had no effect on the pharmacokinetics of alfentanil, fentanyl, or sufentanil, but it increased the area under the concentration–time curve of morphine and decreased its elimination half-life.**

Conclusions: **The findings indicate that the effects of epinephrine on the spinal pharmacokinetics of these opioids are complex and often antithetical across compartments and opioids. In addition, the data clearly indicate that the pharmacokinetic effects of epinephrine in spinal "compartments" cannot be predicted from measurements of drug concentration in plasma, as has been assumed for decades.**

EPINEPHRINE has been added to epidurally administered local anesthetics and opioids for decades. Reasons for adding epinephrine include prolongation and potentiation of opioid[1,2] or local anesthetic effect and decreased local anesthetic peak plasma concentration. Although the ability of epinephrine to produce these salutary pharmacologic effects is clear, the mechanism by which it does so is not.

Because epinephrine decreases local anesthetic peak plasma concentrations, it has been assumed that its primary mechanism of action is to reduce drug clearance from the epidural space *via* local vasoconstriction. Decreased drug clearance would be expected to prolong and potentiate local anesthetic block by increasing local anesthetic concentrations in the epidural space and in adjacent neural sites of local anesthetic action. However, decreased clearance is not the only possible explanation for the lower local anesthetic peak plasma concentrations that result from addition of epinephrine. Lower peak plasma concentrations could also result from an epinephrine-induced increase in clearance from plasma or an increase in volume of distribution (V_d). Because systemic absorption of epinephrine from the epidural space produces a significant increase in cardiac output,[3] it is not unreasonable to expect that plasma clearance may be increased because of more rapid drug delivery to the liver or kidneys. In addition, epinephrine absorption significantly reduces systemic vascular resistance,[3] which could, in turn, increase local anesthetic V_d. Increases in either plasma clearance or V_d caused by systemic actions of absorbed epinephrine would reduce the peak plasma concentration of epidurally administered drugs regardless of whether the rate of drug absorption from the epidural space was altered.

Evidence supporting a systemic, as opposed to epidural, effect of epinephrine on peak plasma concentration comes from work by Sharrock *et al.*[4] These investigators demonstrated that low-dose intravenous epinephrine decreased local anesthetic peak plasma concentrations during epidural anesthesia.

Similarly, there are alternative explanations for the ability of epinephrine to prolong and potentiate the pharmacodynamic effects of epidurally administered opioids and local anesthetics that do not require a reduction in drug clearance from the epidural space. In particular, epinephrine itself is analgesic in the spinal cord *via* its ability to activate α_2-adrenergic receptors. Thus, prolonged duration and potentiation of local anesthetics and opioids may be explained by an additive or synergistic analgesic effect of epinephrine in the spinal cord dorsal horn.

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

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The reason that the mechanism by which epinephrine improves the actions of epidurally administered drugs is unclear is that drug concentration in the epidural space has never been measured directly. Consequently, we developed a pig model that uses microdialysis techniques to measure opioid concentration in the extracellular fluid of the epidural space. In the present study, we used this model to investigate the effect of epinephrine on the epidural, intrathecal, and plasma pharmacokinetics of morphine, fentanyl, alfentanil, and sufentanil.

Materials and Methods

All studies were approved by the University of Washington's Institutional Animal Care and Use Committee. The animals studied are the same as those described in Part 1, in this issue. The reader is referred to this article for a detailed description of the study methods. In brief, opioid pharmacokinetics were studied after intravenous and epidural opioid administration with and without epinephrine in each animal. All animals received morphine in combination with fentanyl, alfentanil, or sufentanil. The study opioids were administered twice to each animal in each experimental session, once with epinephrine and once with an equal volume of saline.

During the intravenous studies, the study opioids were administered into the central venous plasma and plasma samples obtained from the central venous plasma. Epinephrine or an equal volume of saline was administered intramuscularly. The intravenous opioid studies preceded the epidural studies by 1 week.

For the epidural studies, the opioids were administered into the L5 epidural space. Microdialysis samples were obtained from the L5 epidural space, L5 intrathecal space, and T12 epidural space for measurement of opioid concentration. Central venous plasma and epidural venous plasma were also collected for measurement of opioid concentration.

For both the intravenous and the epidural studies, the injections were made approximately 4.5 h apart, and drug concentrations in all samples obtained after the second

