The CSF and Plasma Pharmacokinetics of Sufentanil after Intrathecal Administration

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Eight patients (7 men and 1 woman, 45–68 yr old) scheduled to undergo thoracotomy were given, preoperatively, 15 μg sufentanil in the lumbar intrathecal space for a study of cerebrospinal fluid (CSF) and plasma kinetics of sufentanil. Multiple samples of plasma and CSF from the lumbar region were obtained through indwelling catheters for 12 h and analyzed for sufentanil by radioimmunoassay. Pharmacokinetic parameters were derived by noncompartmental analysis. In plasma, the maximal concentration of sufentanil appeared after 0.65 ± 0.17 h (mean ± SEM). No equilibrium was reached between the sufentanil concentration in CSF and plasma, but the CSF/plasma concentration ratio declined from approximately 140 at 2 h to about 15 at 10 h. Extrapolation indicates that another 10 h would be required before the concentration in CSF would that in plasma. The mean residence time (MRT) of sufentanil in CSF was 0.92 ± 0.08 h and in plasma was 6.8 ± 0.6 h. The volume of distribution at steady state (Vₐ) in the subarachnoid compartment was 1.54 ± 0.39 ml/kg, and the clearance from the CSF was 27 ± 5 μl·kg⁻¹·min⁻¹. The intrathecal administration of 15 μg sufentanil at the beginning of the operation did not produce analgesia that lasted into the postoperative period. Most patients had urinary retention; but none experienced any serious complications. This study demonstrates that the lipophilic opioid sufentanil undergoes rapid clearance from CSF and absorption to plasma after intrathecal administration. These pharmacokinetic characteristics are slower for the less lipophilic opioids meperidine and morphine. The rapid pharmacokinetics of sufentanil explain its rapid onset of action and short-lasting effects. (Key words: Analgesics: sufentanil; postoperative pain. Anesthetic technique: spinal. Pharmacokinetics: CSF/plasma concentrations.)

The discovery in the late 1970s of spinal mechanisms for the control of nociception opened new possibilities for segmental analgesia for postoperative as well as cancer pain. The effectiveness of intrathecally and epidurally administered opioids have been demonstrated repeatedly since their widespread acceptance in clinical practice.

A large variety of opioid drugs have been used, but morphine remains the most common choice. A number of clinical studies have demonstrated that morphine produces effective and long-lasting postoperative analgesia by the intrathecal and epidural route but at the cost of a high frequency of side effects, such as nausea, vomiting, itching, urinary retention, and respiratory depression. Some of these side effects have been associated with a cephalad spread of morphine in cerebrospinal fluid (CSF) from lumbar to supraspinal areas. Hypothetically, compared to hydrophilic opioids, the more lipid-soluble opioids are less liable to redistribute supraspinally in CSF and for reasons of safety are more suitable for spinal use.

Sufentanil is a new potent mu-receptor ligand characterized by a very high lipid solubility and a high affinity to opioid receptors. Epidural administration of sufentanil for postoperative analgesia has been tested in adults and children, but the clinical experience with intrathecal administration is sparse. Compared to morphine, spinal sufentanil has been found to produce more intense analgesia much more rapidly. However, the duration of spinal sufentanil analgesia appeared to be shorter, and moreover, respiratory depression after epidural sufentanil appeared to be a side effect. In order to properly validate the clinical use of intrathecal and epidural sufentanil it is necessary to clarify the sequence by which sufentanil is taken up by, distributed to, and eliminated from both CSF and plasma. However, very little information is yet available on the concentrations of epidurally and intrathecally administered sufentanil in plasma, and no information is available on its disposition in CSF. The aim of this study was to evaluate the pharmacokinetics of sufentanil in plasma and CSF after intrathecal administration of a bolus dose of sufentanil to patients scheduled to undergo thoracic surgery.

Materials and Methods

This study was approved by the Ethics Committee of the Medical Faculty at the University of Gothenburg and the Swedish Social Board of Welfare (Socialstyrelsen). The patients gave their informed consent for participation. Patients with liver disease (bilirubin >21 μM [12.3 mg/dl]), aspartate aminotransferase >0.7 μkat/l [42 IU], and alanine aminotransferase >0.7 μkat/l [42 IU]), kidney disease (creatinine >110 μM [12.5 mg/dl]) disease, or neurologic disorders affecting the CNS or the spine were ex-
cluded. The patients were free from opioids prior to entering the study.

