Pharmacokinetic Aspects of Intrathecal Morphine Analgesia

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Fifteen patients undergoing thoracotomy were given 0.25 or 0.50 mg morphine intrathecally (L2–L3 or L3–L4) for an analgetic and pharmacokinetic study. Administration of morphine at the end of the operation resulted in a highly variable duration of analgesia ranging from 1–20.5 and 1–40 h for the 0.25 and 0.50 mg groups, respectively. Calculation of cumulative consumption pattern of additional analgesics given indicated a related dose-related analgesia lasting around 12 h. Morphine concentrations in the CSF were high and dose dependent. Thus, at 1 h, CSF concentrations (mean ± SEM) were 4.228 ± 361 ng/ml and 10.447 ± 1,538 ng/ml for the 0.25- and 0.50-mg groups, respectively. The plasma concentrations generally were very low, i.e., under 1 ng/ml.

For the 0.50 and 0.25 mg groups, the terminal elimination half-life in CSF was 175 ± 9 min and 156 ± 13 min, respectively; the volume of distribution was 0.88 ± 0.16 ml·kg⁻¹ and 1.06 ± 0.17 ml·kg⁻¹ respectively; and the clearance from CSF was 2.81 ± 0.41 μl·kg⁻¹·min⁻¹ and 3.41 ± 0.55 μl·kg⁻¹·min⁻¹, respectively (mean ± SEM).

The study indicates that the significant pharmacokinetic parameter related to the long duration of analgesia after intrathecal morphine administration probably is the high CSF concentrations found, since the rate of elimination from CSF is similar to what is reported for morphine in plasma. Furthermore, modulation of nociceptive input in the thoracic region also may be achieved by lumbar administration, but a slower onset should be anticipated. (Key words: Analgesics: morphine. Anesthetic techniques: spinal. Pain: postoperative. Pharmacokinetics: morphine, intrathecal.)

AUTORADIOGRAPHIC STUDIES have revealed a high density of opiate receptors in the substantia gelatinosa in the posterior horn of the spinal cord. The endogenous ligands for these receptors are the opioids, acting as neurotransmitters or neuromodulators in a pain-controlling system. The efficacy of opiate analgesia is supposed to be related to the existence of significant amounts of the drug at the receptor level in, for example, the dorsal horn of the spinal cord. Studies in animals and in humans on intrathecal and epidural opiate administration demonstrated that administration of minute doses of various opiates induced profound and long-lasting analgesia. Furthermore, epidural morphine administration is related to the existence of very high levels of the drug in the CSF. The concentrations of morphine after epidural administration are 100–200 times the corresponding plasma levels.

In humans, epidural administration generally is preferred to the intrathecal route, primarily for reasons of safety. However, from a theoretic standpoint it would be preferable to administer the drug as close to the receptor level as possible, i.e., intrathecally. In order to optimize efficacy and minimize side effects from this route of administration, it is essential to study the pharmacokinetics of intrathecally administered morphine and to relate these data to analgesia. The purpose of this study was to evaluate the pharmacokinetic properties of different doses of morphine administered intrathecally. Furthermore, we examined the efficacy of lumbar intrathecal morphine administration for alleviating pain after thoracic surgery.

Patients and Methods

The study, which involved 15 patients, had the approval of the Ethical Committee at the University of Göteborg. Oral and written informed consent was obtained from the patients who were to undergo elective thoracotomy because of pulmonary tumor.

An analgetic, meperidine (50–75 mg), and a minor tranquilizer (fentanyl derivative), dixyrazine (10–20 mg), were given intramuscularly as premedication to all patients except two who received 100 mg pentobarbital orally each instead of dixyrazine. The operation was performed under general anesthesia. Anesthetics used were thiopental, fentanyl, and nitrous-oxide in oxygen; the muscle relaxant was pancuronium. The surgical procedure included resection of varying amounts of lung parenchyma. At the end of the operation but before terminating the anesthesia, all patients received morphine intrathecally for postoperative analgesia. The drug was administered at the L2–L3 or L3–L4 interspace by standard technique using thin needles (Antoni-Sise 0.5 mm external diameter). Preservative-free morphine hydrochloride, 0.25 mg or 0.5 mg in 5 ml saline, was prepared by sterile techniques in the hospital pharmacy on the same day it was to be used.