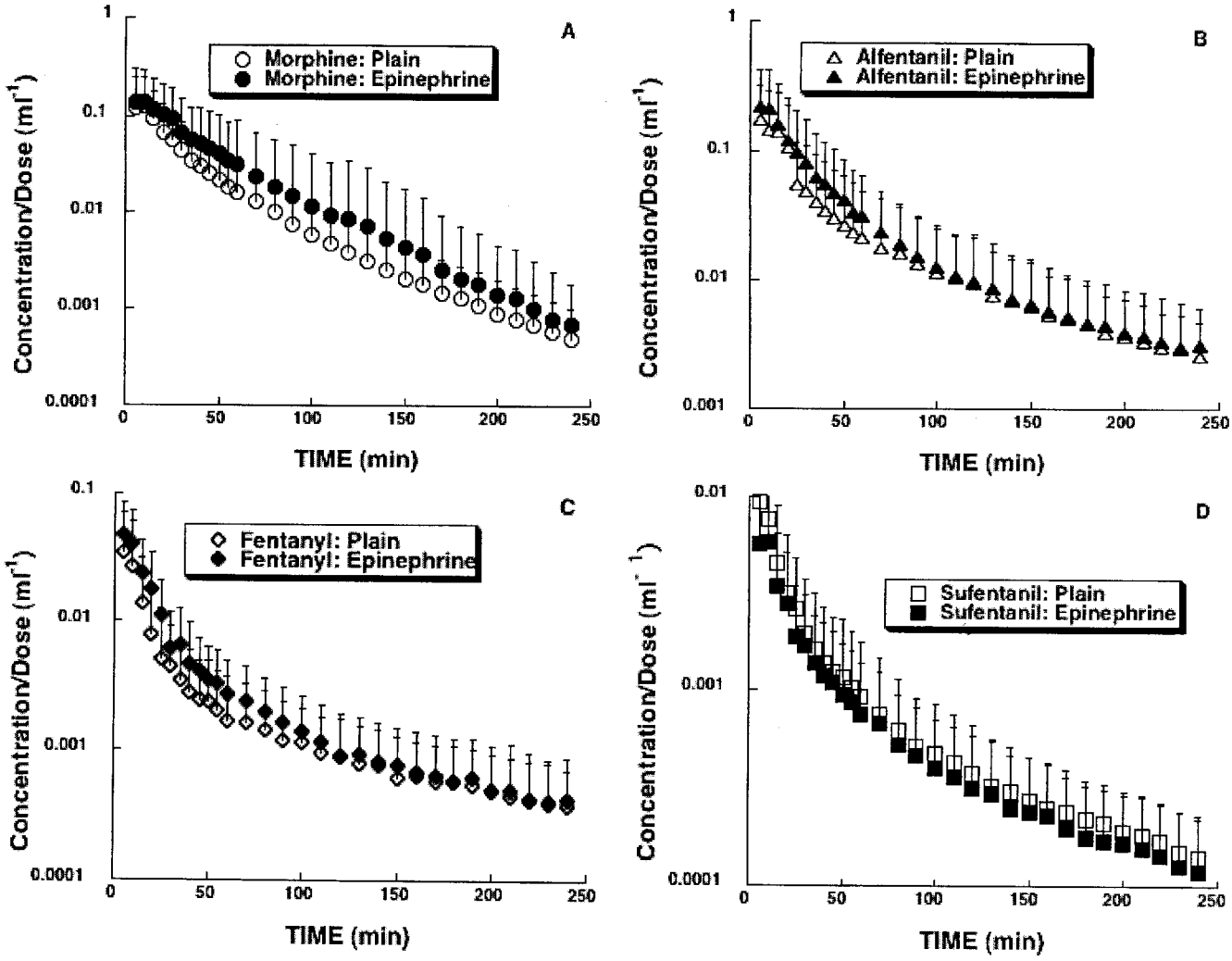

Fig. 1. Dose-normalized concentration–time plots of morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in the extracellular fluid of the lumbar (L5) epidural space with and without epinephrine.

Table 1. Epidural and Intrathecal Pharmacokinetic Parameters

	Opioid							
	Morphine		Alfentanil		Fentanyl		Sutentanil	
Sampling Site, Parameter	Plain	Epinephrine	Plain	Epinephrine	Plain	Epinephrine	Plain	Epinephrine
Lumbar epidural								
AUC/dose nmol · min^{-1} · ml^{-1}	9.8 ± 5.9	12.5 ± 5.4*	10.8 ± 4.9	10.2 ± 3.9	1.3 ± 1.0	1.7 ± 1.1	2.9 ± 2.0	3.1 ± 1.4
MRT, min	36.1 ± 12.8	41.1 ± 12.4*	58.6 ± 48.5	62 ± 50	88 ± 65	68 ± 55*	148 ± 76	87 ± 42*
Clearance, ml/min	0.15 ± 0.12	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.04	1.2 ± 0.9	0.9 ± 0.7	0.8 ± 0.8	0.4 ± 0.2
Volume of central compartment, ml	3.9 ± 3.0	3.2 ± 1.5	2.5 ± 2.0	3.0 ± 2.2	38 ± 44	31 ± 37	38 ± 58	13 ± 6
Volume of distribution, ml	12.6 ± 11.5	6.4 ± 3.9*	14.7 ± 9.6	15.3 ± 9.5	244 ± 240	140 ± 182*	139 ± 103	66 ± 33
Term elim. $t_{1/2}$, min	51.5 ± 12.7	47.9 ± 18.5	100.4 ± 46.5	98.1 ± 36.1	126 ± 40	88 ± 46*	165 ± 67	110 ± 25*
Lumbar intrathecal								
AUC/dose, nmol · min^{-1} · ml^{-1}	1.7 ± 1.6	2.7 ± 2.4*	0.84 ± 0.67	0.87 ± 0.63	0.19 ± 0.14	0.33 ± 0.25	0.41 ± 0.21	0.40 ± 0.21
MRT, min	102 ± 59	82 ± 25	71 ± 29	57 ± 50	67 ± 40	56 ± 20	93 ± 30	70 ± 21
Term elim. $t_{1/2}$, min	80 ± 40	62 ± 14*	110 ± 89	100 ± 45	97 ± 36	64 ± 36	100 ± 35	95 ± 15
Thoracic epidural								
AUC/dose, nmol · min^{-1} · ml^{-1}	4.3 ± 4.1	5.0 ± 4.8	4.85 ± 3.41	4.92 ± 4.63	0.19 ± 0.14	0.33 ± 0.27	0.30 ± 0.25	0.23 ± 0.18
MRT, min	49 ± 35	44 ± 20	97 ± 96	89 ± 84	76 ± 43	48 ± 25	103 ± 46	82 ± 18
Term elim. $t_{1/2}$, min	60 ± 26	50 ± 15	139 ± 124	111 ± 53	107 ± 21	84 ± 37	128 ± 35	123 ± 63

* $P < 0.05$ compared with plain opioid.

AUC = area under concentration-time curve; MRT = mean residence time; Term. Elim. $t_{1/2}$ = terminal elimination half-life.

injection were corrected for the concentration of residual drug from the first injection. The order of epinephrine administration was counterbalanced, with half of the animals receiving the epinephrine-containing solution first and the other half receiving epinephrine second.

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 L5 epidural site of injection with and without coadministered epinephrine. Table 1 presents the corresponding pharmacokinetic parameters. Epinephrine had no significant effect on the lumbar epidural pharmacokinetics of alfentanil. However, epinephrine significantly increased the dose-normalized area under the concentration–time curve (AUC/dose) and mean residence time (MRT) of morphine. In contrast, coadministered epinephrine significantly shortened the MRT and terminal elimination half-life of both fentanyl and sufentanil. Interestingly, figure 2 demonstrates a strong negative linear relationship between the octanol:buffer$_{7.4}$ distribution coefficients of the opioids and the percent change in MRT with addition of epinephrine ($P < 0.0013$).

Thoracic Epidural Space. Figure 3 shows the dose-normalized extracellular fluid space concentration–time plots for all four opioids in the thoracic epidural space with and without coadministered epinephrine. Table 1 presents the corresponding pharmacokinetic parameters. In contrast to the lumbar epidural space, epinephrine had no apparent effect on any of the pharmacokinetic parameters of any opioid in the thoracic epidural space.

