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Cephalad Movement of Morphine and Fentanyl in Humans after Intrathecal Injection

James C. Eisenach, M.D., David D. Hood, M.D.,† Regina Curry, R.N.,‡ Steven L. Shafer, M.D.§*

Background: **Despite decades of use, controversy remains regarding the extent and time course of cephalad spread of opioids in cerebrospinal fluid (CSF) after intrathecal injection. The purpose of this study was to examine differences between two often used opioids, morphine and fentanyl, in distribution in the CSF after intrathecal injection.**

Methods: **Eight healthy volunteers received intrathecal injection of morphine (50 μg) plus fentanyl (50 μg) at a lower lumbar interspace. CSF was sampled through a needle in an upper lumbar interspace for 60–120 min. At the end of this time, a sample was taken from the lower lumbar needle, and both needles were withdrawn. CSF volume was determined by magnetic resonance imaging. Pharmacokinetic modeling was performed with NONMEM.**

Results: **Morphine and fentanyl peaked in CSF at the cephalad needle at similar times (41 ± 13 min for fentanyl, 57 ± 12 min for morphine). The ratio of morphine to fentanyl in CSF at the cephalad needle increased with time, surpassing 2:1 by 36 min and 4:1 by 103 min. CSF concentrations did not correlate with weight, height, or lumbosacral CSF volume. The concentrations of morphine and fentanyl at both sampling sites were well described by a simple pharmacokinetic model. The individual model parameters did not correlate with the distance between the needles, CSF volume, patient height, or patient weight.**

Conclusions: **Fentanyl is cleared more rapidly from CSF than morphine, although their initial distribution in the first hour after injection does not differ greatly. The pharmacokinetic model demonstrates that mixing is the primary determinant of early concentrations and is highly variable among individuals.**

MOVEMENT of a drug in cerebrospinal fluid (CSF) and subsequent penetration into spinal cord tissue determine the time course and dermatomal extent of analgesia after intrathecal opioid injection. Decades of clinical use demonstrate clear differences between morphine and fentanyl in time course and dermatomal extent of analgesia. Lumbar intrathecal fentanyl injection in women in labor results in rapid (less than 5 min) onset of pain relief[1] mediated by afferents that enter in the lower thoracic spinal cord and, in the case of sufentanil, widespread dermatomal distribution to upper thoracic and cervical levels within 15 min,[2] accompanied by cases of respiratory depression at this time.[3] In contrast, morphine has a slow onset of analgesia in postoperative patients or volunteers and a very slow (2–8 h) cephalad dermatomal progression associated with delayed respiratory depression.[4,5]

Few studies have attempted to determine the causes for these gross differences in clinical effects between poorly lipid-soluble and highly lipid-soluble opioids. In pigs, intrathecally administered fentanyl is cleared from CSF within a relatively short distance, whereas morphine extends to a much greater dermatomal distribution.[6] This is clearly at variance with the clinical observations listed in the previous paragraph, yet these data support a supposition from a review published nearly 20 yr ago that stated that lipid-soluble opioids would have very limited spread in CSF and therefore would carry minimal risk of respiratory depression.[7] Other studies in humans show an extensive spread (to C7) within 15–30 min after lumbar epidural injection of fentanyl in humans,[8] which is at variance with the animal study but consistent with clinical experience.

The purpose of the present study was to test whether speed of cephalad spread in CSF and clearance from CSF differ between fentanyl and morphine in humans. Previous studies have been limited by studying epidural administration with intrathecal catheters, which acutely perturb kinetics, or not directly comparing the two drugs in the same volunteer. To minimize this perturbation, in the present study we inserted two small (No. 27) needles separated by several interspaces and injected an equal amount by mass of fentanyl and morphine. In addition, it has been suggested that variability in dermatomal spread and duration of spinal anesthesia from injection of local anesthetics can be predicted by the volume of the lumbosacral CSF volume,[9] and we tested this directly by correlating the time course of movement of drug, drug concentration, and gradient between injection and cephalad sampling sites with CSF volume as measured by magnetic resonance imaging.

