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Pharmacokinetics of Epidural Morphine and Meperidine in Humans

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Five groups of surgical patients, each comprising six individuals, received epidural doses of morphine or meperidine, and the plasma and CSF kinetics were studied. Three groups received epidural doses of morphine 3 mg in 1 or 10 ml or meperidine 30 mg in 1 ml. Cerebrospinal fluid (CSF) and central venous blood opioid concentrations were measured intermittently for 6 h after injection. Two groups received epidural doses of morphine 3 mg in 1 ml or meperidine 30 mg in 1 ml, and opioid CSF concentrations were determined over a 24-h period. Morphine appeared rapidly in plasma, and maximum plasma concentrations were usually detected 5 min after injection and averaged 33 ng · ml^{-1} in the 1-ml volume group and 40 ng · ml^{-1} in the 10-ml volume group. The terminal plasma half-life averaged 91 ± 34 min and 87 ± 27 min, respectively (mean ± SEM). Maximal plasma concentrations of meperidine were usually detected 10 or 15 min post-injection and averaged 196 ± 29 ng · ml^{-1}. The terminal plasma half-life averaged 124 ± 26 min. Morphine crossed the dura relatively slowly, and the absorption half-life across the dura averaged 22 min. Maximal CSF concentrations were usually seen 60–90 min post-injection. In contrast, meperidine crossed the dura quickly, with an absorption half-life averaging 7.6 ± 2.0 min. Maximal CSF concentrations were seen 15 or 30 min post-injection. Morphine and meperidine concentrations remained several times higher in the CSF than in the plasma. The fraction of the opioid dose crossing the dura was calculated to be 3.6% for morphine and 3.7% for meperidine. There were no significant differences in the kinetics of morphine administered in 1 or in 10 ml when CSF was sampled close to the site of lumbar epidural injection. The CSF concentration-time curves of both drugs decreased biexponentially after the initial rise due to diffusion across the dura. The early half-life in CSF averaged 73.3 ± 11.5 min for morphine and 71.3 ± 3.1 min for meperidine, and the late half-life averaged 369 ± 113 min for morphine and 982 ± 449 min for meperidine. Dose-normalized morphine and meperidine CSF concentrations after epidural administration showed that meperidine concentrations were down to one-fourth the corresponding morphine concentrations from the 2nd to the 15th h after administration, which may partly explain the longer duration of analgesia from morphine. Compartment analysis showed that meperidine is removed faster than morphine from the CSF after epidural administration, which may reduce the risk of cephalad transport and supraspinal adverse effects. (Key Words: Analgesics: meperidine; morphine. Anesthetic techniques: epidural. Pharmacokinetics: epidural meperidine; epidural morphine.)

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EPIDURAL ADMINISTRATION of opioids typically results in powerful analgesia. Other sensory modalities or motor function are not blunted.[1] Analgesia after epidural opioids has been reported in the presence of very low blood concentrations, supporting the notion of a local spinal drug action.[2–4] Double blind studies have confirmed a dose-response relationship for epidural morphine when used for pain relief postoperatively.[5,6]

The duration of action varies with different opioids. The following rank order of analgesia duration has been reported: morphine > methadone = meperidine > fentanyl.[7] The onset of analgesia also varies between the drugs. Morphine has a reported onset of action exceeding 20 min, and maximum pain relief appears 40–90 min after administration,[5,6,8,9] while meperidine and fentanyl have a shorter onset of action (5–10 min) with maximum pain relief 12–30 and 20 min after injection, respectively.[2,10,11]

It has been proposed that these differences, and the most serious potential complication of the method, *i.e.*, respiratory depression occurring several hours after the administration, are related to the physico-chemical properties of the drugs.[1,12–14] According to this hypothesis, hydrophilic drugs as morphine should be more prone to retention in cerebrospinal fluid, increasing the possibility of cephalad spread with the CSF bulk flow to supraspinal centers.

Using volunteers, Bromage *et al.* have shown that side effects from epidural morphine follow a temporal and topographical pattern consistent with cephalad migration of morphine inside the dural sac.[4,15] Cephalad migration of morphine after lumbar epidural administration has been demonstrated in animal and human stud-

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

	Sex (M:F)	Age	Weight (kg)	BSA (m^2)	Blood Loss (ml)	Duration Anesthesia (min)	Fentanyl Consumption ($mg \cdot h^{-1}$)
Group I	4:2	43.5 ± 6.4	68.2 ± 6.9	1.84 ± 0.08	1040 ± 470	265 ± 37	0.19 ± 0.03
Group II	3:3	36.7 ± 7.3	63.7 ± 4.6	1.77 ± 0.07	1290 ± 340	260 ± 27	0.13 ± 0.02
Group III	2:4	38.0 ± 4.2	59.3 ± 1.5	1.71 ± 0.04	1030 ± 460	221 ± 15	0.13 ± 0.01
Group IV	3:3	31.6 ± 2.5	71.5 ± 7.6	1.86 ± 0.08	1370 ± 320	283 ± 15	0.17 ± 0.02
Group V	0:6	28.8 ± 3.6	64.3 ± 8.9	1.72 ± 0.10	780 ± 340	233 ± 13	0.12 ± 0.01

ies,[16–19] whereas there were no signs of cephalad transport for the lipophilic methadone.[16,17]

Respiratory depression after epidural administration of morphine can occur several hours after administration, consistent with rostral spread of morphine inside the dural sac, but also earlier, within 1–2 h after the injection.[1,12,14] The latter effect has been assumed to depend on systemic effects of morphine due to vascular absorption. There are no reports of late respiratory depression following epidural meperidine or fentanyl in patients, and epidural fentanyl did not cause respiratory depression in volunteers.[20]

This indicates that cephalad transport of lipophilic drugs is likely to be less than that of hydrophilic drugs. Consequently, the use of lipophilic opioids has been recommended for postoperative use in order to minimize the risk of respiratory depression.[12]

The physico-chemical properties of an opioid will probably determine the spinal pharmacokinetics, which influence the time course and the intensity of the effects. Existing reports on CSF pharmacokinetics of epidural morphine and meperidine have been based on relatively small number of samples from individual patients or short study periods.[2,6,21]

The aim of the present study was to investigate the pharmacokinetics of two opioids with different physicochemical properties. The CSF and plasma kinetics were studied in several groups of patients over a 24-h period following epidural administration of a hydrophilic opioid, morphine, with an octanol-water partition coefficient of 1.42,[22] and a more lipophilic opioid, meperidine, with a partition coefficient of 38.8.[22] A second objective of the study was to investigate the effects of different bolus volumes on the drug kinetics.