Lumbar Intrathecal Space. Figure 4 shows the dose-normalized concentration–time plots for all four opioids with and without epinephrine in the lumbar intrathecal space opposite the epidural site of injection. Table 1 presents the corresponding pharmacokinetic parameters. As in the lumbar epidural space, epinephrine significantly increased the dose-normalized AUC of morphine. In contrast to the lumbar epidural space, the terminal elimination half-life of morphine was decreased significantly by epinephrine. Epinephrine had no statistically significant effects on the intrathecal pharmacokinetics of alfentanil, fentanyl, or sufentanil.

Plasma Pharmacokinetics

Epidural Opioid Administration and Central Venous Sampling. Figure 5 shows the central venous plasma dose-normalized concentration–time plots for

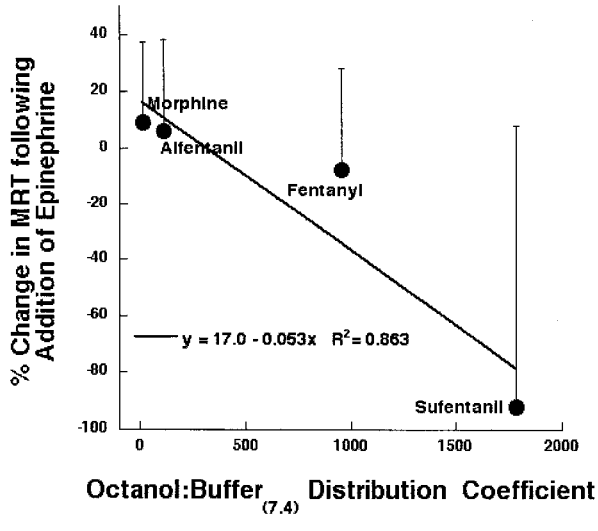

Fig. 2. Relationship between the octanol:buffer$_{(7.4)}$ distribution coefficient and MRT of the opioids in the lumbar (L5) epidural space.

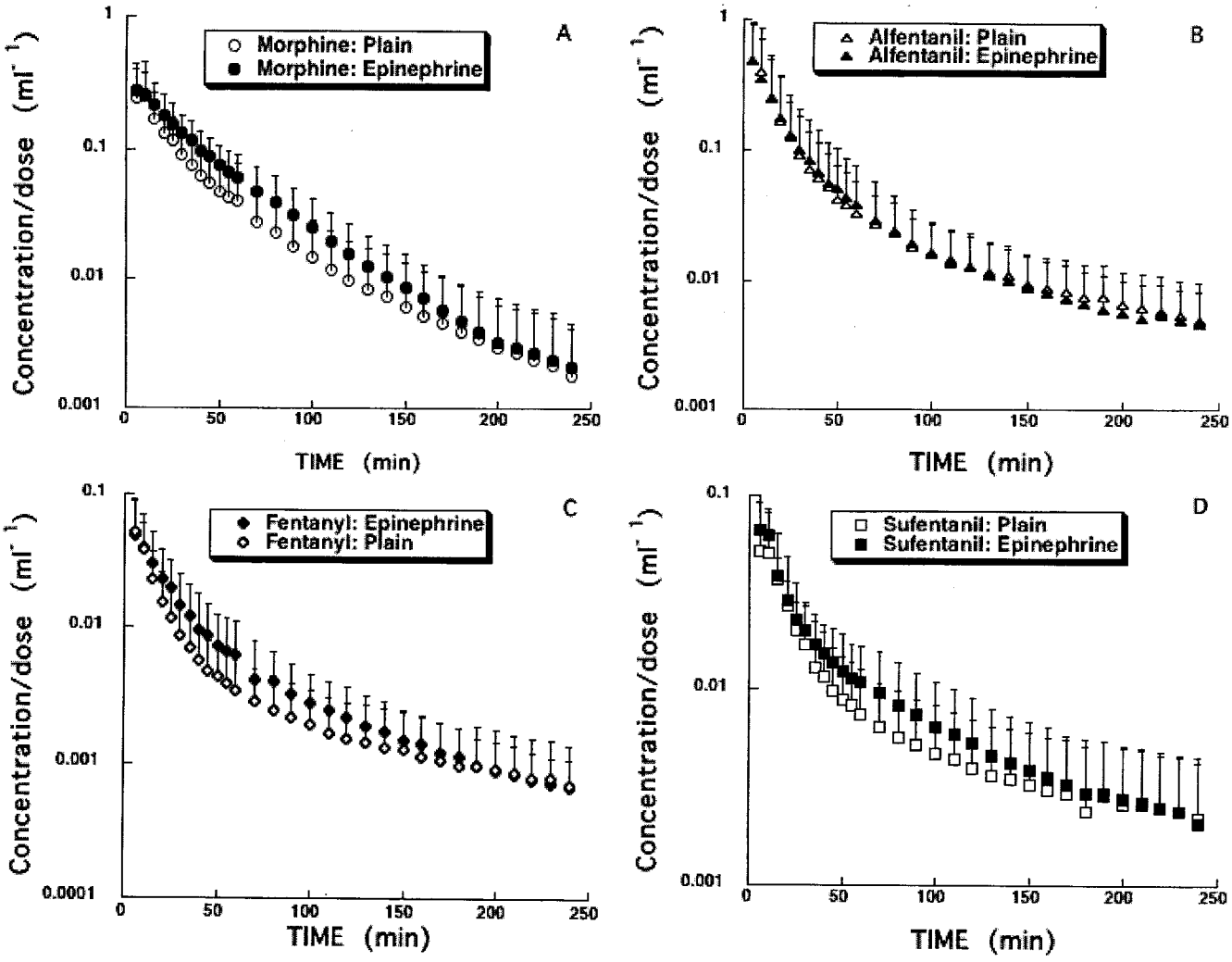

Fig. 3. Dose-normalized concentration–time plots of morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in the extracellular fluid of the thoracic (T12) epidural space with and without epinephrine.

morphine, alfentanil, and sufentanil administered into the lumbar epidural space with and without added epinephrine. There are no data for fentanyl because too few of the samples had measurable concentrations. Table 2 presents the derived pharmacokinetic parameters. Epidural epinephrine decreased the peak plasma concentration of morphine significantly, by nearly 30%, and delayed the time to reach the peak concentration by approximately 30 min. The MRTs of both morphine and alfentanil were increased significantly in the central venous plasma by epinephrine. In contrast, adding epinephrine had no effect on the central venous plasma pharmacokinetics of epidurally administered sufentanil.

Epidural Opioid Administration and Epidural Venous Sampling. Figure 6 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. Epinephrine decreased the peak concentration of morphine in epidural venous blood significantly but did not affect any other pharmacokinetic parameters of any opioid.