Materials and Methods

After we had obtained Institutional Review Board and General Clinical Research Center Protocol Review Committee approval and written informed consent, eight healthy volunteers were studied. Inclusion criteria were American Society of Anesthesiologists physical status I or II, weight less than 115 kg, age between 18 and 50 yr, taking no opioids or other analgesics, without acute or chronic pain, and without allergy to opioids. A pregnancy test was performed on all women volunteers to exclude pregnant volunteers. To determine CSF volume, a magnetic resonance imaging scan was performed in

* F.M. James III Professor of Anesthesiology, † Professor of Anesthesiology, ‡ Research Nurse, Department of Anesthesiology and Center for the Study of Pharmacologic Plasticity in the Presence of Pain, Wake Forest University School of Medicine. § Professor of Anesthesiology, Stanford University School of Medicine, Stanford, California.

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Address reprint requests to Dr. Eisenach: Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina, 27157-1009. Address electronic mail to: eisenach@wfubmc.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

the first four volunteers from the lower thorax to perineum. CSF from T10 to the termination of the thecal sac was calculated by use of an approach similar to that previously described.[9]

On a subsequent day, the volunteer reported to the General Clinical Research Center in the morning after having had nothing to eat or drink since midnight. A peripheral intravenous catheter was inserted into a vein in an upper extremity, and lactated Ringer's solution was infused at 1.5 ml · kg^{-1} · h^{-1} for the duration of the study. The volunteer was positioned in the left lateral decubitus position, and a standard abdominal flat x-ray plate was positioned under the hips and ribs. A No. 27 Whitacre spinal needle was inserted at the lowest palpable interspace (L5–S1 or L4–L5). After confirmation of clear CSF, the stylet was reinserted in this needle to prevent loss of CSF, and a second No. 27 Whitacre spinal needle was inserted at L2–L3. After confirmation of clear CSF in this more cephalad needle, a three-way stopcock was inserted to prevent CSF loss during sampling, and portable x-ray equipment was obtained to determine the distance between the tips of the two needles.

After the radiograph was obtained, a mixture of 50 μg of fentanyl and 50 μg of morphine in a 2-ml volume of normal saline was injected through the more caudad spinal needle over 5 s, and the stylet was replaced in the needle. Then at the designated intervals, 0.1 ml of CSF was withdrawn through the stopcock attached to the more cephalad needle to clear the dead space in the system, and 0.4 ml of CSF was removed. CSF samples were immediately placed in ice, then frozen at −80°C and stored at this temperature until assay. After the last sample from the more cephalad needle was obtained, the stylet was removed from the more caudad needle, 0.2 ml was removed and discarded, and 0.4 ml was removed for assay. Then both needles were removed, and the volunteer remained in the General Clinical Research Center for an additional 6 hr for monitoring, using correction for magnification.

CSF was sampled in the first four volunteers at 2, 5, 10, 20, 30, 45, and 60 min after drug mixture injection through the lower needle. Interim analysis revealed that in some cases, opioid concentrations in CSF were still increasing at the last (60 min) time, and the protocol was amended to include, in the last four volunteers, additional sampling at 75, 90, 105, and 120 min after injection.

Pharmacodynamic measures were not obtained in this study, but the volunteers were monitored for safety. This included frequent assessment of level of sedation, measuring oxyhemoglobin saturation every 30 min by pulse oximetry, and measuring blood pressure and heart rate at 15-min intervals throughout the study by use of a noninvasive device.

Opioid concentrations were measured under a contract with the University of Washington Department of Anesthesiology (Laboratory Director, Evan Kharash, M.D., Professor of Anesthesiology, University of Washington, Seattle, WA). A 200-μl aliquot of CSF was placed in a tube containing 20 ng of fentanyl-d_5 (free base) and 20 ng of morphine-d_3 (free base) in 20 μl methanol. The mixture was diluted with 1 ml of deionized water and vortexed. Samples were extracted with a Sephedex column and analyzed by gas chromatography–mass spectrometry using fentanyl-d_5 and morphine-d_3 as internal controls for extraction efficiency. Standard curves were linear over a 5- to 1500-ng/ml range, and the minimum detectable amount was 5 ng/ml.