Methods and Material

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

PATIENTS

Thirty patients scheduled for major abdominal surgery gave their informed consent to participate in the study. The patients were divided into five groups with six individuals in each. The groups did not differ with respect to age, weight, or body surface area (BSA). A majority of the patients suffered from inflammatory bowel diseases. Patients with symptoms or signs of hepatic or renal failure, alcohol or drug abuse, or psychic disease were not included. 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 $mg \cdot kg^{-1}$. The lungs were mechanically ventilated with oxygen and nitrous oxide 3:7. 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.

PHARMACOKINETIC STUDY DESIGN

Group I received a 1-ml bolus of morphine 3 mg in saline. CSF and blood samples were collected for 6 h.

Group II received a 10-ml bolus of morphine 3 mg in saline. CSF and blood samples were collected for 6 h.

Group III received a 1-ml bolus of morphine 3 mg in saline. CSF samples were collected for 24 h.

Group IV received a 1-ml bolus of meperidine 30 mg in saline. CSF and plasma samples were collected for 6 h.

Group V received a 1-ml bolus of meperidine 30 mg in saline. CSF samples were collected for 24 h.

The drugs used were preservative-free morphine hydrochloride or meperidine hydrochloride.

Preparations for Drug Administration and Sample Collection

Immediately after induction of anesthesia, a central venous catheter for blood sampling was placed percutaneously (*via* the internal jugular vein) in the superior caval vein. The position of the catheter was confirmed radiographically. The epidural space was then identified at the L2–L3 interspace with the "hanging drop" technique.

Subsequently, an 18-gauge catheter for CSF sampling was introduced into the subarachnoid space through a dural puncture with an 18-gauge Tuohy needle at the L3–L4 interspace. The catheter was advanced 5 cm beyond the tip of the needle, with the bevel of the needle directed cranially. Baseline samples of blood and CSF were collected. Morphine 3 mg in 1 ml (groups I and III) or in 10 ml (group II), or meperidine 30 mg in 1 ml (groups IV and V) was then injected over 30 s through the epidural needle at the L2–L3 interspace, and the needle was flushed with air 0.2 ml. The epidural needle was then removed and the patient prepared for surgery.

Blood and CSF Sampling

In groups I, II, and IV, 5-ml samples of central venous blood were collected in heparinized plastic syringes. Plasma was separated by centrifugation at 3000 rpm for 10 min, and was stored in plastic tubes at −20° C until analyzed. In the same groups, 1-ml samples of CSF were collected in disposable plastic syringes without additives, and the samples were immediately frozen to −20° C in plastic tubes.

Parallel samples of blood and CSF were collected before drug administration and 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min after the epidural bolus in these groups.

In groups III and V, 0.3-ml samples of CSF were collected. A volume equal to the internal volume of the sampling catheter was withdrawn and discarded before every sample collection. CSF samples were collected before drug administration and 5, 240, 360, 480, and 720 min after the bolus. In the morphine group (III), CSF samples were also collected 60 and 90 min, and, in the meperidine group (V), 15 and 30 min after the bolus. The subarachnoid catheter was removed after 12 h. In all patients except one in group III, a dural puncture was performed at the L2–L3 interspace 24 h post-injection, and 1 ml of CSF was collected for analysis.

Drug Assay

Morphine[23,24] and meperidine[25] in plasma and CSF were assayed by gas chromatography with electron-capture detection. Results are expressed as concentrations of morphine and meperidine base. The limits of detection of the methods used were 1 $ng \cdot ml^{-1}$ for morphine and 5 $ng \cdot ml^{-1}$ for meperidine. The coefficients of variation of the methods were 10%.

Derivation of Pharmacokinetic Parameters

Rate constants and half-lives were calculated using the least squares method,[26] and were calculated for each individual patient.

The terminal plasma elimination rate constants (β_{pl}) and half-lives ($t_{1/2\beta_{pl}}$) were determined for each individual.

The time to reach maximal concentrations (t_{max}) and the maximum concentrations (C_{max}) in plasma and CSF were also established.

The absorption rate constant (k_a) and absorption half-life ($t_{1/2abs}$) for the passage of opioid from the epidural space to the CSF was determined by curve stripping in the 6-h groups, I, II, and IV.[26]

The 24-h CSF concentration-time curves in groups III and V appeared to follow a biexponential disposition process after the initial absorption phase. An early rapidly declining phase was followed by a slower phase starting after 8–12 h. The rate constants (α and β) and half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$) of the early and late phases, and the intercepts (A and B) with the ordinate were determined using curve stripping.

The kinetic parameters above were used in an equation describing the absorption-distribution-elimination process in the CSF ($C_{CSF(t)}$) following an epidural bolus:

$$C_{CSF(t)} = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} - (A + B) \cdot e^{-k_a t} \quad (1)$$

The area under the concentration-time curves (AUC) in plasma and CSF were calculated using the trapezoidal rule in groups I, II, and IV. The residual areas after 6 h were not included in the CSF AUCs. However, the residual areas were included in the plasma AUCs and were estimated using the equation:

$$AUC_{res} = C/\beta_{pl}, \quad (2)$$

where C is the last plasma concentration measured and β_{pl} the plasma elimination rate constant.

The fraction (F) of the epidural bolus crossing the dura was calculated using the equation:

$$F = \frac{AUC\ (epidural) \times D\ (intrathecal)}{AUC\ (intrathecal) \times D\ (epidural)}, \quad (3)$$

where AUC (epidural) was the mean area under the CSF concentration curve in group I, AUC (intrathecal) was the mean area under the CSF concentration curve in a parallel study of intrathecal morphine and meperidine in which an identical study design was used.[27] D (intrathecal) and D (epidural) were the doses used.

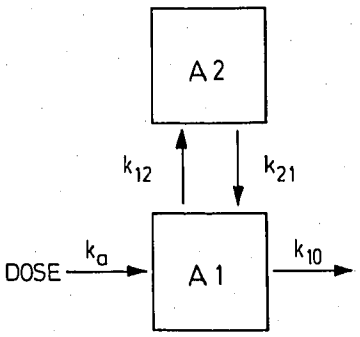

FIG. 1. The compartment model used in the compartment analysis. A1 is a sampling compartment (CSF) in the subarachnoid space, A2 is a tissue compartment in the subarachnoid space, k_a is the absorbtion rate constant across the dura, and k_{12}, k_{21}, and k_{10} are the transfer rate constants between the compartments and elimination from compartment A1, respectively.

In groups III, IV, and V, the opioid concentrations in lumbar CSF at the time of request for additional pain relief were estimated from the individual CSF concentration-time curves.

