Pharmacokinetics of Intrathecal Morphine
and Meperidine in Humans

Staffan Sjöström, M.D.,* Anders Tamsen, M.D., Ph.D.,† M. Peter Persson, Pharm.D.,‡ Per Hartvig, Pharm.D., Ph.D§

Two groups of surgical patients each comprising six individuals received an intrathecal injection of morphine 0.3 mg or meperidine 10 mg. Cerebrospinal fluid (CSF) and plasma were sampled frequently during a 6-h period and analyzed for morphine or meperidine. Maximum plasma morphine concentrations were found 5–10 min after injection, and averaged 4.5 ± 1.1 ng·ml^{-1} (mean ± SEM). Maximum CSF morphine concentrations were considerably higher than maximum plasma concentrations, 6410 ± 1290 ng·ml^{-1}. Maximum plasma concentrations of meperidine were also measured 5 or 10 min after injection and were low (36 ± 9 ng·ml^{-1}) compared with the maximum CSF concentrations (364 ± 105 µg·ml^{-1}). After a rapid initial decline for about 15 min after injection, the CSF concentrations decreased with a half-life of 89.8 ± 16.1 min for morphine and 68.0 ± 5.1 min for meperidine during the rest of the study period. The initial volume of distribution in CSF was similar for both drugs, or 22 ± 8 ml for morphine and 18 ± 5 ml for meperidine. After 6 h, $1.6 \pm 0.9\%$ of the injected morphine dose and $0.41 \pm 0.09\%$ of the meperidine dose remained in the initial volume of distribution. Large inter-individual differences in morphine and meperidine CSF kinetics existed, which may explain some of the reported individual differences in duration of effects. The disappearance of meperidine from CSF tended to be faster than that of morphine, which may be explained, in part, by the differences in lipid solubilities of the drugs. (Key words: Analgesics: meperidine; morphine. Anesthetic techniques: intrathecal. Pharmacokinetics: intrathecal meperidine; intrathecal morphine.)

SPINAL ADMINISTRATION of opioids usually results in long-lasting analgesia without blunting other sensory

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* Staff, Department of Anesthesiology, University Hospital.

† Associate Professor, Department of Anesthesiology, University Hospital.

‡ Pharmacist, Hospital Pharmacy, University Hospital, and Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala.

§ Associate Professor of Department of Analytical Pharmaceutical Chemistry, University of Uppsala, and Hospital Pharmacy, University Hospital.

Address reprint requests to Dr. Sjöström: Department of Anesthesiology, Kantonspital, CH-4031 Basel, Switzerland.

modalities or motor function. It can be achieved with either epidural or intrathecal administration of the drugs.[1,2] The epidural route allows reinjection via a catheter according to patient's needs.

Intrathecal administration of a single dose of opioid, on the other hand, is technically easy. The resulting pain relief is long-lasting; for morphine, it is up to 24 h or more.[3,4,¶,**]

Intrathecal meperidine in high doses has been used as the sole anesthetic for urologic surgery and surgery of the perineum and lower limbs with ensuing long-lasting postoperative pain relief.[5–8] The pain relief, lasting 24 h or more, without motor block, reported after the intrathecal administration of 10–30 mg of meperidine,[3] is probably due to an action on the endogenous opioid system in the spinal dorsal horn. The sensory and motor block created by high doses (about 1 mg·kg^{-1}) of intrathecal meperidine is, on the other hand, thought to depend on a weak local anesthetic action of meperidine.[9]

The late respiratory depression that occasionally occurs several hours after spinal opioids is related to transport of opioids by bulk flow of CSF to supraspinal respiratory centers.[1] The fraction of cephalad transport of significant amounts of drug is thought to be greater with hydrophilic drugs, such as morphine, than with lipophilic drugs, such as meperidine or fentanyl. There is experimental evidence of cephalad spread of spinal morphine from animal[10] and human[11,12] studies. In most cases of late respiratory depression after spinal opioids, morphine has been used.[13–17] It is noteworthy that epidural fentanyl did not cause late respiratory depression in volunteers,[18] and, until now, there are no reports of late respiratory depression after epidural meperidine.