In the first part of the study, three patients (1 male patient, 2 female patients) were given 0.5 mg morphine in 5 ml saline intrathecally, and only late CSF samples at approximately 14, 16, and 18 h were obtained in order to characterize the terminal elimination phase.

In the second part, performed as a double-blind study, 12 patients were allocated to receive either 0.25 mg (n = 6) or 0.5 mg (n = 6) morphine intrathecally according to a randomization list known only by the staff of the
hospital pharmacy. For these patients, analgetic efficacy was evaluated and a more extensive pharmacokinetic analysis of morphine in CSF and plasma was performed. One ml of CSF was collected after 60, 180, 300 min and 18–20 h postmorphine administration. Each CSF sample was collected with a separate puncture one interspace below the site of administration using Antoni-Sise needles. Frequent arterial blood samples were drawn from a radial catheter during 5 h and at approximately 18–20 h. Blood and CSF for morphine determination were collected in plastic tubes. The plasma was separated immediately and, as with the CSF, frozen until analyzed using gas chromatography with electron capture detection.

During the postoperative phase the patients were nursed in an intensive care unit. Heart rate, blood pressure, respiratory frequency, and blood gases were monitored at regular intervals postoperatively. The need for additional analgetics (meperidine) in the two groups during a 48 h period after intrathecal morphine administration was registered and the consumption patterns between the two groups were compared. The research nurses, who were well trained in observing pain reactions, were instructed to administer meperidine intramuscularly (50–75 mg) when one or several of the following criteria were fulfilled: 1) when returning pain prompted the patients to ask for further analgetics; 2) when coughing was restricted due to pain; 3) when the patients showed evident signs of pain, e.g., groaning, sweating, anxiously moving around in the bed. The meperidine consumption pattern was determined individually and calculated as the amount of meperidine consumed per hour. The meperidine consumption in the 0.25- and 0.50-mg groups was statistically compared in blocks of 12 h using a nonparametric test (Wilcoxon).

Side effects, such as itching, nausea, headache, and vomiting were recorded by active questioning during the study period. If urinary retention was present at 12 h postoperatively, carbacholine was administered and if unsuccessful, the bladder was catheterized.

The elimination half-life of morphine in CSF/t1/2B was calculated from the elimination rate constant obtained from a monoequilibrium fit to the individual data points from 1 to 20 h. The area under curve, AUC, was calculated individually by the log–log trapezoidal rule10 with the addition of the residual area. The volume of distribution, Vd, and clearance of the drug, Cl, were calculated from the formulas

\[ V_d = \frac{\text{Dose}}{C_{1/2B}} \]

\[ Cl = \frac{\text{Dose}}{\text{AUC}} \]

Statistics were performed using the Student’s t test and Wilcoxon test. P values less than 0.05 were considered significant. Data are presented as mean ± SEM.

### Results

Body composition, surgical trauma, as well as the amount of fentanyl administered intraoperatively did not differ between the groups (table 1). The patient characteristics also were similar in the subjects participating in part 1 (table 1).

#### Plasma and CSF Pharmacokinetics

**Part 1.** Three CSF samples were collected in each patient at about 14, 16, and 18 h postmorphine injection. Elimination half lives were calculated to be 190 ± 12 min (fig. 1).

**Part 2.** The CSF morphine concentrations were measured at 1, 3, 5, and around 18 h postinjection (figs. 2, 3). The CSF samples from one patient in the 0.25-mg group were lost, reducing this group to five patients. The CSF concentration curves indicated a biphasic elimination in both groups, but with the limited CSF samples a distribution phase could not be characterized. At 1, 3, and 5 h, the morphine concentrations were significantly higher in the 0.5-mg group. At 18 h, the morphine concentrations in the two groups did not differ significantly (fig. 2).