Unless otherwise stated, data are presented as mean ± SEM or median, as appropriate. Comparisons of single observations between opioids was performed by a Student t test for parametric or Mann–Whitney U test for nonparametric data. Correlation analysis was performed by linear regression. A value of $P < 0.05$ was considered significant.

Population pharmacokinetic analysis was performed with NONMEM (Beal SL, Sheiner LB: NONMEM User's Guide. San Francisco, University of California, San Francisco, 1979) using "first-order conditional estimates." The interindividual variability was estimated assuming a log-normal distribution of model parameters among the individuals. Intraindividual (residual) variability was estimated by use of a constant coefficient of variation model. Individual pharmacokinetic parameters were *post hoc* Bayesian estimates derived from the population model. The NONMEM control file is available from the authors (S.S.) at http://anesthesia.stanford.edu/pkpd. The performance of the models was assessed graphically by use of residual error plots and by comparison of the log-likelihood objective function. Decreases in log-likelihood of 4 or more per added model parameter were considered significant at a value of $P < 0.05$ on the chi-square distribution.

Results

We recruited four male and four female volunteers with an average height of 176 ± 4.7 cm, weight of 79 ± 4.9 kg, and age of 32 ± 3.3 yr. All volunteers completed the study without incident, and there were no postdural puncture headaches on telephone follow-up over the week after the study. Two volunteers became drowsy beginning 45 min after intrathecal injection. Oxyhemoglobin saturation was measured continuously in these individuals and never decreased below 95% without oxygen supplementation. Their respiratory rate never decreased below 12 breaths per minute. Blood pressure and heart rate remained within 15% of baseline values, and no volunteer received treatment for any adverse event in the study.

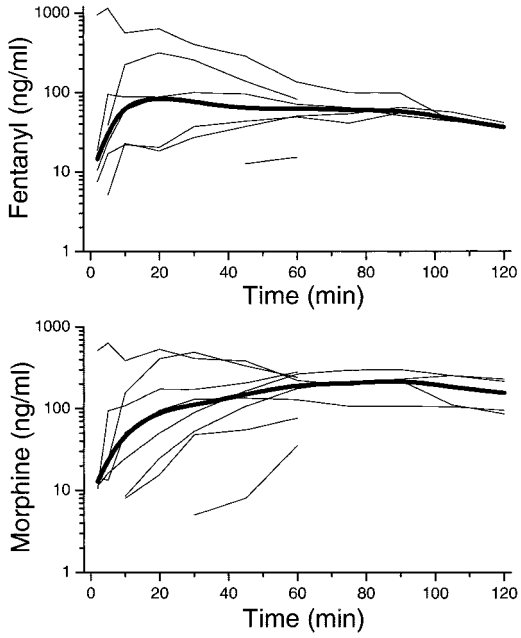

Fig. 1. Cerebrospinal fluid concentrations of fentanyl (*top*) or morphine (*bottom*) at the cephalad needle sampling site after intrathecal injection at time 0 from the caudad needle. *Thin lines* represent each subject, and *thick lines* represent median values.

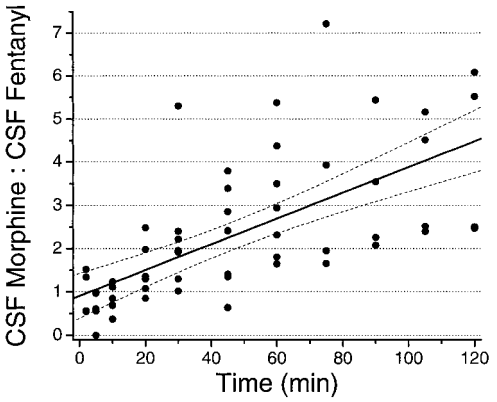

Fig. 2. Correlation between cerebrospinal fluid (CSF) ratio of morphine to fentanyl concentration at the cephalad needle sampling site *versus* time after injection at time 0 from the caudad needle. *Points* represent individual observations, and *lines* represent linear regression with 95% confidence limits.

CSF concentrations of fentanyl were above the minimum detectable limit at a median of 4 min after injection (range, 2–45 min), similar to those of morphine (median, 2 min; range, 2–30 min). In five volunteers, the first sample with detectable opioid occurred at the same time for both drugs; in two volunteers, morphine appeared before fentanyl (10 min for morphine *vs.* 30 min for fentanyl in one individual and 30 min for morphine *vs.* 45 min for fentanyl in another); and in one volunteer, fentanyl appeared before morphine (10 min for morphine *vs.* 5 min for fentanyl).