COMPARTMENT ANALYSIS

A two-compartment model, depicted in figure 1, was used to estimate the amount of morphine and meperidine present in the subarachnoid space following epidural administration. The rate constants in the model were calculated by using the previously calculated kinetic constants, according to the methods used by Wagner.[26] The dose in the model was calculated to be the fraction of an epidural bolus passing to the subarachnoid space; that is, F · D(epidural). The calculations were done using a continuous system simulation program (DARE-P®) on an IBM 370 computer.

STATISTICS

Results are given as mean ± SEM in the text and the 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 with respect to blood loss or duration of anesthesia between the groups (table 1). The time from the end of operation to request for pain relief in the morphine groups averaged 5.9 ± 2.3 h in group I, 7.1 ± 2.0 h in group II, and 3.4 ± 0.6 h in group III. In the meperidine groups, the corresponding times were 1.2 ± 0.4 h in group IV and 3.1 ± 1.4 h in group V. The differences between the three morphine groups were not significant, nor were the differences between the two meperidine groups. There was no correlation between fentanyl consumption during anesthesia and the time from the end of operation to request for pain relief.

PLASMA KINETICS

Morphine. Morphine appeared rapidly in plasma after an epidural bolus (tables 2–4; fig. 2). Maximum plasma concentrations were usually measured 5 min after the epidural injection. Maximum plasma concentrations were slightly higher in the 10-ml volume group—39.5 ± 2.9 ng · ml^{-1}—than in the 1-ml volume group—33.3 ± 7.4 ng · ml^{-1}—but the difference was not significant. The plasma concentrations were, however, significantly higher in the large volume morphine group as compared to the small volume group 10 and 15 min after injection, and there was a tendency towards higher plasma concentrations in samples taken later than 15

TABLE 2. Mean ($\bar{X}$ ± SEM) Morphine CSF and Plasma Concentrations in Groups I–V (n.d. = Not Detectable)

Time (min)	Group I		Group II		Group III	Group IV		Group V
	CSF (ng · ml^{-1})	Plasma (ng · ml^{-1})	CSF (ng · ml^{-1})	Plasma (ng · ml^{-1})	CSF (ng · ml^{-1})	CSF (ng · ml^{-1})	Plasma (ng · ml^{-1})	CSF (ng · ml^{-1})
5	84.4 ± 41.5	33.3 ± 7.4	178 ± 94.6	37.8 ± 2.7	62.9 ± 18.0	7790 ± 1230	106 ± 36	10800 ± 3370
10	281 ± 102	24.3 ± 4.4	473 ± 170	38.2 ± 2.7	—	12700 ± 2680	117 ± 31	—
15	510 ± 153	18.0 ± 3.6	683 ± 254	32.5 ± 2.4	—	16000 ± 1680	188 ± 30	18100 ± 6450
30	911 ± 212	11.4 ± 2.9	977 ± 174	19.1 ± 2.0	—	17300 ± 1290	117 ± 15	16700 ± 6450
60	1070 ± 224	4.9 ± 1.4	1070 ± 143	8.2 ± 1.4	1190 ± 247	11000 ± 952	80 ± 13	—
90	1120 ± 240	3.0 ± 0.9	1050 ± 160	5.9 ± 1.5	1140 ± 252	8280 ± 1160	66 ± 19	—
120	769 ± 177	2.4 ± 0.7	900 ± 159	3.4 ± 0.9	—	4670 ± 817	32 ± 7	—
180	530 ± 149	1.6 ± 0.8	648 ± 135	2.9 ± 0.9	—	2720 ± 435	29 ± 8	—
240	243 ± 80.0	1.1 ± 0.4	419 ± 103	1.6 ± 0.6	327 ± 72.2	1650 ± 300	22 ± 6	2030 ± 420
300	162 ± 49.0	n.d.	212 ± 45.8	1.2 ± 0.4	—	1200 ± 245	16 ± 4	—
360	110 ± 32.6	n.d.	155 ± 48.8	n.d.	162 ± 36.0	747 ± 173	13 ± 4	858 ± 184
480	—	—	—	—	77.3 ± 20.7	—	—	304 ± 63
720	—	—	—	—	24.5 ± 6.0	—	—	178 ± 42
1440	—	—	—	—	3.2 ± 1.5	—	—	91 ± 38

TABLE 3. Pharmacokinetic Parameters in Group I (Morphine 3 mg in 1 ml, Sampling Period 6 h). Maximum Concentration and Time to Reach Maximum Concentration in CSF and Plasma (C_{max}, t_{max}), Absorption Rate Constant and Half-life Across the Dura (k_a and $t_{1/2abs}$), Elimination Rate Constant and Half-life in Plasma (β_{pl}, $t_{1/2\beta_{pl}}$) and Area Under the CSF and Plasma Concentration Curves (AUC)

	Patient						
Group I	1	2	3	4	5	6	$\bar{X} \pm SEM$
CSF							
C_{max} (ng · ml^{-1})	540	1150	1930	1400	349	1450	1140 ± 243
t_{max} (min)	90	90	90	60	90	90	
k_a (min^{-1} · 10^{-2})	3.41	3.27	3.36	3.43	3.49	2.51	3.25 ± 0.15
r^2 (k_a)	1.00	1.00	1.00	0.99	0.98	0.99	
$t_{1/2abs}$ (min)	20	21	21	20	20	28	21.7 ± 1.3
AUC (μg · min · ml^{-1})	70.2	179	251	248	57.4	317	187 ± 42.9
Plasma							
C_{max} (ng · ml^{-1})	5.4	37.4	34.1	61.7	34.1	27.0	33.3 ± 7.4
t_{max} (min)	5	5	5	5	5	5	
β_{pl} (min^{-1} · 10^{-3})	17.9	16.5	5.64	2.78	16.1	14.6	12.3 ± 2.6
r^2 (β)	0.98	0.98	0.97	0.93	1.00	0.92	
$t_{1/2\beta_{pl}}$ (min)	39	42	123	249	43	47	90.5 ± 34.3
AUC (ng · min · ml^{-1})	149	916	2220	1590	1830	767	1250 ± 313

min following epidural injection in the 10-ml volume group. As a consequence, the mean plasma AUC was 68% larger in the large volume group, although the difference was not statistically significant.

The terminal plasma half-lives in the two 6-h groups were 90.5 ± 34.3 min and 87.3 ± 26.5 min, respectively. Six hours after injection, the plasma concentrations of morphine were too low for accurate assay in all patients.

Meperidine. Meperidine also appeared rapidly in plasma after the epidural injection, and maximal plasma concentrations were measured 10 or 15 min post-injection (tables 2, 5; fig. 3). The mean maximal concentration was 196 ± 29.0 ng · ml^{-1}, and the terminal plasma half-life was 124 ± 26 min.