CSF pharmacokinetics after intrathecal morphine have been studied earlier using a few samples in each patient[4] or data from a single patient.[19]

The aim of this study was to perform a detailed analysis of the CSF and plasma pharmacokinetics of the hydrophilic[20] morphine and the more lipophilic[20] meperidine after intrathecal administration.

¶ Katz J, Nelson W: Intrathecal morphine for postoperative pain relief. Regional Anesthesia 6:1–3, 1981.

** Bengtsson M, Löfström JB, Merits H. Postoperative pain relief with intrathecal morphine after major hip surgery. Regional Anesthesia 8:140–143, 1983.

TABLE 1. Sex, Age, Body Weight, Body Surface Area (BSA), Peroperative Blood Loss, Duration of Anesthesia, and Fentanyl Consumption during Anesthesia (Mean ± SEM) for the Groups in the Study

Group	Sex (M:F)	Age	Weight (kg)	BSA (m²)	Blood Loss (ml)	Duration Anesthesia (min)	Fentanyl Consumption (mg·h⁻¹)
Morphine	2:4	36.7 ± 5.9	63.5 ± 5.3	1.76 ± 0.07	880 ± 200	281 ± 17	0.15 ± 0.01
Meperidine	5:1	39.5 ± 3.1	66.0 ± 4.9	1.77 ± 0.08	1590 ± 530	276 ± 30	0.16 ± 0.03

Methods and Material

The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University.

PATIENTS

Two groups of patients, each comprising six individuals, scheduled for major abdominal surgery gave informed consent to participate in the study. None of the patients had any symptoms or signs of hepatic or renal failure, alcohol or drug abuse, or psychic disease. Patient data are shown in table 1.

ANESTHESIA

After an overnight fast, all patients were premedicated with oral diazepam 10–15 mg and intramuscular atropine sulphate 0.5 mg. Anesthesia was induced with thiopental q.s. and a single dose of droperidol 5 mg. Orotracheal intubation was performed after pancuronium bromide 0.1 mg·kg⁻¹. The lungs were mechanically ventilated with oxygen and nitrous oxide 3:7.[21,22] Additional increments of pancuronium 1–2 mg were given as required. Intraoperative analgesia was provided with increments of iv fentanyl in 0.1–0.2-mg doses as required.

When the surgical procedure was completed and following tracheal extubation, the patients were transferred to a recovery room where they remained overnight.

Intravenous fluids and blood transfusions were given in accordance with the clinical requirements in each case.

PREPARATIONS FOR DRUG ADMINISTRATION AND SAMPLE COLLECTION

After induction of anesthesia, a central venous catheter was inserted percutaneously *via* the internal jugular vein with its tip located in the superior caval vein just above the right atrium (position confirmed by x-ray). This catheter was used for collection of blood samples. With the anesthetized patient in the left lateral position, a 25-gauge spinal needle was placed in the subarachnoid space at the L2–L3 interspace. This needle was used a few minutes later for the administration of the opioid dose.

A dural puncture was then performed with an 18-gauge epidural Tuohy needle at the L3–L4 interspace. With the bevel of the needle directed cranially, an 18-gauge epidural catheter was inserted into the subarachnoid space and advanced approximately 5 cm beyond the tip of the needle. The epidural needle was then removed over the catheter.

The intrathecal catheter was used for the collection of CSF samples. It had an internal volume of 0.2 ml.

Baseline samples of central venous blood and CSF were then collected. Morphine 0.3 mg in saline 1 ml or meperidine 10 mg in saline 1 ml was thereafter injected over 30 s. No further doses of morphine or meperidine were administered during the 6-h study period. The spinal needle was removed and the patients were turned on their backs to be prepared for surgery.

BLOOD AND CSF SAMPLING

Samples of 5 ml of blood and 1 ml of CSF were collected in plastic syringes, the plasma was separated by centrifugation, and the samples were stored in plastic tubes at −20° C until analyzed.

CSF and plasma samples were collected before the bolus administration and 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min after injection. The intrathecal catheter was then removed.

DRUG ASSAYS

Morphine[23,24] and meperidine[25] were assayed using gas chromatography with electron capture detection. Concentrations are expressed as morphine and meperidine base. The limits of detection of the methods were 1 ng·ml⁻¹ for morphine and 5 ng·ml⁻¹ for meperidine. The coefficients of variation of the methods were 10%.