In most volunteers, morphine and fentanyl appeared at the site of the cephalad needle with increasing concentrations over 20–60 min, then stable or very slowly decreasing concentrations over the next hour (fig. 1). However, in volunteer 6, concentrations of morphine and fentanyl were highest 5 min after injection and decreased slowly thereafter. In two other volunteers, there was a long delay before appearance of drug at the cephalad sampling site. Of these, volunteer 1 showed only one positive fentanyl sample, at 30 min after injection, and morphine was measurable from 10 to 60 min. The other, volunteer 4, had measurable concentrations of fentanyl at 45 and 60 min and of morphine from 30 to 60 min.

The time course of opioid concentrations at the cephalad sampling site was grossly similar for morphine and fentanyl (fig. 1). Time to reach the maximum observed concentration (T_{max}) did not differ between the drugs (41 ± 13 min for fentanyl; 57 ± 12 min for morphine). Similarly, the maximum observed concentration (C_{max}) did not differ between the drugs (225 ± 145 ng/ml for fentanyl; 275 ± 77 ng/ml for morphine). These values of T_{max} and C_{max} were not calculated from pharmacokinetic models but rather were the average of those actually observed in each individual. T_{max} could be less than the true T_{max} in some individuals in whom concentrations were still increasing at the end of the study. For both drugs, the variability in concentration decreased over time (fig. 1). This is particularly evident for fentanyl, for which the concentrations in all individuals appear to converge on 40 ng/ml at 120 min.

There was a gradual increase in the ratio of morphine to fentanyl concentration at the cephalad sampling site over time (fig. 2), and this was highly significant ($P < 0.0001$; $r = 0.67$). Linear regression revealed a *y*-intercept of 0.91, statistically not different from the actual injected ratio of 1.0. The slope of the regression was 0.03 per min, indicating that the ratio of morphine to fentanyl at this sampling site would exceed 2:1 by 36 min and 4:1 by 103 min.

At the end of the period of sampling, a gradient in drug concentration remained between the site of injection and the cephalad sampling site. The median ratio of concentration at injection site to concentration at cephalad sampling site was 3.1:1 for fentanyl and 1.8:1 for morphine (groups do not differ; $P = 0.15$). However, this was skewed by one volunteer, individual 4, who, as noted above, had a very slow appearance of drugs at the cephalad site. This individual had a very large gradient at the end of the study (60 min) of 33:1 for fentanyl and 20:1 for morphine. Excluding this individual, the ratio of concentration at the injection site to that at the cephalad sampling site was 2.5 ± 0.4 for fentanyl and 1.6 ± 0.3 for morphine ($P = 0.08$).

Needle tips were separated by 8.8 ± 1.6 cm, and CSF volume averaged 25 ± 4.0 ml. There was no relationship between any variable of CSF concentrations (time to first appearance at the cephalad site, T_{max}, C_{max}, or gradient

Table 1. Individual Cerebrospinal Fluid Opioid Concentration Variables and Subject Characteristics

Subject/Drug	Height, cm	Weight, kg	Interneedle Distance, cm	Time to Appear at Cephalad Site, min	T_{max}, min	C_{max}, ng/ml	Gradient
1	157	68	10.5				
Fentanyl				30	30	9	N/C
Morphine				10	60	76	1.6
2	185	93	14.8				
Fentanyl				5	20	315	1.1
Morphine				5	30	491	0.6
3	180	62	9.0				
Fentanyl				2	5	94	3.1
Morphine				2	60	280	2.2
4	180	82	7.5				
Fentanyl				45	60	15	32.5
Morphine				30	60	35	19.7
5	157	68	3.6				
Fentanyl				2	90	55	1.4
Morphine				2	90	299	0.9
6	174	75	4.5				
Fentanyl				2	5	1145	3.5
Morphine				2	5	634	2.1
7	191	98	6.4				
Fentanyl				5	90	64	2.6
Morphine				10	105	253	1.3
8	184	89	14.0				
Fentanyl				2	30	99	3.3
Morphine				2	45	133	2.4

C_{max} = maximum observed concentration; N/C = not calculated, because of no detectable fentanyl in cerebrospinal fluid at the cephalad site; T_{max} = time to reach maximum observed concentration.

at injection site to cephalad site) and needle tip distance, CSF volume, subject weight, or subject height (table 1).