CSF KINETICS DURING THE FIRST 6 H AFTER AN EPIDURAL DOSE (GROUPS I, II, AND IV)

Morphine. The diffusion of morphine across the dura was relatively slow, and peak concentrations in CSF were usually reached 60–90 min after the epidural injection (tables 2–4; fig. 2).

The absorption half-lives across the dura ($t_{1/2abs}$) varied from 4.6 to 36 min, and averaged 21.7 ± 3.0 min in the small-volume group, group I, and 22.0 ± 5.5 min in the large volume group, group II.

The maximum CSF concentrations were not significantly higher in the large-volume group, −1290 ± 182 ng · ml^{-1} as compared to 1140 ± 243 ng · ml^{-1} in the small volume group.

TABLE 4. Pharmacokinetic Parameters in Group II (Morphine 3 mg in 10 ml, Sampling Period 6 h). Maximum Concentration and Time to Reach Maximum Concentration in CSF and Plasma (C_{max}, t_{max}), Absorption Rate Constant and Half-life Across the Dura (k_a, $t_{1/2abs}$), Elimination Rate Constant and Half-life in Plasma (β_{pl}, $t_{1/2\beta_{pl}}$), and Area Under the CSF and Plasma Concentration Curves (AUC)

	Patient						
Group II	7	8	9	10	11	12	$\bar{X} \pm SEM$
CSF							
C_{max} (ng · ml^{-1})	1180	1520	1360	467	1770	1430	1290 ± 182
t_{max} (min)	120	90	30	90	30	90	
k_a (min^{-1} · 10^{-2})	1.95	2.05	10.4	2.52	15.2	2.99	5.85 ± 2.29
r^2 (k_a)	1.00	0.99	1.00	1.00	1.00	0.99	
$t_{1/2abs}$ (min)	36	34	6.7	28	4.6	23	22.0 ± 5.5
AUC (μg · min · ml^{-1})	242	341	217	61.0	199	226	214 ± 36.7
Plasma							
C_{max} (ng · ml^{-1})	48.5	28.5	44.5	38.4	34.9	42.1	39.5 ± 2.9
t_{max} (min)	5	5	10	5	5	10	
β_{pl} (min^{-1} · 10^{-3})	3.98	4.48	42.3	12.1	21.8	7.59	15.4 ± 6.0
r^2 (β)	0.97	0.91	0.97	0.93	0.96	1.00	
$t_{1/2\beta_{pl}}$ (min)	174	155	16	57	32	91	87.3 ± 26.5
AUC (ng · min · ml^{-1})	3110	2710	1510	2510	1120	1940	2150 ± 310

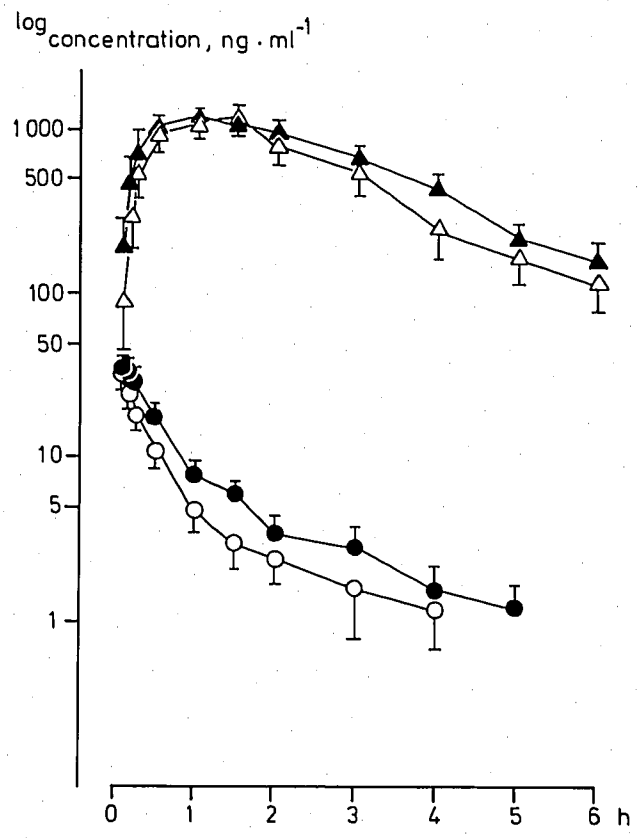

FIG. 2. Mean morphine CSF (open triangles = group I; filled triangles = group II) and plasma concentrations (open circles = group I; filled circles = group II) after epidural administration of morphine 3 mg in 1 ml (group I) and 10 ml (group II).

The CSF concentrations of morphine were at all times higher than the simultaneous plasma concentrations. The CSF:plasma ratios were 2.5-5, 130-220, and 220-260 after 5, 60, and 240 min, respectively.

There was a tendency towards higher CSF concentrations and correspondingly larger AUCs in the 10-ml volume group as compared to the small volume group. The difference between the mean AUCs was 14%, which was not a significant difference.

The fraction (F) of an epidural bolus dose crossing the dura was calculated to be 3.6%.

Meperidine. The diffusion of meperidine across the dura was faster than with morphine, and peak CSF concentrations were usually seen 15 or 30 min after the epidural injection (tables 2, 5; fig. 3).

The absorption half-life across the dura ($t_{1/2abs}$) varied from 2.7 to 14 min, and averaged 7.6 ± 2.0 min.

The CSF concentrations were at all times higher than the concurrent plasma concentrations. The CSF:plasma ratios were 75, 135, 75, and 55 after 5, 60, 240, and 360 min, respectively.

The fraction of an epidural meperidine bolus passing to the subarachnoid space (F) was calculated to be 3.7%.

The mean meperidine CSF concentration at the time of request for supplementary pain relief was 1100 ± 260 ng · ml^{-1} (range 100–1700).

CSF Kinetics over a 24-h Period (Groups III and V)

Morphine. The CSF concentration-time curves in the 24-h group displayed a biphasic disposition process with a slower fall after 8–12 h in four of the patients. One of the patients, number 14, displayed an extremely rapid fall in CSF morphine concentrations which were below the limit of detection 6 h after injection (tables 2, 6; fig. 4).

The early and late half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$) averaged 73.3 ± 11.5 min (range 31–107 min) and 369 ± 113 min (range 190–693 min), respectively.