Intravenous Opioid Administration. Figure 7 shows the dose-normalized central venous plasma concentration–time plots for all four opioids administered intravenously with and without intramuscular epinephrine. Table 2 shows the derived pharmacokinetic parameters. Intramuscular epinephrine had no effect on the plasma pharmacokinetics of any opioid administered intravenously.

Effect of Epidural Epinephrine on Spinal Cord Blood Flow. Compared with baseline measurements, epinephrine had no demonstrable effect on spinal cord blood flow measured in the lumbar, thoracic, or cervical spinal cord at 15 and 60 min after epinephrine administration (fig. 8).

Discussion

The effect of epinephrine on the pharmacokinetics of epidurally administered drugs has been the subject of

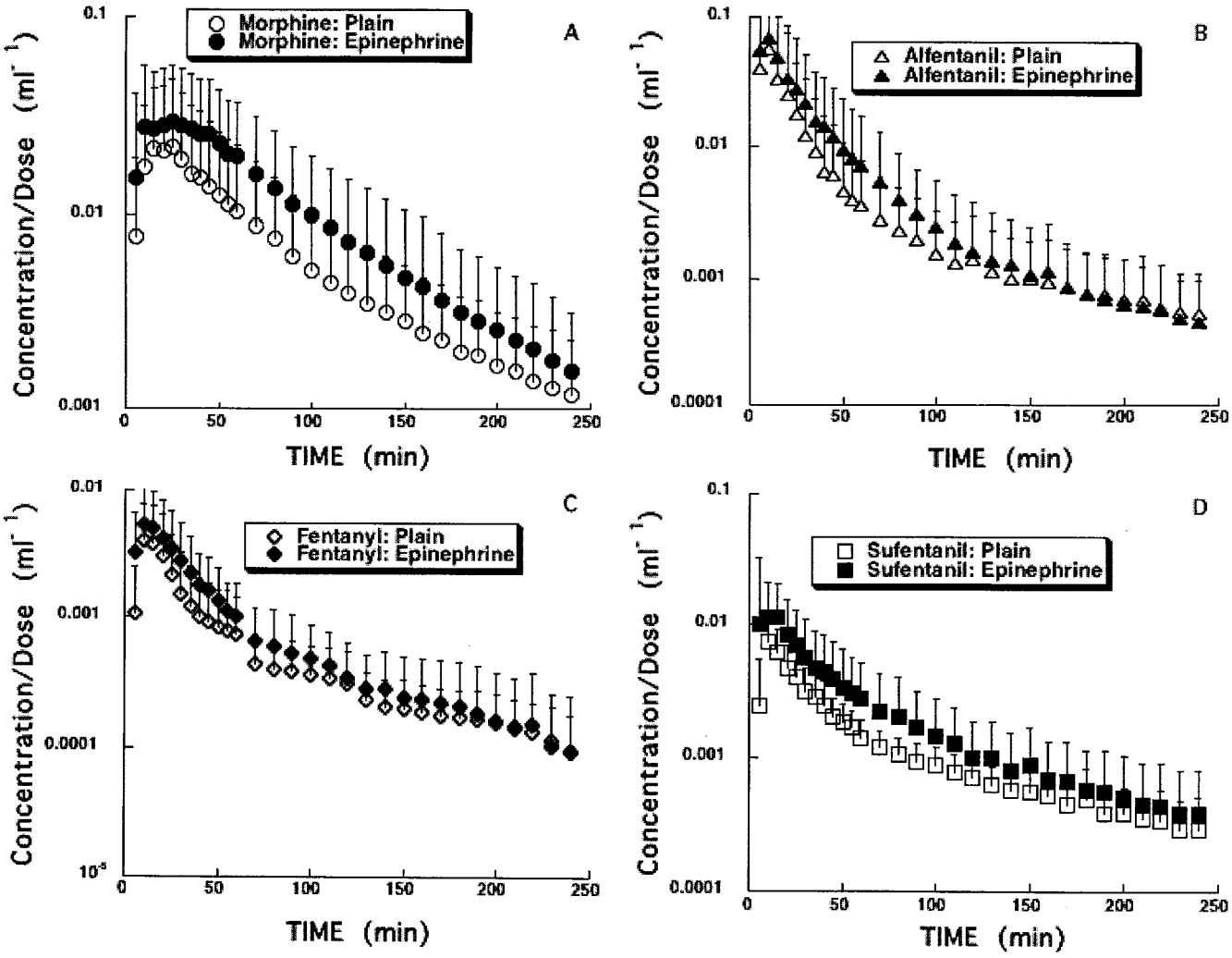

Fig. 4. Dose-normalized concentration–time plots of morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in the cerebrospinal fluid of the lumbar (L5) intrathecal space with and without epinephrine.

numerous studies. To the best of our knowledge, however, this is the first study to characterize the effect of epinephrine by actually measuring drug concentration in the relevant anatomic sites, *i.e.*, epidural space, intrathecal space, and epidural vein. Not surprisingly, our findings confirm some conventional wisdoms and cast doubt on others.

Epinephrine increased the dose-normalized AUC, prolonged the MRT, and decreased the apparent V_d of morphine at the site of drug injection in the lumbar epidural space. In addition, epinephrine decreased the peak concentration of morphine in the central venous plasma and significantly delayed the time to reach the peak concentration. These findings are consistent with the view that epinephrine decreases the rate of clearance of morphine from the epidural space.

Although epinephrine altered the pharmacokinetics of morphine in the lumbar epidural space, it had no effect on the pharmacokinetics of morphine in the thoracic epidural space. The reason for this is unclear, although a possible explanation is that the concentration of epinephrine decreases with increasing distance from the injection site (just as opioid concentrations decrease) and that the concentration of epinephrine at this more distant epidural sampling site was too low to be effective. Alternatively, the explanation may stem from pharmacokinetics in the thoracic epidural space being governed by two independent processes, namely, rostral distribution from the lumbar site of injection and elimination from the thoracic sampling site. If rostral spread is the rate-limiting step controlling the concentration of morphine in the thoracic epidural space, then one would not expect epinephrine to affect morphine concentration significantly even if it did decrease elimination rate.