Multiple pharmacokinetic models were investigated, all built around the basic two-compartment model shown in figure 3. This model has four parameters: (1) a volume term, which applies to the upper and lower sampling sites; (2) a rate constant for drug flux between the two sampling sites; (3) an elimination rate for fentanyl, which applies to both compartments; and (4) an elimination rate for morphine, which applies to both compartments. Interindividual variability was permitted on all model parameters.

Figure 4 shows the fit of this simple model to the data from the cephalad sampling site. The model captures both the early spread of the data points for fentanyl and morphine and the decrease in variability over time. Figure 5 shows the fit of the model to the data from the caudad sampling site. The model has captured the fent-

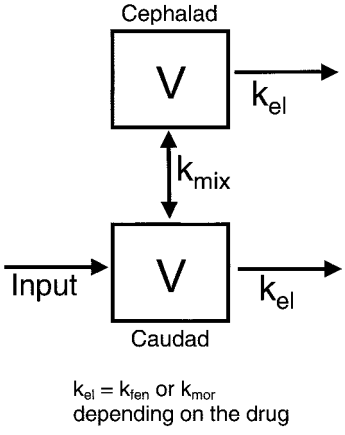

Fig. 3. Basic pharmacokinetic model containing two compartments of identical volume, *V*, a mixing rate constant, k_{mix}, and an elimination rate constant, k_{el}. k_{el} has two values: k_{mor} for the elimination of morphine, and k_{fen} for the elimination of fentanyl. The model was applied to fit the fentanyl and morphine concentrations at the injection site and the cephalad sampling site simultaneously.

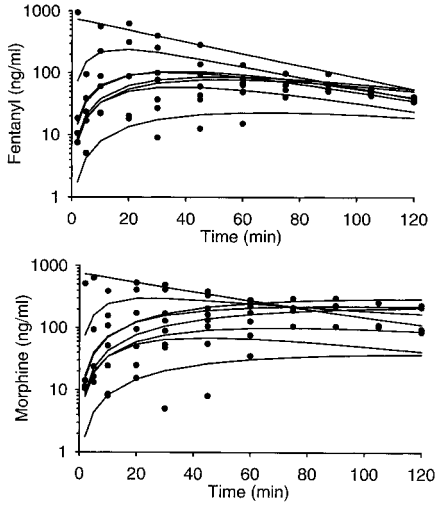

Fig. 4. Fit of the basic pharmacokinetic model to the observations at the cephalad sampling site. The model captures both the scale of the observations and the loss of variability over time.

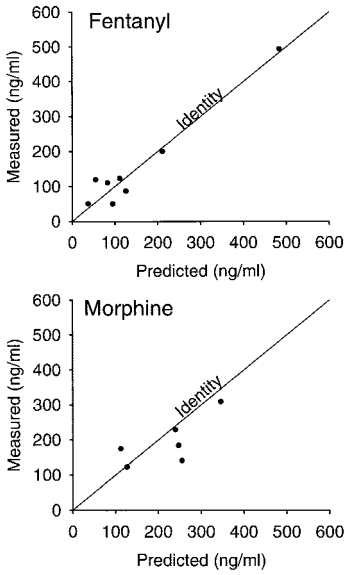

Fig. 5. Fit of the basic pharmacokinetic model to the observations at the caudad sampling site. Only one caudad sample was taken in each individual.

anyl concentrations fairly accurately. There is a slight bias toward underprediction of the caudad morphine concentrations.