DERIVATION OF PHARMACOKINETIC PARAMETERS

Rate constants and half-lives were calculated using linear regression analysis with the least squares method.[26]

The CSF concentration-time curves exhibited two phases. An initial rapid declining phase during the first 15–30 min was followed by a slower phase. The intercepts with the ordinate of these two phases were obtained from curve-stripping,[26] and the sum of the inter-

cepts was used to define the hypothetical drug concentration in CSF at time 0 ($C_{CSF\ 0}$). The half-life of opioid in CSF from 15 min post-injection and onwards ($t_{1/2CSF}$) was determined.

To estimate the initial volume of distribution of opioid in CSF (V_{CSF}) the following equation was used:

$$V_{CSF} = Dose/C_{CSF\ 0}$$

The fraction of the opioid dose remaining in the initial volume of distribution in the CSF at the end of the study period ($f_{CSF\ 6}$) was calculated as follows:

$$f_{CSF\ 6} = \frac{C_{CSF\ 6} \cdot V_{CSF}}{Dose},$$

where $C_{CSF\ 6}$ is the measured CSF concentration at 6 h (i.e., end of the study).

The area under the CSF concentration-time curve (AUC) was calculated using the trapezoidal rule. The residual area was not calculated. The time to reach maximum concentrations (t_{max}) and the maximum concentrations (C_{max}) in CSF and plasma were recorded.

STATISTICS

Results are given as mean ± SEM in the text and figures. Student's t test for independent means was used to compare the groups. $P < 0.05$ was considered as statistically significant.

The coefficient of determination (r^2) in the linear regression indicates the fraction of variance of the Y-values which is accounted for by the variable X.[26]

Results

The clinical course was uneventful in all patients during the study period. There were no significant differences in duration of anesthesia or peroperative blood

TABLE 2. Mean ($\bar{X}$ ± SEM) CSF and Plasma Concentrations of Morphine and Meperidine

Time (min)	Morphine Group		Meperidine Group	
	CSF (ng·ml⁻¹)	PLASMA (ng·ml⁻¹)	CSF (ng·ml⁻¹)	PLASMA (ng·ml⁻¹)
5	5660 ± 1580	1.1 ± 0.3	361000 ± 107000	29 ± 11
10	5540 ± 1320	3.7 ± 1.2	299000 ± 94800	23 ± 6
15	4440 ± 880		198000 ± 70500	20 ± 7
30	3850 ± 755		141000 ± 48800	10 ± 5
60	2630 ± 506		76000 ± 28000	8 ± 4
90	1820 ± 527		42700 ± 17000	
120	1380 ± 370		31000 ± 11800	
180	899 ± 263		13100 ± 3400	
240	623 ± 221		6400 ± 2000	
300	432 ± 177		4800 ± 1300	
360	332 ± 137		3200 ± 900	

loss between the groups (table 1). The time from the end of operation to the request of pain relief averaged 3.5 ± 0.8 h (range 1–6.5 h) in the morphine group and 2.4 ± 0.6 h (range 1–5.5 h) in the meperidine group.

PLASMA KINETICS

Plasma concentrations after the intrathecal morphine bolus were very low, and morphine could only be detected at 5 and 10 min post-injection in five of the patients, and not at all in one patient (tables 2, 3; fig. 1). The mean maximum plasma concentration in the remaining five patients was 4.5 ± 1.1 ng·ml⁻¹, and plasma concentrations were below the limit of detection in all patients 15 min post-injection and onwards. Plasma concentrations after the intrathecal meperidine bolus were also low (tables 2, 4; fig. 2). The maximum concentrations were usually measured 5 min post-injection (in four of the six patients) and averaged 36 ± 9 ng·ml⁻¹. The concentrations of meperidine fell rapidly