TABLE 5. Pharmacokinetic Parameters in Group IV (Meperidine 30 mg in 1 ml, Sampling Period 6 h). Maximal Concentration and Time to Reach Maximal Concentration in CSF and Plasma (C_{max}, t_{max}), Absorption Rate Constant and Absorption Half-life Across the Dura (k_a, $t_{1/2abs}$), Elimination Rate Constant and Half-life in Plasma (β_{pl}, $t_{1/2\beta_{pl}}$), and Area Under the CSF and Plasma Concentration Curves (AUC)

	Patient						
Group IV	19	20	21	22	23	24	$\bar{X}$ ± SEM
CSF							
C_{max} (ng · ml^{-1})	21200	17300	19500	13600	17000	19600	18000 ± 1090
t_{max} (min)	15	15	15	30	30	30	
k_a (min^{-1} · 10^{-1})	2.53	1.96	1.21	0.508	0.982	0.520	1.29 ± 0.33
r^2 (k_a)	0.98	1.00	1.00	0.95	0.94	0.93	
$t_{1/2abs}$ (min)	2.7	3.5	5.7	14	7.0	13	7.6 ± 2.0
AUC (μg · min · ml^{-1})	2520	1480	1640	1440	1840	1770	1780 ± 161
Plasma							
C_{max} (ng · ml^{-1})	210	140	190	115	200	320	196 ± 29.0
t_{max} (min)	10	15	5	15	10	15	
β (min^{-1} · 10^{-3})	4.99	3.08	6.10	6.99	5.11	23.7	8.33 ± 3.11
r^2 (β)	0.87	0.70	0.90	0.69	0.77	0.99	
$t_{1/2\beta}$ (min)	139	225	114	99	136	29	124 ± 26
AUC (μg · min · ml^{-1})	24.0	21.8	23.4	10.5	29.3	8.55	19.6 ± 3.36

There were no significant differences in CSF concentrations in group III and group I at similar times.

The morphine concentration in lumbar CSF at the time of request for additional pain relief postoperatively was 150 ± 53 ng·ml^{-1} (range <1–380).

Meperidine. The meperidine CSF concentration-time curves in the 24-h group also displayed a biphasic disposition process with a slower phase between 8–12 and 24 h after injection (tables 2, 7; fig. 5). The early half-life ($t_{1/2\alpha}$) averaged 71.3 ± 3.1 min (range 59–78 min), and the late half-life averaged 982 ± 449 min (range 233–3140 min).

The CSF concentrations were not significantly different from those in the 6-h group at corresponding times (table 2).

The mean meperidine CSF concentration at the time of request for supplementary pain relief was 1100 ± 310 ng·ml^{-1} (range 160–2000).

Compartment Analysis of Morphine and Meperidine Amounts

The results of the compartment analyses are presented graphically in figures 6 and 7. Figure 6 shows the fraction of the total amount of the drug reaching the subarachnoid space which remains in the subarachnoid space, that is:

$$(Am1 + Am2)/F \cdot D,$$

where Am1 is the amount of drug present in compartment A1, Am2 is the amount present in compartment A2, D is the epidural dose, and F is the fraction of the dose crossing the dura.

Figure 7 shows the fractions of the total amount of drug in the subarachnoid space which are present in the CSF compartment (Am1/(Am1 + Am2)) and the tissue compartment (Am2/(Am1 + Am2)), respectively.

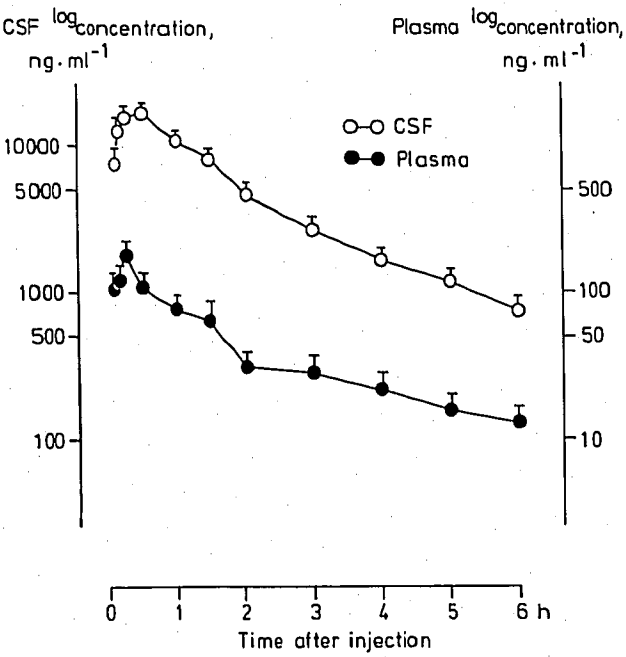

FIG. 3. Mean meperidine CSF concentrations (open circles) and plasma concentrations (filled circles) after epidural administration of meperidine 30 mg in the 6-h study (group IV).

Discussion

Plasma Kinetics

Morphine. Morphine appeared rapidly in superior caval vein blood in the present study, and maximum plasma concentrations were measured as early as 5 min after the epidural injection. This C_{max} occurs earlier than when blood is sampled from a peripheral vein or an artery.[3,6,28] The blood concentrations can be ex-

TABLE 6. Pharmacokinetic Parameters in Group III (Morphine 3 mg in 1 ml, Sampling Period 24 h). Maximum Concentration and Time to Reach Maximum Concentration in CSF (C_{max}, t_{max}), Early and Late Rate Constants and Half-lives in CSF (α, $t_{1/2\alpha}$, β, $t_{1/2\beta}$), and Intercepts with Ordinate of the Monoexponential Lines Describing the Early and Late Phases of the Disposition in CSF (A, B). The Late Rate Constants and Half-lives Could Not be Determined in Patients 14 and 15, Since the Morphine CSF Concentrations were Below the Limit of Detection 24 h after Administration

	Patient						
Group III	13	14	15	16	17	18	$\bar{X}$ ± SEM
CSF							
C_{max} (ng·ml^{-1})	2120	571	984	2040	1380	1020	1350 ± 253
t_{max} (min)	90	60	90	60	60	60	—
α (min^{-1}·10^{-3})	11.4	22.4	6.79	10.4	9.67	6.49	11.2 ± 2.4
r^2 (α)	0.94	0.97	0.96	1.00	0.92	0.99	—
$t_{1/2\alpha}$ (min)	61	31	102	67	72	107	73.3 ± 11.5
A (ng·ml^{-1})	4700	2570	2220	3250	2980	840	2760 ± 518
β (min^{-1}·10^{-3})	1.00	—	—	2.86	1.98	3.64	2.37 ± 0.57
r^2 (β)	1.00	—	—	1.00	1.00	1.00	—
$t_{1/2\beta}$	693	—	—	242	350	190	369 ± 113
B (ng·ml^{-1})	70	—	—	242	147	476	234 ± 88