The parameters of the model are given in table 2. The individual parameters are the *post hoc* Bayesian estimates in each individual provided by NONMEM. The mixing parameter, k_{mix}, is notable primarily for its variability, ranging from 0.001 to 1.010 min^{-1}. This suggests that in some individuals, the drug mixes exceedingly rapidly, whereas in others, the mixing occurs quite slowly. This is entirely consistent with the data (figs. 2 and 3), which show that some individuals have a nearly instantaneous peak, whereas in others, the peak is delayed for nearly 90 min. The median volume parameter of 28 ml is large, suggesting that this volume incorporates some local distribution of drug into tissue. The median rate constants for fentanyl and morphine elimination were 0.017 and 0.0092 min^{-1}, respectively, yielding elimination rate constants of 40 and 75 min. The "typical value" in the population and the interindividual variability as estimated by NONMEM are also shown.

None of the rate constants correlated with any measured patient covariate. Surprisingly, the compartment volume was inversely correlated with CSF volume (r^2 = 0.64), but this was based on observations in only the four individuals for whom CSF volume was estimated.

Multiple variations of the basic pharmacokinetic model shown in figure 3 were explored, including the addition of other mixing compartments cephalad and caudad to the sampled compartments, the addition of spacing compartments between the two sampling compartments, and the addition of distribution compartments for morphine and fentanyl. None of these enhancements significantly improved the performance beyond that obtained with the basic model.

Discussion

The present study, although limited by the relatively short distance between needles over which observations were made and the lack of pharmacodynamic endpoints, carries important implications for future research regarding drug distribution in the intrathecal space. First, there was a remarkable similarity between fentanyl and morphine in initial distribution after injection, as depicted in figure 1 and as reflected in the lack of difference between them in T_{max} or C_{max}. In six of eight volunteers, opioids appeared in measurable concentrations within 5 min from the time of injection. This rate of movement, accompanied by the presumed rapid penetration of drug into the spinal cord, is consistent with the onset of pain relief at low thoracic dermatomes in women in labor 5–10 min after lumbar intrathecal injection of fentanyl.[1]

Table 2. Pharmacokinetic Model Parameters

Volunteer	Height, cm	Weight, kg	Needle Distance, cm	CSF Volume, ml	k_{mix}, min^{-1}	V, l	k_{fen}, min^{-1}	k_{mor}, min^{-1}
1	157	68	10.5	13	0.010	0.119	0.017	0.0141
2	185	93	14.8	26	0.053	0.062	0.019	0.0093
3	180	62	9.0	21	0.008	0.051	0.020	0.0040
4	180	82	7.5	39	0.001	0.043	0.014	0.0092
5	157	68	3.6		0.015	0.086	0.017	0.0027
6	174	75	4.5		1.010	0.033	0.022	0.0184
7	191	98	6.4		0.007	0.071	0.014	0.0029
8	184	89	14.0		0.004	0.051	0.015	0.0115
Mean	176	79	8.8					
Median					0.009	0.057	0.017	0.0092
Population typical value					0.469	0.033	0.015	0.0106
Interindividual variability, %					430	43	24	106

Kinetic constants for mixing (k_{mix}) and drug elimination of fentanyl (k_{fen}) or morphine (k_{mor}) are from the model described in the text and Figure 3. The interindividual variability is the standard distribution of the interindividual variability in the log domain, reflecting the log-normal distribution of the data. It is expressed as percentage, because it is approximately the same as the coefficient of variation in the standard domain when it is less than 30%.

CSF, cerebrospinal fluid.

Interestingly, fentanyl concentrations were relatively constant from 30 to 120 min after injection at the upper lumbar sampling site, in contradistinction to the loss of effective analgesia 90–120 min after injection during labor,[1] although we measured fentanyl in CSF some distance from the cord rather than at its site of action in the cord itself. One could argue that there is a very rapid drop-off in fentanyl concentration with distance, but there clearly was no relationship between distance between injection and sampling needle and drug concentrations, and the gradient between these sites, even 120 min after injection, was less than 3:1. Alternatively, one could argue that acute tolerance could develop to the very high local concentration of opioid exposure with intrathecal injection or that fentanyl distributes within the spinal cord away from its analgesic site of action over time.