This study also helps shed some light on the mechanism by which epinephrine decreases drug clearance. Some have speculated that drugs are cleared from the epidural space by diffusing directly through the walls of the epidural venous plexus,[5] which drains the contents

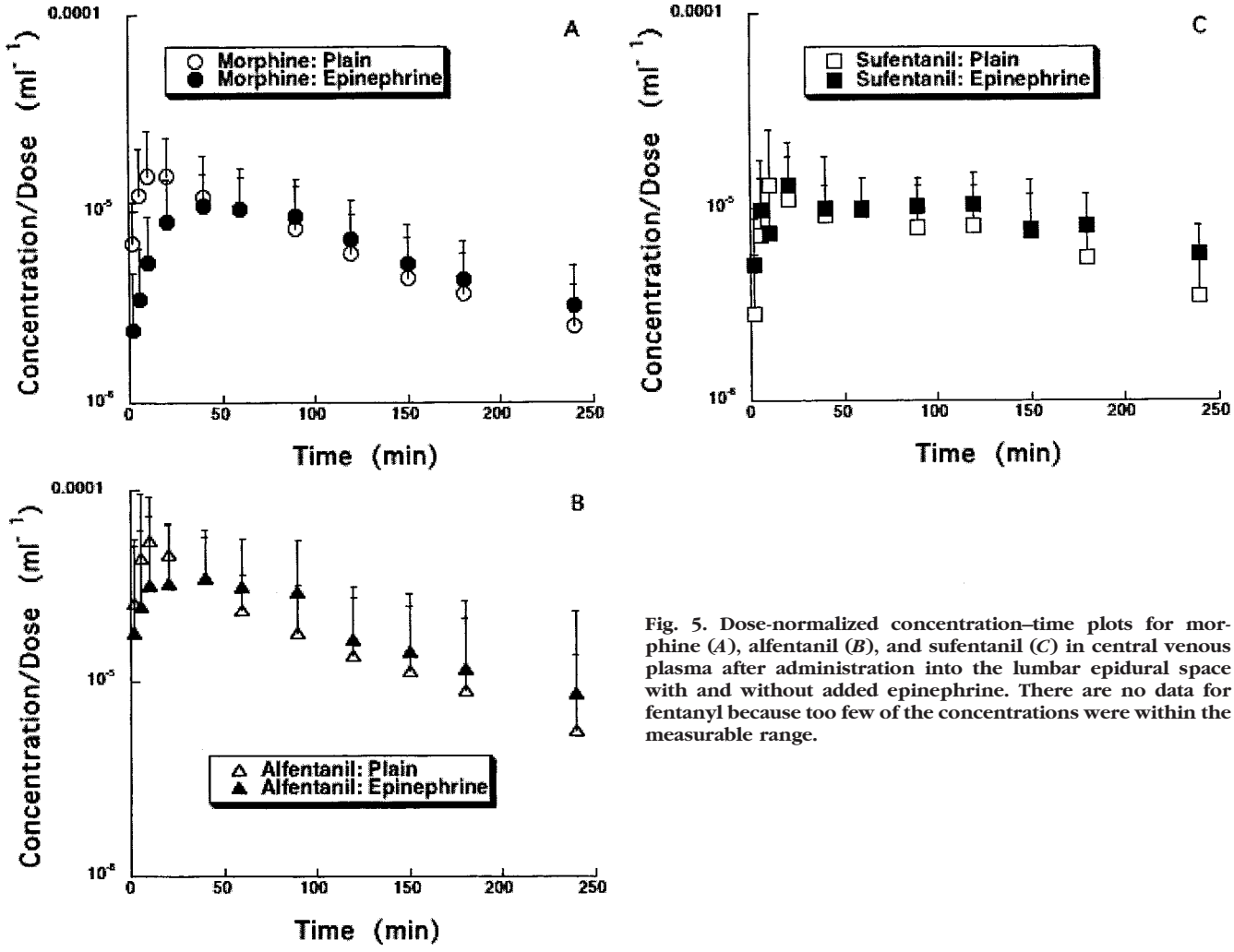

Fig. 5. Dose-normalized concentration–time plots for morphine (*A*), alfentanil (*B*), and sufentanil (*C*) in central venous plasma after administration into the lumbar epidural space with and without added epinephrine. There are no data for fentanyl because too few of the concentrations were within the measurable range.

of the epidural space, and that epinephrine decreases clearance by constricting these veins and decreasing epidural venous blood flow. If this were true, then one would expect to find that the peak concentration of morphine is higher in epidural venous blood when epinephrine is present because of a lower epidural venous volume. However, epinephrine actually decreased the peak concentration of morphine in epidural venous blood. This finding is most consistent with morphine entering the epidural venous blood by first diffusing into surrounding tissues (*e.g.*, epidural fat, dura mater) with subsequent clearance *via* capillaries into the epidural venous system. According to this view, epinephrine decreases morphine clearance by constricting arterial inflow to these tissues and thereby decreasing morphine uptake. Consistent with this mechanism, Kozody *et al.*[6,7] have shown that epinephrine decreases blood flow in the dura mater, which is the most highly perfused nonneural tissue adjoining the epidural space.[8]

Numerous previous studies have documented that adding epinephrine can decrease the peak plasma concentration of some epidurally administered drugs. However, it was not clear from these studies whether this was a local effect of epinephrine within the epidural space or a systemic effect of absorbed epinephrine. In our study, however, intramuscular epinephrine, equivalent to the dose administered epidurally, had no effect on the plasma pharmacokinetics of any of the study drugs when they were administered intravenously. This finding, combined with the observation that epinephrine prolonged the MRT of morphine in the epidural space and increased its AUC, suggests that the effect of epidural epinephrine on the plasma pharmacokinetics of some drugs is not mediated systemically but rather is a local effect within the epidural space. One caveat to bear in mind is that we do not know with certainty that the intramuscular epinephrine administered as part of the intravenous opioid studies produced the same plasma epinephrine concentrations that would result from epidural administration of the same dose of epinephrine. That said, it is still clear from the morphine data that epinephrine can increase the residence time of a drug in the epidural space.