TABLE 3. Maximum Concentration and Time to Reach Maximum Concentration in CSF and Plasma (C_{max}, t_{max}), Extrapolated Concentration at Time 0 in CSF (C_{CSF0}), Initial Volume of Distribution in CSF (V_{CSF}), Half-life in CSF ($t_{1/2CSF}$), Fraction of Morphine Remaining in the Initial Volume of Distribution in the CSF at the End of the Study Period (f_{CSF6}), and Area Under the CSF Concentration-time Curve (AUC)

| Morphine Group	Patient						$\bar{X}$ ± SEM
	1	2	3	4	5	6	
CSF							
C_{max} (ng·ml⁻¹)	9880	4160	5410	3400	4720	10900	6410 ± 1290
t_{max} (min)	5	10	5	5	30	5	
C_{CSF0} (ng·ml⁻¹)	12800	—	6030	23900	—	30100	18200 ± 5400
V_{CSF} (ml)	22	—	45	11	—	9	22 ± 8
$t_{1/2CSF}$ (min)	135	83	89	54	136	42	89.8 ± 16.1
r^2 ($t_{1/2}$)	0.91	0.97	0.98	0.99	0.99	0.99	
f_{CSF6}	0.034	—	0.029	0.001	—	0.001	0.016 ± 0.009
AUC (μg·min·ml⁻¹)	774	479	469	121	800	489	524 ± 101
Plasma							
C_{max} (ng·ml⁻¹)	7.8	4.4	5.5	3.4	1.2	<1	4.5 ± 1.1
t_{max} (min)	10	10	10	10	5	—	
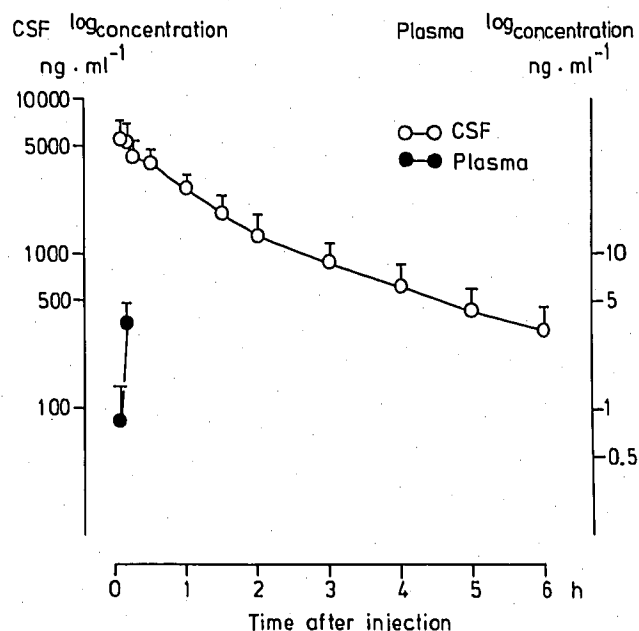
FIG. 1. Mean CSF (open circles) and plasma (filled circles) concentrations of morphine following an intrathecal bolus of 0.3 mg.

and were usually below the limit of detection after 30–60 min. The elimination half-lives from plasma could not be calculated.

CSF KINETICS

The maximum morphine CSF concentration averaged 6410 ± 1290 $ng \cdot ml^{-1}$ and was obtained at the first measurement 5 min after the injection in four patients, at 10 min in one patient, and not until 30 min post-injection in one patient (no. 5) (table 3).

The maximum meperidine CSF concentrations were

measured 5 min after the injection in five patients and 10 min post-injection in one patient, and averaged 364 $\pm$ 105 $\mu g \cdot ml^{-1}$ (table 4).

The initial volume of distribution in the CSF (V_{CSF}) averaged 22 ± 8 ml (range 9–45 ml) for morphine and 18 ± 5 ml (range 8–36 ml) for meperidine (not significant). The volume of distribution could not be determined in three patients, numbers 2, 5, and 10, in whom the maximum CSF concentrations were not measured 5 min post-injection.

The half-life in CSF ($t_{1/2CSF}$) averaged 89.8 ± 39.5 min (range 42–136 min) for morphine and 68.0 ± 5.1 min (range 58–83 min) for meperidine (not significant) (tables 3, 4; figs. 1, 2).

The fraction of the opioid bolus remaining in the initial volume of distribution in CSF 6 h after injection ($f_{CSF\ 6}$) averaged 0.016 ± 0.009 for morphine and 0.0041 ± 0.0009 for meperidine (not significant).