Ten patients undergoing elective thoracotomy were included in the study, but two were excluded from kinetic calculation because of technical errors in CSF sampling or sufentanil analysis. Of the remaining patients, seven were operated on for pulmonary tumors and one for spontaneous pneumothorax. The age of these eight patients (seven men and one woman) ranged from 45 to 68 yr (mean 57 yr) and their weight was 69 kg ± 2.4 kg (mean ± SEM). Preanesthetic medication consisted of morphine hydrochloride 10 mg and scopolamine hydrobromide 0.4 mg intramuscularly (im). Anesthesia was induced with thiopental to achieve loss of consciousness. After muscle relaxation with pancuronium bromide 0.1 mg/kg, orotracheal intubation was performed, and anesthesia was maintained with nitrous oxide in oxygen in proportions according to blood gases. Incremental doses of fentanyl 0.05–0.1 mg and pancuronium bromide 0.5–2 mg and the vasodilator dihydralazine 6.25 mg were given when required throughout the operation. When the surgical procedure had been completed, the airways were aspirated by bronchoscopy. After reversal of muscle relaxation and recovery of spontaneous ventilation, the trachea was extubated.

With the anesthetized patient in the lateral position, a subarachnoid catheter (external diameter 0.85 mm and dead space 150 μl) was inserted through a 18-G Touhy-Flower’s needle at the L3–L4 or L4–L5 interspace, and a Spinocon® needle (0.5–0.8 mm external diameter, B. Braun Melsungen AG, West Germany) was inserted one interspace above the site of the subarachnoid catheter. Preoperatively, 15 μg sufentanil diluted in isotonic saline to a volume of 3 ml was administered through the intrathecal needle. The needle then was removed. CSF samples (1 ml) were collected through the subarachnoid catheter at 1, 3, 5, 10, 15, 30, 45, 60, 75, 90, 120, 240, 360, 480, 600, and 720 min after the administration of sufentanil. The intrathecal catheter then was removed. In order to keep the fluid loss to a minimum, great care was taken to avoid any extra CSF losses aside from that taken to clear the dead volume of the catheter and aside from the CSF samples taken for sufentanil analysis.

A radial artery catheter was inserted for blood sampling, and 10 ml was collected at 1, 3, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180, 240, 300, 360, 480, 600, and 720 min after administration of intrathecal sufentanil. Plasma was separated by centrifugation, and the plasma and CSF samples were stored at −20°C until analyzed.

Sufentanil concentrations were determined by radioimmunoassay (RIA). The sensitivity of the initially developed direct RIA method (0.1 ng/ml), which is described in detail elsewhere, was enhanced by extraction of the plasma (2 ml) or CSF (1 ml) at pH 13 with heptane–isoamyl alcohol (98.5:1.5, v/v) and by the use of a radio-ligand having a two- or four-fold higher specific activity, i.e., 33 and 54 Ci/mM instead of 15 Ci/mM. In this way, the lowest detectable concentration of sufentanil, displacing at least 20% of the tracer from the antibodies, was 0.02 ng/ml in plasma and 0.05 ng/ml in CSF. The specificity was demonstrated by the good agreement between patient plasma levels measured by gas chromatography–mass spectrometry and the described RIA procedure.

Analysis of blindly analyzed quality control samples, analyzed with the study samples, revealed intraassay coefficients of variation of 9.9% at 0.054 ng/ml sufentanil (n = 48), 7.1% at 0.65 ng/ml (n = 57), and 7.9% at 1.10 ng/ml for plasma (n = 25). Interassay coefficients of variation were 15.3 (n = 150), 11.1 (n = 120), and 13.1% (n = 55), respectively.

Postoperatively, blood pressure, heart rate, respiratory rate, and blood gases were monitored at regular intervals in the intensive care unit. If a patient showed obvious signs of pain, additional analgesics (intravenous [iv] or im morphine) were given. Any need for analgesics was recorded during the 24 h after sufentanil administration.

Side effects such as pruritus, nausea, vomiting, headache, and sedation were recorded during the 24 h after the operation. If the patients had not voided spontaneously 10–12 h after the administration of sufentanil, the bladder was catheterized; urinary retention was considered present if the urinary volume was more than 300 ml.