Interestingly, epinephrine had no effect on the epi-

Table 2. Plasma Pharmacokinetic Parameters

	Morphine		Alfentanil		Fentanyl		Sufentanil	
Opioid Administration Site	Plain	Epinephrine	Plain	Epinephrine	Plain	Epinephrine	Plain	Epinephrine
Epidural								
Central venous								
AUC/dose, min/ml	0.0027 ± 0.0011	0.0030 ± 0.0013	0.0054 ± 0.0048	0.0065 ± 0.0008	UM	UM	0.0022 ± 0.0009	0.0031 ± 0.0006
MRT, min	150.3 ± 63.2	223.9 ± 134.7*	100.5 ± 54.6	126.6 ± 54.3*	UM	UM	192 ± 53	235 ± 105
Terminal elim. $t_{1/2}$, min	114.2 ± 62.2	156.9 ± 114.8	73.2 ± 37.3	74.4 ± 42.1	UM	UM	132 ± 43	139 ± 68
Peak conc./dose, $\times 10^{-9}$/ml	0.025 ± 0.011	0.018 ± 0.008*	0.066 ± 0.044	0.049 ± 0.029	UM	UM	0.019 ± 0.013	0.017 ± 0.008
Time to peak conc., min	21.5 ± 21	55 ± 33*	17.9 ± 13.1	31.2 ± 26	UM	UM	33 ± 19	46 ± 48
Epidural venous								
AUC/dose, min/ml	0.033 ± 0.021	0.033 ± 0.27	0.043 ± 0.024	0.053 ± 0.03	0.034 ± 0.033	0.032 ± 0.011	0.049 ± 0.04	0.066 ± 0.058
MRT, min	60.3 ± 43.3	68.8 ± 23.6	75.5 ± 20.8	69.6 ± 31.9	82.5 ± 41.4	191 ± 128	163 ± 83	115 ± 35
Terminal elim. $t_{1/2}$, min	69.6 ± 38.3	69.6 ± 28.9	60.3 ± 31.5	64.0 ± 30.4	149 ± 79	186 ± 132	144 ± 50	110 ± 35
Peak conc./dose, $\times 10^{-9}$/ml	1.2 ± 1.3	0.62 ± 0.57*	1.2 ± 1.1	1.0 ± 0.73	1.1 ± 1.1	0.57 ± 0.51	1.3 ± 1.3	1.5 ± 1.1
Time to peak conc. (min)	13.0 ± 14.1	15.5 ± 14.1	12.4 ± 11.7	9.1 ± 9.1	7.0 ± 3.2	4.3 ± 3.9	4.8 ± 3.3	3.0 ± 1.2
Internal jugular								
Central venous								
AUC/dose, min/ml	0.0039 ± 0.0035	0.0045 ± 0.0045	0.012 ± 0.009	0.009 ± 0.008	0.0022 ± 0.0006	0.0023 ± 0.0007	0.0024 ± 0.0011	0.0026 ± 0.0010
MRT, min	77 ± 20	103 ± 68	154 ± 188	98 ± 80	85.9 ± 31	85.8 ± 20	55.3 ± 18.6	80.4 ± 28.9
Vd, ml	53 ± 37	18 ± 18	33 ± 53	22 ± 19	53 ± 9	49 ± 7	41.9 ± 15.6	53.3 ± 31.6
Clearance, ml/min	482 ± 502	480 ± 319	139 ± 88	175 ± 91	498 ± 190	497 ± 134	552.8 ± 314.7	457.1 ± 219.8
Terminal elim. $t_{1/2}$, min	78 ± 21	92 ± 32	108 ± 81	99 ± 70	68 ± 33	56 ± 30	59.2 ± 22.0	78.9 ± 28.2
Peak conc./dose, $\times 10^{-9}$/ml	0.20 ± 0.19	0.17 ± 0.15	1.1 ± 1.1	1.1 ± 1.3	0.062 ± 0.02	0.061 ± 0.017	0.083 ± 0.04	0.078 ± 0.046
Time to peak conc., min	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0	2.0 ± 0

* $P < 0.05$ compared with plain opioid solution.

AUC = area under concentration-time curve; Conc. = concentration; MRT = mean residence time; Term. elim. $t_{1/2}$ = terminal elimination half-life; UM = unmeasureable; Vd = volume of distribution.

dural pharmacokinetics of alfentanil and actually shortened the persistence of fentanyl and sufentanil in the lumbar epidural space. In particular, the terminal elimination half-life and MRT of fentanyl and sufentanil were decreased significantly by epinephrine. In fact, there was a strong negative linear relationship between lipid solubility as measured by octanol:buffer$_{(7.4)}$ distribution coefficient and MRT in the epidural space (fig. 2). The reason for this is unclear. It may be that at some point in time, the low concentrations of epinephrine that were reached as it was cleared or metabolized resulted in an increase in local blood flow because of a predominantly β_2-adrenergic effect. If the clearance of hydrophobic opioids were blood flow limited, then any increase in local blood flow would be expected to increase their clearance. However, this would not explain why the terminal elimination half-life of morphine was not similarly affected, unless the vascular uptake of morphine is limited by the rate at which it penetrates the capillary endothelium and not by blood flow. Given that penetration through capillary endothelium is slower for more hydrophilic molecules, this is quite possible.[9]

Another possible explanation is that hydrophilic drugs (*e.g.*, morphine) are cleared from the epidural space by a different route than are very lipid-soluble drugs (*e.g.*, fentanyl, sufentanil) and that epinephrine affects clearance from these sites differently. For example, Part 1 of this study and earlier work from our laboratory[10] demonstrate that opioids partition to very different degrees into different perispinal "tissues" (*e.g.*, epidural fat, cerebrospinal fluid, spinal cord) depending on their lipid solubility. Consequently, the effect of epinephrine on the clearance of any given drug would depend on the effect of epinephrine on blood flow to the tissue(s) into which that drug had preferentially distributed. If epinephrine affects epidural fat blood flow differently from dura mater blood flow, then one would expect epinephrine to affect the clearance of drugs that partition preferentially into epidural fat differently from drugs that do not.