Discussion

METHODOLOGICAL CONSIDERATIONS

Distribution in the subarachnoid space of a drug injected intrathecally is influenced by age, body position, intra-abdominal pressure, site of injection, pH of the CSF, specific gravity and volume of the bolus, and speed of injection.[27–30]

The volume of the boluses was kept small in the present study to reduce turbulence and pressure fluctuations in the dural sac.

Any sampling of CSF could disturb the kinetics of spinally administered drugs, as does leakage from the dural punctures. It is virtually impossible to bypass these sources of error if the kinetics are to be studied *in vivo*. The total sampled volume of CSF in the present study was 12 ml. This is a significant fraction of the volume of

TABLE 4. Maximum Concentration and Time to Reach Maximal Concentration in CSF and Plasma (C_{max}, t_{max}), Hypothetical Concentration in CSF at the Time of Injection (C_{CSF0}), Initial Volume of Distribution in CSF (V_{CSF}), Half-life in CSF ($t_{1/2CSF}$), Fraction of Meperidine Remaining in the CSF 6 h Post-injection (f_{CSF6}), and Area Under the CSF Concentration-time Curve (AUC)

Meperidine Group	Patient						$\bar{X} \pm SEM$
	7	8	9	10	11	12	
CSF							
C_{max} ($\mu g \cdot ml^{-1}$)	118	557	129	142	589	648	364 ± 105
t_{max} (min)	5	5	5	10	5	5	
C_{CSF0} ($\mu g \cdot ml^{-1}$)	365	1060	247	—	963	798	687 ± 162
V_{CSF} (ml)	25	8	36	—	9	11	18 ± 5
$t_{1/2CSF}$ (min)	70	58	83	83	58	56	68.0 ± 5.1
r^2 ($t_{1/2}$)	0.95	0.93	0.94	0.96	0.97	0.91	
f_{CSF6}	0.0028	0.0020	0.0032	—	0.0063	0.0061	0.0041 ± 0.0009
AUC ($\mu g \cdot min \cdot ml^{-1}$)	3730	17500	3610	10550	32300	29700	16200 ± 5130
Plasma							
C_{max} ($ng \cdot ml^{-1}$)	25	70	20	25	20	55	36 ± 9
t_{max} (min)	15	5	5	5	10	5	

CSF in the spinal canal, which has been reported to be 25–75 ml.[27,28] The formation of CSF during the sampling period can be estimated to be about 110–140 ml $(0.3$–0.4 ml $\cdot$ min^{-1}),[28] or ten times the sampled volume. The introduction of an intrathecal sampling catheter probably disturbs the kinetics less than repeated lumbar punctures, each of which can cause leakage of CSF. Furthermore, our technique permits detailed studies of the CSF pharmacokinetics of both intrathecally and epidurally administered drugs.

PLASMA KINETICS

The plasma concentrations of morphine after the 0.3 mg intrathecal bolus in this study were very low, which is in agreement with earlier findings.[4,31] The intrathecal administration of 10 mg of meperidine also resulted in low plasma concentrations, and the maximal concentration was usually measured 5 min post-injection.

The rapid plasma peaks probably reflect a rapid absorption through the arachnoid granulations in close proximity to the epidural veins. The epidural veins are mainly drained via the azygos vein into the superior caval vein. However, both the morphine and meperidine plasma concentrations were low compared to the CSF concentrations, and the mean CSF concentrations were 5,000–10,000 times higher than the mean plasma concentrations 5 min after injection.

Earlier studies have indicated maximum plasma concentrations of morphine 3–5 h after injection following intrathecal administration,[4,31] but, in those studies, larger volumes of drug solutions were injected, and this might have resulted in altered plasma kinetics. The divergent results may also be explained by different assay-methods. Radioimmunoassays co-determine pharmacologically inactive morphine glucuronide, and the amount of morphine glucuronide exceeds that of unchanged morphine from the second hour after a single intravenous dose.[32] The gas chromatography assay used here does not co-determine the glucuronide.

Minimum analgesic morphine plasma concentrations during systemic patient-controlled analgesia have been stated to be about 20–40 ng $\cdot$ ml^{-1}.[33,34] This is far above the maximum plasma concentrations seen after the administration of a 0.3-mg intrathecal bolus, and it is not even plausible that the low plasma concentrations resulting from higher doses of 0.5–1 mg of morphine could contribute significantly to the prolonged analgesic effect.