Patients with respiratory rate less than 10 breaths per min and with F CO2 greater than 60 mmHg were treated with iv naloxone, and respiratory depression was considered present. Sedation was recorded according to a scale of three grades: awake, somnolent, and sleeping. If a patient was either somnolent or sleeping, he or she was regarded as sedated.

**PHARMACOKINETIC ANALYSIS**

CSF pharmacokinetics were derived by means of non-compartmental analyses based on the theory of statistical moments. Values at 720 min (the last sampling point) could be obtained only in two patients, and therefore the mean concentration curve is presented up to 10th h. Mean residence time (MRT) in the CSF was calculated from the ratio of the area under the first-moment CSF curve (AUMC₀₋₅₅) to the area under the CSF curve (AUC₀₋₅₅). AUC was calculated by the linear trapezoidal method with extrapolation to infinity. The extrapolated area was calculated as the ratio of the last calculated concentration (Cₜₕ) and the slope of the terminal phase. The mean residual AUCₜₕ was 1.0% (range 0.2–2.0%) of the total AUCₜₕ. The volume of distribution at steady state (Vₜₕ)
of sufentanil in the CSF compartment was computed with the formula:

\[ V_{SS} = \text{dose} \cdot \frac{\text{AUMC}_{CSF}}{(\text{AUC}_{CSF})^2}. \]

The clearance of sufentanil from the CSF was computed from the ratio of the intrathecal dose of \( \text{AUC}_{CSF} \).

The MRT of sufentanil in plasma (MRT\( \text{P} \)) was calculated from the ratio of the area under the first-moment plasma curve (AUC\( \text{P} \)) to the area under the plasma curve (AUC\( \text{P} \)). The mean residual AUC\( \text{P} \) (calculated in a way analogous to that for CSF) was 24% (range 12–92%) of the total curve. The maximal concentration of sufentanil measured (C\( \text{max} \)) in plasma was determined in each patient; t\( \text{max} \) was defined as the time until C\( \text{max} \) was reached.

Data are presented as means and standard errors (mean ± SEM). Statistical analysis was performed with Student's \( t \) test for independent values. \( P < 0.05 \) was considered statistically significant.

**Results**

**Pharmacokinetics of Sufentanil**

**Plasma**

The C\( \text{max} \) of sufentanil in plasma was 0.15 ± 0.02 ng/ml and was reached at 39 ± 10 min (t\( \text{max} \)) (table 1, fig. 1). The MRT in plasma of sufentanil was 6.8 ± 0.6 h (table 1).

**CSF**

The concentrations of sufentanil in CSF were higher than those in plasma, but the MRT in CSF, 0.92 ± 0.08 h (table 1), was shorter than that in plasma in all patients (\( P < 0.001 \)). The CSF/plasma concentration ratio declined gradually; e.g., at 2 h after intrathecal administration the CSF concentration was 139 ± 23 times that in plasma, but after 10 h it was only 15 ± 5 times that in plasma (fig. 2). Extrapolation to a CSF/plasma ratio of 1 indicates that it would take another 10 h for this to occur. The V\( \text{ss} \) of sufentanil in the CSF compartment was 1.54 ± 0.59 ml/kg, and the clearance from the CSF compartment was 27 ± 5 \( \mu \)l·kg\(^{-1}\)·min\(^{-1}\) (table 1).

**Pharmacodynamics of Sufentanil**

The clinical course of all of the patients was uncomplicated. The mean total blood loss was 0.6 l (range 0.2–1.8 l). The tracheas of all patients could be extubated immediately after the operation. The mean time from intrathecal administration of sufentanil to the end of anesthesia was 3.2 h (range 2.1–4.3 h). During the op-

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**Table 1. Sufentanil in CSF and Plasma after Intrathecal Administration of 15 \( \mu \)g Sufentanil**