Morphine was eliminated terminally in the CSF with a half-life of 175 ± 9 min and 196 ± 13 min for the 0.5- and 0.25-mg groups, respectively. The volume of CSF distribution (Vd) was 0.88 ± 0.16 ml·kg⁻¹ and 1.06 ± 0.17 ml·kg⁻¹, respectively; and the clearance was 2.81 ± 0.41 and 3.41 ± 0.55 ml·kg⁻¹·min⁻¹, respectively (table 2).

Plasma morphine concentrations generally were very low, i.e., under 1 ng/ml (fig. 3). A peak seemed to appear 3–5 h after injection. No significant differences in concentrations between the two groups were seen.

#### Analgesia and Side Effects

The duration of analgesia was calculated as the time interval between intrathecal morphine administration and the first meperidine injection. Presumably because of delayed onset of analgesia, a large interindividual variation was observed, with five patients requiring additional an-
algesia within 1 h after the intrathecal morphine administration. The three patients with the longest duration of algesia (22, 26, and 40 h) belonged to the 0.5-mg group (fig. 4).

The cumulative meperidine consumption patterns after intrathecal morphine administration indicated that after the early small consumption in the first hour, there was a progressive increase beginning 12–24 h after the in-

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**Fig. 1.** CSF morphine concentration time curves for two women (A, C) and one man (B) given 0.5 mg morphine intrathecally. Curves were determined to fit an exponential function by least-squares regression analysis. The following values for the correlation coefficient, elimination half-life and elimination rate constant were obtained: patient A ▲ ▲ 1.0, 200 min, 0.21 h⁻¹; patient B ○ --- ○ 0.98, 205 min, 0.21 h⁻¹; and patient C ■ ■ 0.99, 166 min, 0.25 h⁻¹.

**Fig. 2.** CSF morphine concentration versus time plots after a single intrathecal dose of either 0.25 or 0.50 mg morphine in five and six patients, respectively. Values shown are means ± SEM. The dotted line represents the regression line obtained by a monoexponential fit to the individual data points. Statistics by Student’s t test. Statistical differences versus the 0.25-mg group. **p < 0.01, ***p < 0.001.
INTRATHecal MORPHINE ANALGESIA

FIG. 3. Plasma morphine concentration versus time plots after a single intrathecal dose of either 0.25 or 0.50 mg morphine. Values shown are means ± SEM for six patients in each group.

terachal morphine administration (fig. 5). Furthermore, the patients given 0.25 mg morphine consumed significantly (P < 0.01) more meperidine during the 12–24 h period after intrathecal morphine administration than did the 0.5-mg group. In contrast, the groups did not differ in consumption pattern in either the preceding or the following 12-h periods.

Urinary retention was observed in four of six patients in the 0.25- and 0.5-mg groups, respectively. One patient experienced nausea, but otherwise no major drug related adverse effects were seen. Two patients reported minor itching and one of these also a minor headache (table 3). Blood gases did not differ between the groups, and no late respiratory depression was seen.

Discussion

In most reports concerned with the intrathecal technique, morphine was administered in doses ranging from 0.5–2 mg, but doses as large as 20 mg have been used. Long-lasting analgesia was reported, possibly enhanced with the higher dose. Unfortunately, an unacceptably high frequency of undesirable side effects has been reported with this technique. According to some reports, the frequency of side effects may be decreased by the administration of morphine in a hyperbaric solution, with the patient in a 40–60° head-up position. It is presumed that rostral distribution thereby is reduced. The optimal dose and regimen for both efficacy and safety have yet to be determined. In view of the reported side effects, we were interested in investigating the efficacy of very low doses, i.e., 0.25 and 0.5 mg. To our knowledge, respiratory depression following an intrathecal morphine dose of less than 1 mg has not been seen.