CSF KINETICS

Intrathecal morphine has been used in widely varying doses, from less than 0.1 mg[35] to 20 mg.[36] Small doses of 0.25–0.5 mg alone or in combination with local anes-
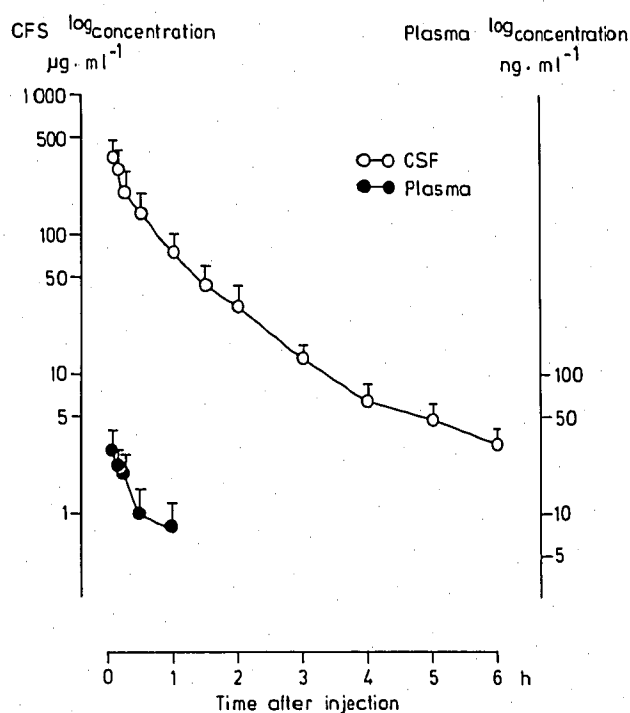

FIG. 2. Mean CSF (open circles) and plasma (filled circles) concentrations of meperidine following an intrathecal bolus of 10 mg.

thetics for spinal anesthesia have been reported to give pain relief for 12–24 h or more.[4] ** The question of optimal dose of intrathecal morphine has recently been discussed.[35] Morphine doses less than 0.1 mg did not seem to produce satisfactory analgesia, and increasing the dose above 0.2 mg did not prolong the duration of analgesia. The information in the report is too scarce to draw conclusions concerning optimal doses, however. Adverse effects including respiratory depression seem to be dose related. There seems to be general agreement that doses of intrathecal morphine should be kept low, certainly less than 1 mg, and doses of 0.25 mg have been recommended.**

The large inter-individual variation in morphine CSF kinetics in the present study with threefold variations in both maximum CSF concentrations and half-lives may explain some of the reported individual differences in the duration of analgesia after intrathecal morphine. It also makes it very difficult, or even impossible, to find a standard dose producing a long duration of pain relief to the individual patient without exposing the patient to the risk of an overdose with potential adverse effects.

Large individual differences also existed in the meperidine CSF kinetics, especially in maximum CSF concentrations, but also in half-lives. The maximum concentrations varied fivefold between 118 and 648 $\mu g \cdot$ ml^{-1}, and the half-lives in CSF varied between 58

and 83 min. Such differences correspond to individual differences in effects after intrathecal meperidine.[7]

Meperidine has been used intrathecally as the sole anesthetic for low abdominal, perineal, and lower-limb surgery. Large doses of 0.8–1.1 mg · kg^{-1} were used by Mircea *et al.*,[5] and this resulted in profound sensory and motor block, allowing surgery to be performed during a period of 100–110 min, and long-lasting postoperative pain relief was seen. No cases of respiratory depression or neurological damage were seen, but a few patients developed signs of hypotension, bradycardia, and hypoxemia 20–30 min after the injection, probably as a sign of a high sympathetic block. Similar experiences are reported by others.[6-8] The motor blockade is thought to be due to the local anesthetic properties of meperidine.[9] Assuming linear CSF kinetics, the data in the present study can be used to calculate the probable intrathecal meperidine concentrations after different doses. An intrathecal meperidine dose of 70 mg, as used by Mircea *et al.*,[5] should result in enormously high CSF concentrations, of about 2.5 mg · ml^{-1} after 5 min. As the motor block disappeared after 90–120 min,[5] the calculated CSF concentrations are 0.2–0.3 mg · ml^{-1}. Motor and sensory blocks thus seem to require very high CSF concentrations.