It should be noted that a differential effect of epinephrine on blood flow in different tissues is not necessary to explain varying effects of epinephrine on opioid clearance. It is likely that epinephrine is as heterogeneously distributed among epidural tissues as are other drugs. Because the effects of epinephrine on blood flow are concentration dependent (*i.e.*, vasoconstriction and decreased flow at "high" concentrations and vasodilation and increased flow at "low" concentrations), one would expect epinephrine to reduce blood flow in tissues in which it was present at high concentrations and increase flow in tissues in which it was present at low concentrations. Given the low lipid solubility of epinephrine,[11] it may never achieve high enough concentrations in epidural fat to produce vasoconstriction and in fact may produce vasodilation only in the epidural fat vascular bed by preferentially activating β_2-adrenergic receptors. This possibility is supported by the work of Millet *et al.*,[12] who demonstrated that β-adrenergic agonists increase blood flow in human fat tissue. Because the concentration of the highly lipid-soluble opioids in epidural

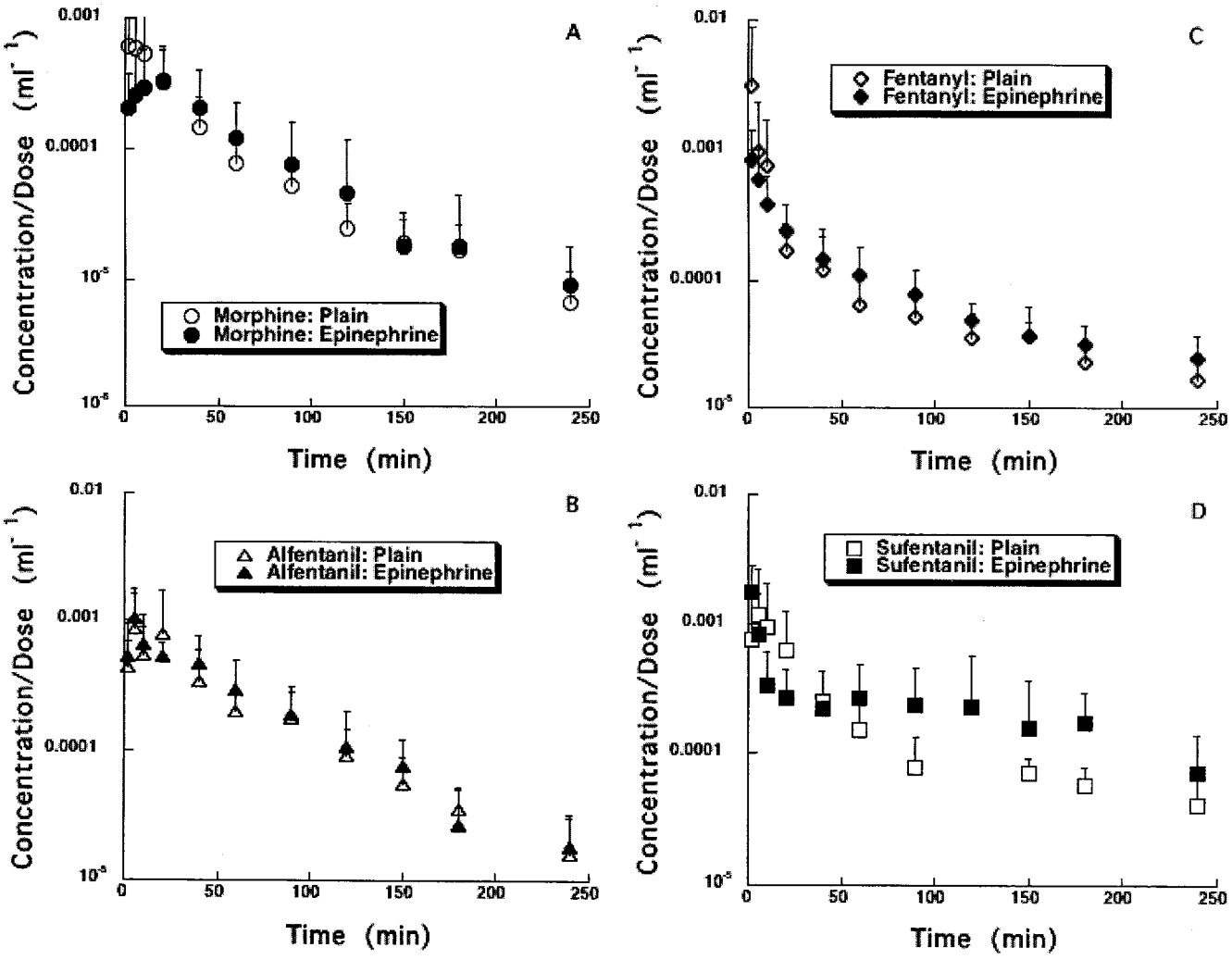

Fig. 6. Dose-normalized concentration–time plots for morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in the epidural venous plasma after lumbar epidural administration with and without epinephrine.

fat is much greater than the concentration of morphine, this could explain why epinephrine decreased MRT and terminal elimination half-life for fentanyl and sufentanil but not morphine. Consistent with this possibility is the interesting observation that the effect of epinephrine on MRT was negatively correlated with the lipid solubility of the opioids (fig. 2).

Regardless of the mechanism(s), the fact that epinephrine exerts different effects on different epidurally administered opioids is consistent with human local anesthetic data. Epinephrine has little or no effect on the plasma pharmacokinetics or blocking characteristics of more lipid-soluble local anesthetics, such as bupivacaine and etidocaine,[13] but does prolong block duration and decrease peak plasma concentrations of more hydrophilic drugs, such as lidocaine and mepivacaine.[14] It is important, however, not to draw too direct a comparison between the behavior of local anesthetics and opioids in the epidural space, because local anesthetics, unlike opioids, can themselves increase local blood flow[6,7] and thereby increase their own elimination. In fact, the ability of local anesthetics to markedly increase local blood flow may explain why the effect of epinephrine on local anesthetic pharmacokinetics is more dramatic (*i.e.*, the effects on plasma concentration are greater) than what we found in this study of opioid pharmacokinetics.

Consistent with epinephrine's increasing the AUC/dose and MRT of morphine in the epidural space, it also increased the AUC/dose of morphine in the intrathecal space. This finding suggests that the ability of morphine to potentiate epidural morphine–mediated analgesia is, at least in part, the result of the effect of epinephrine on the pharmacokinetics of morphine. Given that the inner surface of the dura mater is highly vascular[8] and that epinephrine has been shown to decrease dura mater blood flow,[6,7] we hypothesize that epidural epinephrine increases the intrathecal bioavailability of epidural morphine by reducing its clearance as it diffuses through the dura mater. This hypothesis does not rule out the possi-