Analysis of the meperidine consumption pattern showed a highly individual variation. Half of the patients received their first meperidine injection within the first hour after intrathecal morphine administration, in con-

<table>
<thead>
<tr>
<th>Dosage (mg)</th>
<th>Patient</th>
<th>$t_{1/2}$ (min)</th>
<th>$V_d$ (mL·kg$^{-1}$)</th>
<th>Cl (mL·kg$^{-1}$·min$^{-1}$)</th>
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<tr>
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<td>0.16</td>
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* The terminal elimination half life ($t_{1/2}$) was calculated from the formula $t_{1/2} = \frac{0.693}{\beta}$, where $\beta$ is the elimination rate constant obtained by a monoexponential fit to the individual data. $V_d = \frac{Dose}{C_{pe}}$ and CI = $\frac{Dose}{AUC}$ where AUC was derived by the log-linear trapezoid rule.
FIG. 4. Intervals between intrathecal morphine (0.25 or 0.50 mg) administration and the first intramuscular meperidine administration in 12 patients undergoing thoracotomy.

In contrast to the other patients experiencing analgesia ranging from 4.5 to 20.5 h (0.25-mg group) and 23–40 h (0.5-mg group). Furthermore, the total meperidine consumption pattern showed that meperidine was requested early in small amounts and again after 12–24 h (fig. 5). This likely indicates a slow onset time, consistent with a slow penetration of morphine into the surrounding nervous tissue but furthermore dependent upon the rostral spread of morphine to thoracic segments. The following 12-h time period is beyond what can be attributable to the early meperidine requests and instead reflects the sustained pain relief associated with the intrathecal morphine. Presumably the problem of a slow onset time can be overcome by administering the drug prior to surgery following the induction of anesthesia. This is supported by a study indicating an increased efficacy of epidural morphine administration if morphine is given before the onset of pain.

As the efficacy of intrathecal morphine is assumed to depend on sufficient amounts of the drug at the receptor level in the spinal cord, it is relevant to determine CSF morphine concentrations following what must be considered clinically safe doses. For ethical reasons, multiple CSF sampling was restricted, limiting the possibility to obtain data for precise pharmacokinetic calculations. Therefore, the study was performed in two parts. In the initial study, late CSF samples were obtained in three patients and the elimination phase was characterized. Thus, between 14 and 18 h after intrathecal morphine administration, CSF concentrations were declining exponentially, with a half-life around 3.2 h. In the latter part of the study, the concentration data indicated that there also might be a distribution phase, but more frequent sampling is needed for characterization. With the limited sample times, a one-compartment analysis was performed, and accordingly the calculated elimination half-lives may be somewhat underestimated. However, these half-lives, i.e., 2.9 and 3.3 h for the 0.50- and 0.25-mg groups, respectively, corresponds very well with those found in part 1, i.e., 3.2 h. This implies that the $t_{1/2\beta}$ derived from a one-compartment analysis is valid or a good approximation of the actual values.

Due to low concentrations, plasma half-lives could not be calculated, making an individual comparison between plasma and CSF values impossible. However, in a number of studies, half-lives of morphine in plasma are reported, but a large variability is found, presumably reflecting a substantial interindividual variability combined with difference in analytic methods and study situations. Our data indicate that the terminal elimination half-life of morphine in CSF is not different from what is reported for morphine in plasma after iv, 3.8 ± 2.7 h (mean ± SD)\(^{17}\); oral, 3.4 ± 1.9 h (mean ± SD)\(^{18}\); or epidural administration, 3.9 ± 2.7 h (mean ± SD)\(^{19}\) and 3.2 ± 0.5 (mean ± SEM)\(^{7}\).

Mean CSF concentrations were very high, with a dose-related difference between the groups. In contrast to the high CSF morphine concentrations, plasma levels were very low and variable during the whole sampling period. It is obvious that the plasma morphine concentrations found after intrathecal administration were unrelated to the analgesia.