The initial volumes of distribution in CSF of intrathecal morphine and meperidine in the present study averaged 22 and 18 ml, respectively. This corresponds to the volume of spinal CSF of 25–75 ml,[27,28] but there is no evidence that opioids diffuse uniformly and immediately throughout the spinal CSF. The initial volume of distribution might represent not only opioid dilution in CSF, but also its uptake by surrounding nervous tissue.

The disposition in CSF of morphine and meperidine from 15 min post-injection and throughout the 6-h study period probably represents a distribution phase and an elimination phase. Nordberg *et al.* studied the CSF kinetics during a period of 18 h after intrathecal morphine.[4] They reported a mean CSF half-life of about 3 h, but their data suggested an early distribution phase and a late elimination phase. Owing to the limited number of samples (about four), they were not able to describe the kinetics in any detail. The existence of a slow elimination phase starting several hours after the injection of intrathecal morphine has been demonstrated by others,[19] and is likely to exist for meperidine as well, although it is not apparent during the first 6 h after injection.

The half-life in CSF tended to be shorter for meperidine than for morphine. Only 0.4% of the intrathecal meperidine bolus remained in lumbar CSF 6 h after injection in the present study, while the corresponding fraction of morphine was 1.6%.

The clinical implications of this study are that the faster elimination from CSF of meperidine is in accord with the belief that morphine carries a higher risk of cephalad spread after intrathecal administration. Furthermore, the large inter-individual difference in CSF kinetics of both morphine and meperidine makes it difficult to predict the effects of the drugs, which is a disadvantage when the intrathecal route of administration is used.

References

1. Yaksh TL: Spinal opiate analgesia: Characteristics and principles of action. Pain 11:293–346, 1981
2. Cousins MJ, Mather LE: Intrathecal and epidural administration of opioids. ANESTHESIOLOGY 61:276–310, 1984
3. Cousins MJ, Mather LE, Glynn CJ, Wilson PR, Graham JR: Selective spinal analgesia. Lancet 1:1141–1142, 1979
4. Nordberg G, Hedner T, Mellstrand T, Dahlström B: Pharmacokinetic aspects of intrathecal morphine analgesia. ANESTHESIOLOGY 60:448–454, 1984
5. Mircea N, Constaninescu C, Jianu E, Busu G, Ene C, Daschievici S, Nedelcu A, Leoveanu A: L'anesthesie sous-arachnoidienne par la pethidine. Ann Fr Anesth Reanim 1:167–171, 1982
6. Saissy JM: Experience de la rachianesthesie a la pethidine dans la chirurgie des fistules vesico-vaginales de la femme africaine (30 cas). Med Trop (Mars) 44:61–64, 1984
7. Ragot P, Tauzin-Fin P, Crozat P, Fonrouge JM, Sabathie M: Comparaison de la pethidine et de la prilocaine en rachianesthesie pour 100 intervention urologiques. Agressologie 25:29–32, 1984
8. Famewo CE, Naguib M: Spinal anaesthesia with meperidine as the sole agent. Can Anaesth Soc J 32:533–537, 1985
9. Way EL: Studies on the local anesthetic properties of isonipecaine. J Am Pharm Assoc 35:44–47, 1946
10. Gregory MA, Brock-Utne JG, Bux S, Downing JW: Morphine concentration in brain and spinal cord after subarachnoid morphine injection in baboons. Anesth Analg 64:929–932, 1985
11. Bromage PR, Camporesi EM, Durant PAC, Nielssen CH: Rostral spread of epidural morphine. ANESTHESIOLOGY 56:431–436, 1982
12. Gourlay GK, Cherry DA, Cousins MJ: Cephalad migration of morphine in CSF following lumbar epidural administration in patients with cancer pain. Pain 23:317–326, 1985
13. Glynn CJ, Mather LE, Cousins MJ, Wilson PR, Graham JR: Spinal narcotics and respiratory depression. Lancet 2:356–357, 1979
14. Davies GK, Tolhurst-Cleaver CL, James TL: CNS depression from intrathecal morphine. ANESTHESIOLOGY 52:280, 1980
15. Davies GK, Tolhurst-Cleaver CL, James TL: Respiratory depression after intrathecal narcotics. Anaesthesia 35:1080–1083, 1980
16. Gustafsson LL, Schildt B, Jacobsen K: Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. Br J Anaesth 54:479–486, 1982
17. Jacobson L: Intrathecal and extradural narcotics, Advances in Pain Research and Therapy, Volume 7. Edited by Benedetti C. New York, Raven Press, 1984, pp 199–236
18. Lam AM, Knill RJ, Thompson WR, Clement JL, Varkey GP,