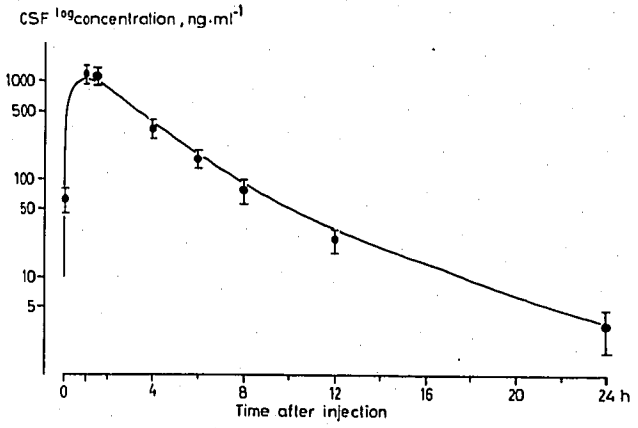

FIG. 4. Mean morphine CSF concentrations after epidural administration of morphine 3 mg in the 24-h study (group III) (circles) and the CSF concentration-time curve following epidural morphine described by equation 1 (see text).

pected to be highest in the superior caval vein as blood from the epidural venous plexa is drained to the superior caval vein *via* the azygos vein.

Peak plasma concentrations of morphine have been reported to be similar after epidural and intramuscular administration, but the peak appears somewhat earlier after epidural administration.[9,28,29]

The analgesia from systemic redistribution to CNS after the administration of a 3 mg epidural bolus is probably minimal after 30–60 min, since the plasma concentrations are below the reported minimum analgesic plasma concentration of about 20–40 $ng \cdot ml^{-1}$.[30,31]

Meperidine. Epidural meperidine has been reported to be slowly absorbed into the blood, reaching peak concentrations after 20–45 min.[2,32] In the present study, the absorption was rapid, however, and maximum meperidine concentration in central venous plasma was measured within 15 min after injection. The difference might depend on differing epidural injection levels, as well as influences of the general anesthesia and surgery.[33]

Even so, the CSF:plasma concentration ratio exceeded 70 as early as 5 min after injection in the present study, and the rapid onset of analgesia reported after epidural meperidine[2,11] is most probably due to a spinal action of the drug.

The meperidine plasma concentrations following epidural administration have been demonstrated to fall below minimum analgetic blood concentrations well before the end of analgesia.[2] This is supported by our finding of rapid dissappearance of meperidine from plasma. Systemically absorbed meperidine might contribute to analgesia during the first hour or so, but not later.

Diffusion Across the Dura

Morphine. The slow onset of action of analgesia reported after epidural morphine, in excess of 20 min,[8,9] is reflected in the present study by a slow morphine passage through the dura with an absorption half-life to the CSF of 22 min. The time to reach maximum CSF concentrations, 60–90 min, also corresponds to the reported time to achieve maximum pain relief.[5,6,8,9]

Only a small fraction, 3.6%, of an epidural bolus of morphine was found to pass to the subarachnoid space. This is higher than the 2% reported earlier,[28] probably due to another method of calculation. The calculation of the CSF availability in the present study was based on the determination of the areas under the CSF concentration-time curves following epidural and intrathecal administration of the drug. It was assumed that the residual areas after the 6-h study periods are proportionally the same after intrathecal and epidural administration; that is, that the elimination kinetics are similar from this time and onwards. This assumption is supported by the reports of a biphasic elimination after intrathecal morphine, similar to that seen after epidural morphine administration.[34,35]

TABLE 7. Pharmacokinetic Parameters in Group V (Meperidine 30 mg in 1 ml, Sampling Period 24 h). Maximal Concentration and Time to Maximal Concentration (C_{max}, t_{max}), Early and Late Rate Constants and Half-lives (α, $t_{1/2\alpha}$, β, $t_{1/2\beta}$), and Intercepts with Ordinate of the Monoexponential Declining Lines Describing the Early and Late Phases of the Elimination (A, B)

	Patient						
Group V	25	26	27	28	29	30	$\bar{X} \pm$ SEM
CSF							
C_{max} ($ng \cdot ml^{-1}$)	7570	16000	27200	10800	13000	48000	20400 ± 6160
T_{max} (min)	5	5	30	30	15	15	
α ($min^{-1} \cdot 10^{-3}$)	9.56	8.83	10.5	9.04	9.15	11.7	9.80 ± 0.45
r^2 (α)	0.98	1.00	1.00	1.00	1.00	0.99	
$t_{1/2\alpha}$ (min)	72	78	66	77	76	59	71.3 ± 3.1
A	7200	3080	36100	13900	11800	57900	21700 ± 8610
β ($min^{-1} \cdot 10^{-4}$)	2.21	29.7	27.6	6.81	12.9	9.74	15.8 ± 5.02
r^2 (β)	1.00	1.00	1.00	1.00	1.00	1.00	
$t_{1/2\beta}$ (min)	3140	233	251	1020	537	711	982 ± 449
B ($ng \cdot ml^{-1}$)	358	722	813	148	776	347	527 ± 113

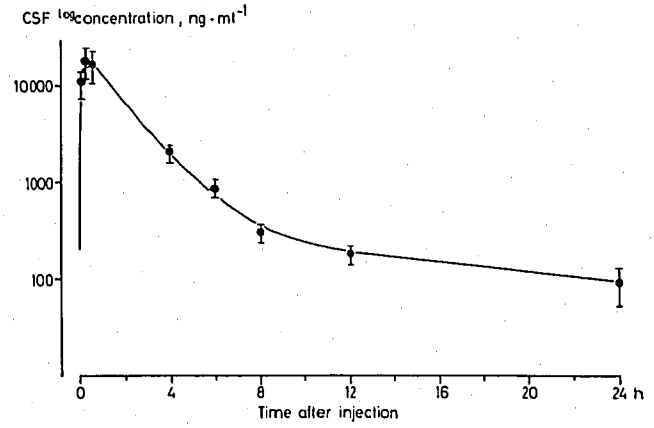

FIG. 5. Mean meperidine CSF concentrations after epidural administration of meperidine 30 mg in the 24-h study (group V) (circles) and the CSF concentration-time curve following epidural meperidine described by equation 1 (see text).