It is interesting to compare these observations to those we previously reported using epidural morphine.\(^{7}\) In that study, administration of epidural doses from 2 to 6 mg resulted in dose-dependent CSF concentrations at 1 h, between approximately 200–1000 ng/ml. This compares with approximately 4,000 and 10,000 ng/ml at 1 h after intrathecal administration of 0.25 and 0.50 mg, respectively. Eighteen hours after the administration, CSF still contained high concentrations of morphine, i.e., 25–40
ng/ml with 2–6 mg morphine epidurally and 180–200 ng/ml with 0.25–0.50 mg morphine intrathecally. The rates of elimination in CSF seemed to be roughly similar in this wide range of concentrations, i.e., a half-life of 3–4 h. After morphine was given epidurally, there was a rapid and substantial uptake into the systemic circulation from the vascular epidural space, which obviously was not seen after intrathecal administration. However, this may be related to the differences in doses used at the various sites of administration. The plasma levels of morphine after epidural administration seemed comparable to those seen after intravenous or intramuscular administration. One thus can not exclude transient systemic effects, elicited by this vascular uptake. However, it is not consistent with the long duration of the analgesia. In contrast, when morphine is given intrathecally in ordinary used doses, the plasma concentrations are too low to produce any systemic analgesia. The efficacy of smaller doses of intrathecal morphine that would result in CSF concentrations equivalent to those found after the usual epidural doses is unknown.

The calculated volume of distribution for morphine in the CSF compartment, i.e., around 70 ml, is very small, compared with the volume of distribution in the central compartment, i.e., around 250 l, and evidently it is reasonable to encounter high concentrations in CSF, even with small amounts of drug applied intrathecally. The volume of distribution is an imaginary volume, but it is interesting to relate this figure to the CSF space. Accordingly, when administered intrathecally in the lumbar region, morphine will distribute in a volume that is approximately half of the total CSF space (approximately 140 ml) but almost equal to the spinal CSF volume (approximately 75 ml). This calculated volume of morphine distribution reflects distribution in the CSF and into surrounding nervous tissue as well as other tissues. However, morphine is highly water soluble, consistent with an extended spread in the CSF compartment further supported by clinical evidence in this and other studies.

If morphine was distributed in a volume of 140 ml, i.e., the total CSF volume, and if elimination was only dependent on bulk flow through the subarachnoid villi, which is around 0.3–0.4 ml/min, the half-life would be expected to be around 4–5.5 h. In the spinal part the CSF flow is considered to be even slower, i.e., CSF morphine elimination half-life of 3–4 h indicates that morphine is eliminated by other means than only CSF bulk flow. Experimental data also has shown dural penetration of morphine: furthermore, the lumbar dura is more permeable than the cranial dura. Canine experiments showing that the elimination of morphine from the CSF is slightly retarded when compared with plasma is not supported by our data. In contrast, it seems like intrathecal administration is associated more with high local concentrations in CSF in the region of opiate receptors than on restricted CSF elimination and thus persisting in the region of opiate receptors for a long period of time.

Urinary retention occurred frequently in both groups,

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<tbody>
<tr>
<td>Itching</td>
<td>0</td>
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</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
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but other side effects were few. It is difficult to draw conclusions regarding urinary retention, since this is a common complication after major surgery irrespective of postoperative analgesia.20 The patients were asked for putative side effects. The itching and headache were minor and seemed to be of no concern to the patients.

In conclusion, our data indicate that intrathecal administration of 0.25 to 0.50 mg morphine results in dose-dependent CSF concentrations, which are higher than the concentrations achieved after epidural administration of 6 mg morphine. In contrast, the plasma concentrations are very low after the intrathecal technique. Morphine in CSF is eliminated with a terminal elimination half-life that is similar as in plasma after various forms of administration. Lumbar intrathecal administration for thoracic pain seems to give sustained pain relief, but there is a considerable time lag before appearance of analgesia, which is consistent with a slow rostral diffusion of morphine as well as a slow penetration of morphine into the surrounding nervous tissue.

References