Morphine moved cephalad with similar rapidity to fentanyl in the present study, and its slow onset for analgesia presumably reflects slow penetration into spinal cord tissue rather than major differences in movement in CSF. The major difference between these two in duration of action and risk of respiratory depression appears to reflect the more rapid clearance from the CSF of fentanyl. This is clearly demonstrated in the present study by the increasing ratio of morphine to fentanyl over time. These observations suggest that the ratio of morphine to fentanyl in upper lumbar CSF at the time of peak respiratory depression from fentanyl (20 min) would be 1.5:1, whereas at the time of peak respiratory depression from morphine (6 h), it would be 10:1. Based on these observations, we reason that early respiratory depression from fentanyl reflects variability in k_{mix}, with some individuals exhibiting a rapid distribution from CSF to tissue, whereas lack of late respiratory depression from fentanyl reflects clearance from CSF itself.

There was a remarkable heterogeneity in time pattern of drug concentrations at the cephalad sampling site in the present study despite injection of an identical volume at a fixed rate using a slightly hypobaric solution. The very large gradient of drug between injection and sampling sites 60 min after injection in volunteer 4 suggests that restricted distribution of drug, known to exist with administration of hyperbaric solutions,[10] can also occur in clinical settings with hypobaric solutions. Conversely, the extremely rapid spread observed in one individual in the present study is consistent with the rapid-onset (less than 10 min) respiratory depression observed occasionally after lumbar intrathecal injection of lipophilic opioids.

We were surprised that the simple model shown in figure 3, with just four parameters, was able to simultaneously fit the concentration of two drugs, each sampled at two locations, with reasonable accuracy. We were also surprised that the model accurately predicted the decrease in variability over time observed in the data. We believe that this reflects the wide variation in the mixing parameter, k_{mix}. k_{mix} is the major determinant of the cephalad concentrations in the first few minutes after injection, and the high variability in k_{mix} reflects the variability in concentration in the first few minutes. Over time, the effect of rapid or slow mixing becomes irrelevant, resulting in a substantial decrease in variability.

The physiologic basis for the variability in k_{mix} is unknown. CSF sloshes back and forth in the spinal intrathecal space in a complex fashion with the cardiac cycle. High-resolution magnetic resonance images, gated to cardiac electrical activity, demonstrate that the spinal cord itself moves caudally within the canal shortly after the R wave of the electrocardiogram, with a velocity of 5–10 mm/s.[11] This is accompanied at the same time by a rapid movement of CSF in a caudal direction, with a peak flow of 80–150 ml/s.[12,13] Later in the cardiac cycle, there is net flow in the cephalad direction. This back-and-forth sloshing movement of CSF is not homogeneous; flow velocity and movement of the cord itself are greater in the cervical than low thoracic cord,[11,14] and there are channels within the intrathecal space of higher velocity, in general lateral for craniocaudal flow and medioventral and mediolateral for caudocranial flow.[14] The variability in k_{mix} could reflect the local anatomy at the site of drug injection, where some sites might be in a channel of rapid CSF sloshing, whereas nearly adjacent sites are in relatively quiescent pools of CSF. Alternatively, the variability in k_{mix} could reflect global differences in CSF mixing, by which some individuals are rapid mixers and some are slow mixers. The data support the local variability hypothesis rather than the global variability hypothesis because of the convergence of observed values at 120 min. If the mixing variability were a global phenomenon, then the rapid mixers should have both a rapid peak and a subsequent rapid decrease as drug continues to mix rapidly into yet more caudad and cephalad regions of CSF.

We were surprised by the inverse relationship between the volume parameter of the model and the measured CSF volume. We cannot explain this finding physiologically. Because CSF volume was measured in only four individuals, this may be an artifact of the small sample size. We have previously proposed the concept of "observation at a distance," whereby the magnitude of observed concentrations in the CSF is inversely proportional to the distance of the sampling site from the site of injection.[15] This concept was demonstrated experimentally by Ummenhofer *et al.*[6] The results of this study do not support the concept of "observation at a distance," in that the concentrations of drug were not correlated with the sampling distance. We can envision three explanations for this. First, perhaps the concept is wrong. We think this is unlikely, because drug necessarily becomes more diluted as it diffuses farther from the injection and because we observe this dilution clinically as