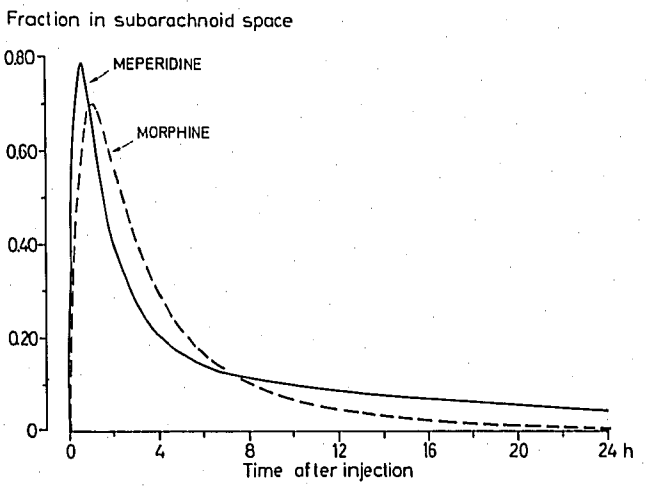

FIG. 6. Compartment analysis of epidural meperidine (continuous line) and morphine (interrupted line). Amounts of meperidine and morphine left in the subarachnoid space (corresponding to the amount in compartments A1 plus A2) related to the total amount of an epidural bolus passing to the subarachnoid space.

In any case, the residual areas are proportionally small, since the CSF concentrations are reduced to 6–10% of the maximal concentrations 6 h after injection, and they are, therefore, not likely to influence the determination of CSF availability more than marginally.

The CSF availability of 3.6% of epidural morphine means that about 0.1 mg of an epidural bolus of morphine 3 mg reaches the subarachnoid space. The most commonly used doses of epidural morphine are in the range of 3–10 mg. Assuming linear kinetics, the corresponding CSF availability after epidural boluses of 5 and 10 mg are 0.2 and 0.4 mg, respectively. It is interesting to note that, for postoperative pain relief, intrathecal morphine doses of 0.25 mg have empirically been found to be most useful.[34]

There were no significant differences between the morphine CSF concentrations measured at corresponding times in groups I and III, despite different total sampling volumes. During the 6 h after injection, 12 ml and 3 ml were sampled, respectively. This indicates that the CSF sampling procedures did not affect the results to any great extent.

Meperidine. The reported short onset of pain relief of 5–10 min after epidural meperidine[2,11] is parallelled in the present study by a rapid passage of meperidine to the CSF. This is in agreement with a report on the early CSF kinetics after epidural injection.[2]

The time required to reach maximal meperidine CSF concentration after epidural administration, 15–30 min, also corresponds closely to the reported times required to achieve maximum pain relief, 12–30 min.[2,11]

In studies of *in vitro* measurements of dural permeability of different substances, including opioids, it has been proposed that molecular weight is the important determinant of dural penetration rate.[36] According to this proposal, morphine and meperidine, with molecular weights of 285 and 247, respectively, would penetrate the dura equally quickly. The present results contradict this hypothesis. A recent *in vivo* study has also shown that the large molecular weight inulin passed the dura as rapidly as morphine.[37] It is reasonable to assume that the observed *in vivo* difference in pharmacokinetics

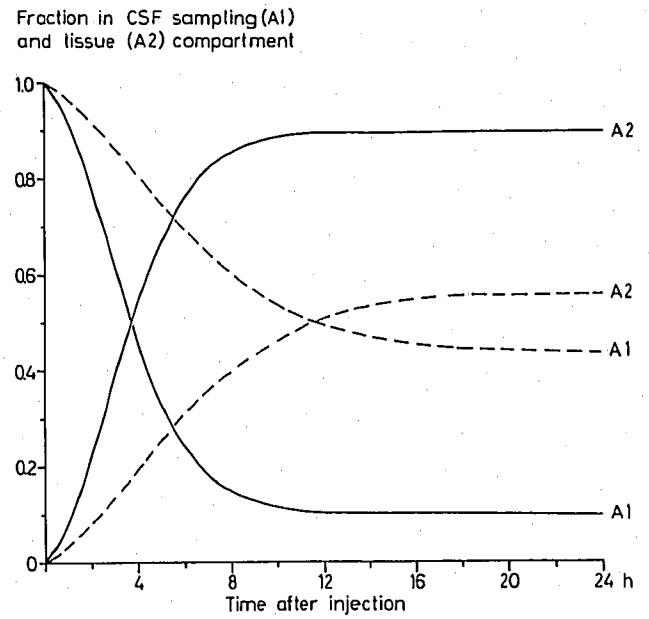

FIG. 7. Compartment analysis of epidural meperidine (continuous line) and morphine (interrupted line). Fractions of meperidine and morphine in the two compartments, A1 (CSF sampling compartment) and A2 (tissue compartment), in relation to the total amount remaining in the subarachnoid space.

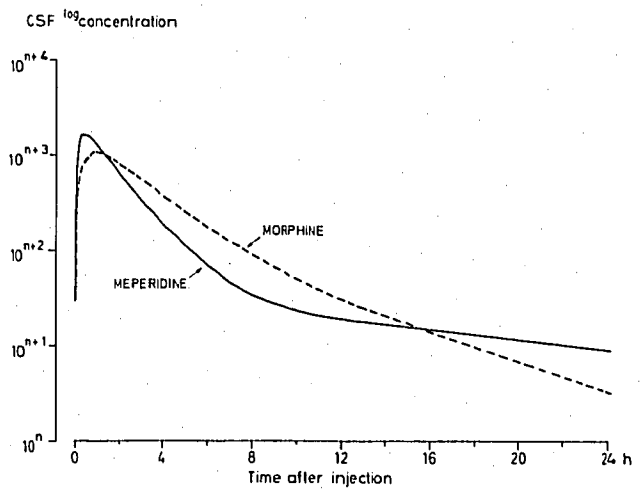

FIG. 8. Dose normalized meperidine and morphine CSF concentrations after epidural administration.

is due primarily to the difference in lipophilicity. Meperidine is more lipophilic than morphine, and will presumably pass biological membranes faster than morphine *in vivo*.

CSF Kinetics and Analgesic Effect

Morphine. Large inter-individual differences with respect to both the CSF and the plasma kinetics were present in all groups. As two extremes, patient number 14 in group III exhibited a very rapid fall in morphine CSF concentrations which were <1 ng·ml^{-1} 6 h post-injection, while patient number 17 in the same group had a slower elimination with an elimination half-life of 6 h and a morphine CSF concentration of 8.5 ng·ml^{-1} 24 h post-injection. This finding helps explain the individual differences in pain relief reported in most studies. The individual differences in pain relief may also be affected by individual activity of the endogenous pain inhibiting systems, such as the endorphin system.[38,39]

Morphine has been reported to be eliminated from CSF slower than from plasma.[40] This is confirmed in our study.