<table>
<thead>
<tr>
<th>Patient</th>
<th>MRT (h)</th>
<th>V( \text{ss} ) (ml/kg)</th>
<th>CL (( \mu )l·kg(^{-1})·min(^{-1}))</th>
<th>t( \text{max} ) (min)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.23</td>
<td>3.89</td>
<td>53</td>
<td>15</td>
<td>8.0</td>
</tr>
<tr>
<td>2</td>
<td>0.80</td>
<td>0.62</td>
<td>13</td>
<td>90</td>
<td>5.6</td>
</tr>
<tr>
<td>3</td>
<td>1.19</td>
<td>1.86</td>
<td>26</td>
<td>3</td>
<td>5.1</td>
</tr>
<tr>
<td>4</td>
<td>0.87</td>
<td>2.22</td>
<td>42</td>
<td>45</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>1.04</td>
<td>1.27</td>
<td>21</td>
<td>45</td>
<td>8.9</td>
</tr>
<tr>
<td>6</td>
<td>0.77</td>
<td>0.58</td>
<td>11</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>7</td>
<td>0.99</td>
<td>1.00</td>
<td>17</td>
<td>60</td>
<td>7.1</td>
</tr>
<tr>
<td>8</td>
<td>0.50</td>
<td>0.91</td>
<td>31</td>
<td>45</td>
<td>4.4</td>
</tr>
<tr>
<td>Mean</td>
<td>0.92</td>
<td>1.54</td>
<td>27</td>
<td>39</td>
<td>6.8</td>
</tr>
<tr>
<td>SEM</td>
<td>0.08</td>
<td>0.39</td>
<td>5</td>
<td>10</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Noncompartment analysis was used for the pharmacokinetic calculations. Mean residence time (MRT) was calculated from the ratio of the area under the first-moment curve (AUC) to the area under the curve (AUC) derived by the Lin–Lin trapezoidal rule. V\( \text{ss} \) was calculated from the formula: dose × AUMC/(AUC)^2. Clearance (CL) was computed from the ratio of intrathecal dose to AUC.
eration, iv fentanyl was administered, and the mean dosage was 0.19 mg/h (range 0.14–0.25 mg/h). However, pain already had appeared within 3 h after the end of anesthesia in all patients, and morphine administration during the first 24 h after sufentanil administration averaged 30 mg (range 20–47 mg). No serious side effects were recorded, but half of the patients were sedated and urinary retention occurred in six of seven patients; one patient had a urinary catheter inserted before the operation, and so urinary retention could not be determined (table 2). Neither headache nor any sign of catheter-induced infection occurred in any patient.

**Discussion**

The CSF concentrations and pharmacokinetics of sufentanil have been investigated with an indwelling subarachnoid catheter. In previous studies of this kind, each CSF sample has been taken through separate dural punctures. However, the model used in the current study improves the kinetic determination, since it allows samples from the CSF to be taken with greater frequency and at exact, predetermined times. Moreover, it eliminates the inconvenience to the patient that multiple dural punctures may cause, apparently without adding any risk of frequently occurring headache nor infection. However, these patients were elderly, and it is possible that headache would occur more often in younger patients.

Theoretically, sampling through the same catheter through which sufentanil was administered would measure the sufentanil concentration at the site of injection more accurately. However, that technique would lead to serious contamination of the samples. Therefore, in the current study, a subarachnoid catheter was inserted exclusively for CSF sampling, as close as possible to the site of sufentanil injection, i.e., one interspace next to the site of injection.

Total CSF volume is approximately 140 ml and is renewed by freshly secreted fluid every 7–8 h. Because of its small volume, CSF probably should not be discarded, aside from what is in the dead space of the catheter, and the number of samples and the size of each sample should be kept to a minimum in order to prevent unnecessary interference with CSF dynamics. Therefore, in the current study, the size of each CSF sample was kept constant, and no extra fluid loss was allowed.

Rigorous pharmacokinetic analysis of drugs in the CSF is complicated. Multicompartamental analysis of CSF concentration data have been used previously for pharmacokinetic calculations after intrathecal bolus administration of opioids. The data cannot be described by a single exponential expression, and the exact number of exponentials, and therefore compartments, that describe the decay of concentrations in CSF after intrathecal administration are not well defined. Regardless of the distribution characteristics, it is possible to determine distribution and elimination parameters by noncompartmental methods based on the theory of statistical moments. After intrathecal administration, CSF is considered the central compartment from which elimination occurs.