Spoerel WE: Epidural fentanyl does not cause delayed respiratory depression. Can Anaesth Soc J 30:S78–S79, 1983

19. Lazorthes Y, Gouarderes C, Verdie JC, Monsarrat B, Bastide R, Campan L, Alwan A, Cros J: Analgesie par injection intrathecale de morphine. Etude pharmacocinetique et application aux doleurs irreductibles. Neurochirurgie 26:159–164, 1980

20. Kaufman JJ, Semo NM, Koski WS: Microelectrometric measurement of the pKa's and partition and drug distribution coefficients of narcotics and narcotic antagonists and their pH temperature dependence. J Med Chem 18:647–655, 1975

21. Engström CH, Herzog P: Ventilation nomogram for practical use with the Engström respirator. Acta Chir Scand (Suppl) 245:37–42, 1959

22. Norlander OP: The use of respirators in anaesthesia and surgery. Acta Anaesthesiol Scand (Suppl) 30:7–18, 1968

23. Dahlström B, Paalzow L: Quantitative determination of morphine in biological samples by gas-liquid chromatography and electron-capture detection. J Pharm Pharmacol 27:172–176, 1975

24. Edlund P-O: Determination of opiates in biological samples by glass capillary gas chromatography with electron-capture detection. J Chromatogr 206:109–116, 1981

25. Hartvig P, Fagerlund C: A simplified method for the gas chromatographic determination of pethidine and norpethidine after derivatization with trichloroethyl chloroformate. J Chromatogr 274:355–360, 1983

26. Wagner JG: Fundamentals of Clinical Pharmacokinetics. Hamilton, Drug Intelligence Publications Inc, 1975, pp 57–126, 287

27. Bridenbaugh PO, Kennedy WF: Spinal, subarachnoid neural blockade, Neural blockade in clinical anesthesia and management of pain. Edited by Cousins MJ, Bridenbaugh PO. Philadelphia, J.B. Lippincott Company, 1980, pp 146–175

28. Reynolds FJM: Spinal and epidural block, A Practice of Anaesthesia. Edited by Wylie WD, Churchill-Davidson HC. London, Lloyd-Luke Ltd, 1984, pp 856–892

29. Greene NM: Uptake and elimination of local anesthetics during spinal anesthesia. Anesth Analg 62:1013–1024, 1983

30. Greene NM: Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 64:715–730, 1985

31. Chauvin M, Samii K, Schermann JM, Sandouk P, Bourdon R, Viars P: Plasma concentration of morphine after i.m., extradural and intrathecal administration. Br J Anaesth 54:843–847, 1981

32. Stanski DR, Paalzow L, Edlund PO: Morphine pharmacokinetics: GLC assay versus radioimmunoassay. J Pharm Sci 71:314–317, 1982

33. Dahlström B, Tamsen A, Paalzow L, Hartvig P: Patient-controlled analgesic therapy, part IV: Pharmacokinetics and analgesic plasma concentrations of morphine. Clin Pharmacokinet 7:266–279, 1982

34. Graves DA, Arrigo JM, Foster TS, Baumann TJ, Batenhorst RL: Relationship between plasma morphine concentrations and pharmacologic effects in postoperative patients using patient-controlled analgesia. Clin Pharm 4:41–47, 1985

35. Takasaki M, Asano M: Intrathecal morphine combined with hyperbaric tetracaine. Anaesthesia 38:76–77, 1983

36. Samii K, Chauvin M, Viars P: Postoperative spinal analgesia with morphine. Br J Anaesth 53:817–820, 1981