The disposition in CSF of epidurally administered morphine followed a biphasic pattern, with an early phase having a half-life of about 1.5 h, followed by a slower phase with a half-life of about 6 h. These phases are probably not pure distribution or elimination phases, since distribution equilibrium between CSF, the blood, and nervous tissues is unlikely. The continuously changing CSF:plasma concentration ratios show that there is not a distribution equilibrium between CSF and plasma during the first hours after injection. Significant morphine concentrations are still present in lumbar CSF several hours after the administration of epidural morphine, a fact that has obvious clinical significance.

The late half-life of about 6 h is in agreement with findings in other studies.[6,28]

The small differences in kinetics between the large volume and the small volume morphine groups indicates that the volume of a bolus is not of major importance. The increased area of the dura exposed to the drug in the large volume group is evidently balanced by the higher concentration gradient across the dura in the small volume group. However, the small group sizes may have made differences difficult to detect. It has been suggested by others that increasing the volume of a morphine bolus should increase the duration of analgesia,[41] but this remains to be shown in a controlled study.

Meperidine. Epidural meperidine is shorter acting than morphine. The reported mean duration of action is about 3–6 h, with large individual variations, after 50–100-mg boluses.[2,7,11,42]

In the present study, meperidine had a mean CSF distribution half-life of 71.3 min and a mean elimination half-life of 16 h (range 3.9–52.3 h). The difference between morphine and meperidine is not statistically significant due to large interpatient variations. The slow elimination phase of meperidine between 12 and 24 h could be due to a slow release of the lipophilic drug from subarachnoid nervous tissue.

Although the fractions of an epidural bolus passing to the subarachnoid space are about the same for meperidine and morphine, or 3.6–3.7%, the mean CSF concentration-time curves following epidural meperidine and morphine differ in several important respects. This can be seen more clearly when the curves are dose normalized (fig. 8).

The initial difference in absorption is obvious, meperidine reaching its maximal CSF concentration earlier. The meperidine concentration falls more quickly from this point, however. From the 2nd to the 15th hour, the morphine CSF concentrations exceed the meperidine concentrations (after the same epidural dose in mg) with a maximum difference of four times at 8 h after the epidural bolus. This difference may partly explain the longer duration of action of morphine. Another factor influencing duration is the greater affinity of morphine for the opioid receptors, compared to meperidine, shown in animal experiments.[43]

Estimated Minimum Effective Opioid CSF Concentrations

Lazorthes *et al.* reported loss of analgesia when CSF morphine concentration was around 90 ng·ml^{-1}.[35] We have tried to estimate minimum effective morphine concentrations in lumbar CSF as the concentration when pain returns by using equation 1 (table 8). These estimated minimum effective CSF concentrations of

morphine are low, and vary between 11 and 68 ng·ml^{-1}.

We propose that this equation reflects what happens at the lumbar level in the CSF. It is based on the assumption that three gross processes predominate: diffusion across the dura from the epidural space to the CSF, distribution in the CSF, and elimination from the CSF. Several mechanisms are probably involved in the removal of the drug from lumbar CSF: dilution in the CSF, distribution and elimination *via* the CSF bulk flow, elimination due to binding to the nervous tissue, and elimination due to vascular absorption in the spinal canal. However, all these processes can be approximated by the relatively simple equation.

The estimated morphine concentrations in lumbar CSF when the patients required pain relief postoperatively in the present study varied between <1–380 ng·ml^{-1}, with an average of 150 ng·ml^{-1}. The varying results reflect differences in patient populations, types of operations, and influence of the anesthesia. The CSF acts as a reservoir for the opioid, and the opioid is more or less rapidly absorbed into the spinal cord and the blood, depending on its lipophilicity.

The estimated lumbar meperidine CSF concentrations at the time of request for additional pain relief averaged 1100 ng·ml^{-1} in the present study. This is five to ten times higher than the calculated mean value for CSF concentration of meperidine of 204 ± 73 ng·ml^{-1} in a similar group of patients who self-administered meperidine intravenously.[38] This supports the view that systemic meperidine does not act primarily on the spinal level.

Opioid Amount in the Subarachnoid Space

Instantaneous homogenous distribution of opioids in CSF is not likely after epidural administration. The model used in the compartment analysis can only demonstrate gross changes and differences in drug kinetics, and does not differentiate between receptor-binding and nonspecific binding in the subarachnoid space, nor between elimination to the blood and elimination with the CSF bulk flow. The analysis suggests that epidural meperidine is removed from the CSF to a subarachnoid tissue compartment, *i.e.*, to the nervous tissue, faster than morphine (fig. 7). Less than 4 h after injection, 50% of the meperidine left in the subarachnoid space remains in the CSF, and the other half has been transferred to the nervous and fat tissues in the subarachnoid space. At the same time, 80% of the morphine still lingers in the CSF. Twelve hours after injection, 50% of the morphine and 10% of the meperidine are present in the CSF. The curves showing total amounts of meperidine and morphine in the subarachnoid space in relation to the amount of an epidural bolus passing to the subarachnoid space (fig. 6) resemble the CSF concentration curves, with a rapid peak for meperidine and a more rapid decrease initially. From about 5 h after injection, the relative amount of meperidine exceeds the relative amount of morphine, which supports the notion that the spinal column will act as an "affinity column" for lipophilic substances after spinal administration.[1]

TABLE 8. Calculated Minimum Analgesic CSF Morphine Concentrations at Reported End of Pain Relief after Different Doses of Epidural Morphine

Morphine Dose (mg)	Duration of Pain Relief (hours)	Calculated Morphine CSF Concentration (ng·ml^{-1})	Reference
2	8.6	51	6
4	13.0	34	6
4	10	68	44
5	16.4	21	8
6	12.3	58	7
6	15.6	30	6
8	15	44	44

In conclusion, only about 4% of an epidural bolus of morphine or meperidine crosses the dura. This explains why much larger doses have to be administered epidurally than intrathecally. The use of a continuous epidural technique allows titration of the dose to the patient's need for analgesics, which, because of the large inter-individual differences seen in the CSF kinetics following epidural and intrathecal opioid administration, favors this approach over a single injection administered by either intrathecal or epidural routes.

There is a close correlation between the time course of drug appearance in CSF and the reported onset of analgesia after epidural morphine and meperidine. Since epidural morphine crosses the dura slowly, it should be given early; if possible, even before the patient has any pain. Meperidine is removed faster from lumbar CSF than morphine. The volume of an epidural bolus does not seem to be a factor of major importance. A lipophilic opioid with a stronger affinity for the opioid receptors than meperidine might theoretically be an "ideal" opioid for spinal use. A rapid onset of pain relief due to rapid absorption through the dura to the spinal cord, a long duration of action because of slow removal from the receptor, and a low risk of rostral transport because of rapid removal from the CSF are advantages which would then be combined.

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