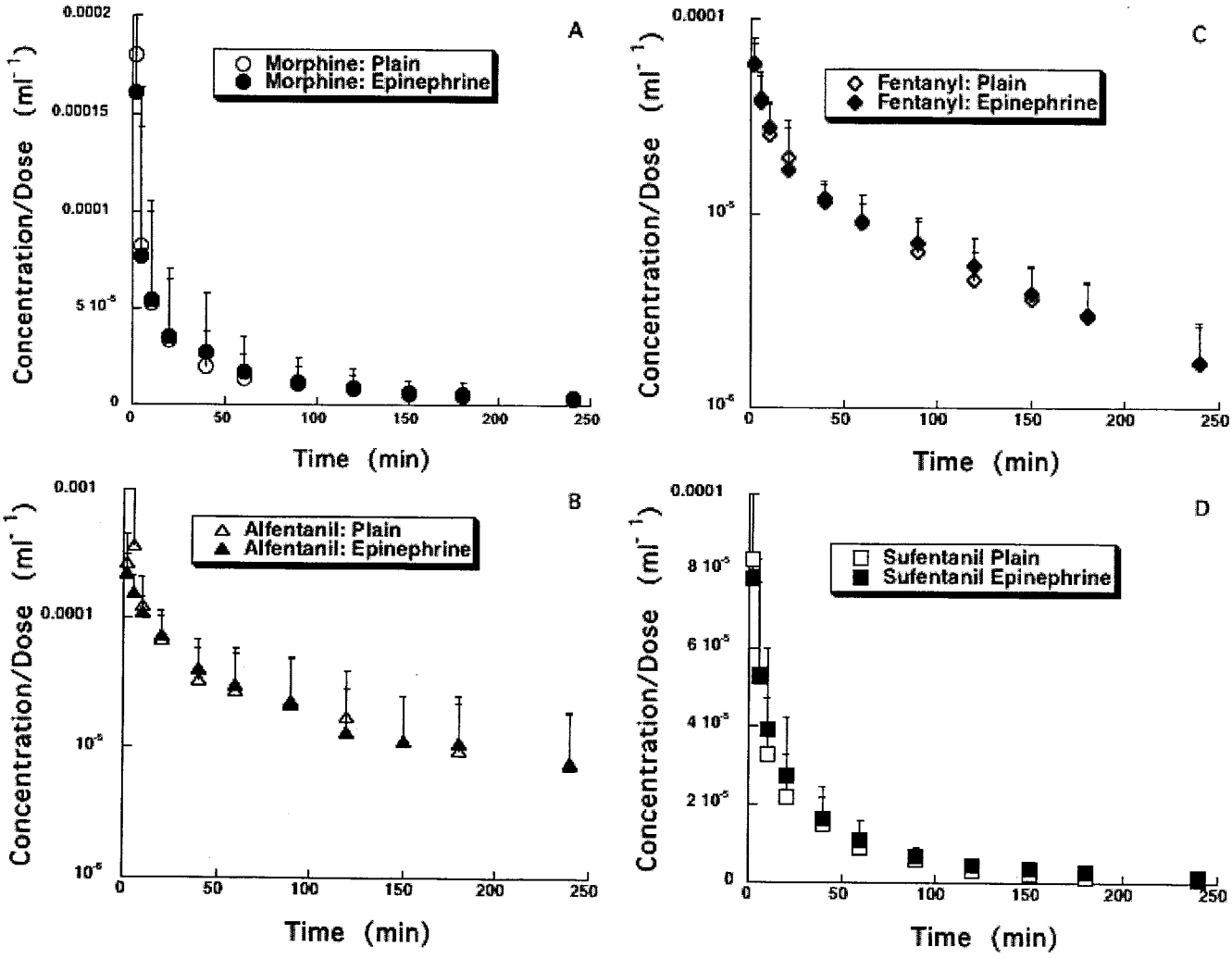

Fig. 7. Dose-normalized concentration–time plots for morphine (*A*), alfentanil (*B*), fentanyl (*C*), and sufentanil (*D*) in central venous plasma after intravenous administration with and without added epinephrine.

bility that epinephrine also potentiates morphine-mediated spinal analgesia by direct actions on spinal α_2-adrenergic receptors. In fact, a spinal site of action for epidural epinephrine is supported by the observation that epinephrine potentiates epidural fentanyl analgesia,[1] despite our finding that epinephrine does not increase the persistence of fentanyl in the epidural or intrathecal spaces.

The possibility that epidural epinephrine acts within the spinal cord to produce analgesia may seem to be inconsistent with our previous results showing that the spinal meninges can metabolize epinephrine *in vitro*.[15] However, meningeal metabolism may simply limit the amount of epinephrine that reaches the spinal cord and not prevent it entirely.

Interestingly, epinephrine had some effects on the intrathecal pharmacokinetics of the study opioids that were different from its effects on their pharmacokinetics in the epidural space. For example, epinephrine had no effect on the terminal elimination half-life of morphine in

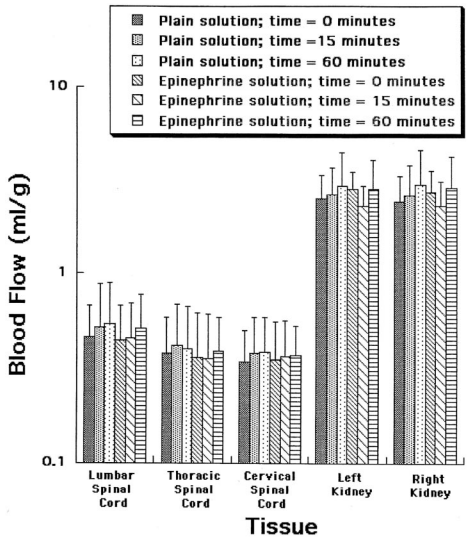

Fig. 8. Spinal cord and renal blood flow at baseline and 15 and 60 min after epidural administration of opioids with epinephrine. Epinephrine had no effect on blood flow in any site at either time point.

the epidural space, but it significantly decreased the terminal elimination half-life of morphine in the intrathecal space. In addition, epinephrine had no effect on the lumbar intrathecal MRT or terminal elimination half-life of fentanyl and sufentanil, even though it decreased both parameters in the lumbar epidural space. Why this is the case is unclear from the data.

However, the fact that the effect of epinephrine varies with the opioid and the sampled compartment is an important observation, if for no other reason than that it clearly demonstrates that the pharmacokinetics of a drug in one compartment (*e.g.*, intrathecal space) cannot be assumed to be representative of those in a different compartment (*e.g.*, epidural space). Likewise, the pharmacokinetics of one epidurally administered opioid cannot be extrapolated to another opioid.

In summary, the effects of epinephrine on the pharmacokinetics of epidurally administered opioids vary with both the opioid and the sampling site. Although not invariably, epinephrine tended to increase measures of the persistence of morphine in the epidural and intrathecal spaces while at the same time decreasing several measures of the persistence of fentanyl and sufentanil in the epidural space. The data suggest that these differences among opioids are the result of differences in their lipid solubility.

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