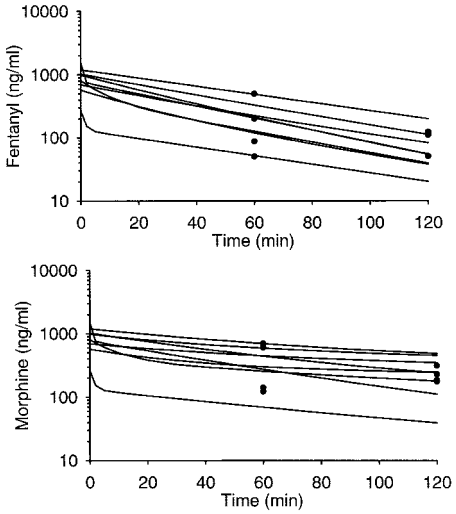

Fig. 6. Predicted concentrations at the sampling site over time, showing the single observation and the parallel elimination curves.

the cephalad diminution of sensory loss every time we perform a spinal anesthetic. A second explanation is that the "observation at a distance" concept is most easily observed within an individual in whom samples are taken concurrently at multiple distances from the site of injection, exactly as described by Ummenhofer *et al*.[6] In this study, there was only one sampling site in each individual, and thus we were unable to examine what happened at sites closer to or farther from the site of injection. It could be that study of a small number of subjects and short distances between needles reduced our ability to resolve the data. The third explanation is that there are two time frames for spinal drug mixing: an early time frame during which concentrations are determined primarily by mixing and a longer time frame during which concentrations are determined primarily by distance from the injection site. In the present study, the effect of mixing clearly dominates the concentrations over the first few minutes, but the effect of mixing is attenuated over time. In our neostigmine study,[15] we gathered samples over 1440 min, and thus, the first few minutes had very little influence on the overall pharmacokinetic profile. It may be that an experiment needs to last for many hours to adequately demonstrate the "observation at a distance" concept.

Another explanation for the difference may be the sampling site. In most pharmacokinetic studies, including our own neostigmine trial, the site of injection was very close to the site of sampling. Figure 6 shows the fentanyl and morphine concentrations predicted by our basic pharmacokinetic model at the site of sampling, as well as the single observed concentration. Our model predicts parallel decay curves analogous to our previously reported curves for neostigmine. It may be that the scaling factor that we attributed to distance in our previous neostigmine article is, in fact, a scaling factor more easily attributable to the mixing rate constant. The best we can conclude from our intrathecal pharmacokinetic models is that additional research is necessary to understand the physiologic basis of intrathecal pharmacokinetic variability.

In designing this study, we expected that the distribution of drug in the intrathecal space would reflect individual subject characteristics. However, there is remarkably little evidence to support this assumption. Neither patient height nor weight predicts the extent of spread of intrathecally administered local anesthetics in women at cesarean section.[16] Others have observed a highly significant correlation between the maximum spread of local anesthetic, as determined by sensory blockade to pinprick and the lumbosacral CSF volume into which the local anesthetic was injected.[9] We failed to observe such a relationship between CSF volume and drug concentrations in the present study. It is conceivable that drug concentrations do not parallel clinical effects, although in the case of opioids, it is clear that diffusion from CSF into spinal cord tissue is the route of entry of drug to its pharmacodynamic effect site. The lumbosacral thecal sack is nearly filled with nerve roots, and the lack of relationship between CSF volume in this area and any aspect of opioid drug concentration in the present study is consistent with the hypothesis that drugs may be effectively compartmentalized in this space.

In summary, fentanyl and morphine appear at a needle inserted on average 9 cm cephalad from the site of intrathecal injection with a remarkably similar initial time course. Fentanyl is cleared more rapidly than morphine from CSF, resulting in a gradually increasing ratio of morphine to fentanyl over time, but both drugs show a remaining gradient of higher concentrations at the injection site compared with 9 cm away for as long as 2 h after injection. The variability in concentration decreased over time. The fentanyl and morphine concentrations at both the injection and sampling sites can be described by a simple pharmacokinetic model. The early concentrations appear to be determined primarily by intrathecal mixing, which can vary by several orders of magnitude among individuals. These data are consistent with clinical observations of rapid-onset labor analgesia as well as extensive spread and early respiratory depression from intrathecal injection of lipophilic opioids. They are similarly consistent with the notion of a CSF reservoir from which the slowly penetrating opioid morphine gains access to spinal sites.

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