The MRT estimates the persistence time in the CSF. Half-life is the time required to eliminate 50% of the dose, and MRT is the time required to eliminate 63.2% of the

**Table 2. Adverse Effects after Intrathecal Administration of Sufentanil**

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Number/Number Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary retention</td>
<td>6/7</td>
</tr>
<tr>
<td>Itching</td>
<td>0/8</td>
</tr>
<tr>
<td>Headache</td>
<td>0/8</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>2/8</td>
</tr>
<tr>
<td>Sedation</td>
<td>4/8</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0/8</td>
</tr>
</tbody>
</table>
dose. After intrathecal administration, the MRT of sufentanil in CSF was approximately 0.9 h and of course the terminal elimination half-life of sufentanil in CSF is shorter. The elimination rate constant is the ratio of clearance to $V_m$ and thus the terminal half life in CSF of sufentanil can be estimated to be 0.6 h. In comparison, data-fitting of CSF sufentanil concentrations to a two-compartment model gave a higher value for the terminal elimination half-life, $1.4 \pm 0.1$ h.

In plasma, however, the terminal half-life calculated by least-squares regression analysis, 4.6 h, did not differ from that derived by noncompartmental analysis, 4.7 h. The time of persistence of sufentanil was found to be considerably longer in plasma than in CSF: the mean MRT was less than 1 h in CSF but almost 7 h in plasma. However, with a mean residual AUC_P and AUC_CSS of 24 and 1%, respectively, the calculation of MRT in plasma may be less reliable than that in CSF. Yet, with a CSF/plasma concentration ratio that is steadily declining, it is conceivable that the time of persistence of sufentanil after intrathecal administration is shorter in CSF than in plasma. Hypothetically, this information indicates that if sufentanil is administered repeatedly into the subarachnoidal space, sufentanil concentrations may accumulate in plasma but not in CSF.

The opioids morphine, meperidine, and sufentanil differ with respect to lipophilicity. The partition coefficient between octanol and water for sufentanil is approximately 40 times higher than that for meperidine and is more than 1,000-fold higher than that for morphine. Although the concentrations of sufentanil, meperidine, and morphine were higher in CSF than in plasma for more than 12 h, the CSF decay of the more lipophilic drug sufentanil as well as its appearance in plasma were more rapid than those of meperidine and morphine.\textsuperscript{23,4} For example, at 30 min, the mean concentration of sufentanil in CSF was approximately 10% of the CSF $C_{max}$, compared to a concentration of 30% of $C_{max}$ for meperidine.\textsuperscript{23} The value for morphine can be estimated to be even higher.\textsuperscript{4} The terminal elimination rate of sufentanil from CSF was also shorter than reported rates of meperidine (8.6 h) and morphine (3.1 h) elimination.\textsuperscript{28,4} The MRT in CSF of sufentanil was shorter than that of 0.05 mg/kg morphine, found by Inoescu et al. to be $137.5 \pm 55$ min.\textsuperscript{26} The shorter time needed to eliminate sufentanil compared to that for morphine and meperidine may be explained by the very rapid clearance of sufentanil from CSF. The clearance rate of sufentanil was approximately two times that of meperidine and two to ten times that of morphine.\textsuperscript{4,23,26-28}

Consistent with the more rapid decay of sufentanil in CSF as compared to meperidine and morphine, $C_{max}$ was reached in plasma approximately 40 min after sufentanil administration but after intrathecal meperidine was reached 2.3 h after administration and after intrathecal morphine 0.5–12 h after administration.\textsuperscript{27-29} Kotob et al.\textsuperscript{30} found consistently that a lipophilic opioid such as heroin is cleared more rapidly from CSF and enters the blood faster than is a hydrophilic opioid such as morphine. Thus, in general, the spinal cord acts like a sieve, letting lipophilic drugs through more easily than hydrophilic drugs.\textsuperscript{31} This is true also after intrathecal administration.

The analgesic effect of intrathecal sufentanil, in contrast to that of morphine, did not last long into the postoperative period. In fact, all patients requested additional analgesics within 3 h after the end of the anesthesia, and the mean morphine consumption during the first postoperative 24 h was similar to that found by others after general anesthesia.\textsuperscript{32,33} In the current study, the time of anesthesia was approximately 3 h, and in most studies the duration of analgesia after 50–75 µg epidural sufentanil was approximately 5–6 h (see ref. 34). However, in the current study, sufentanil was administered before the start of the operation to yield data that could be compared to previous studies with morphine and meperidine.\textsuperscript{4,23} This most likely explains the lack of effect of sufentanil in the postoperative period. Hypothetically, the duration of analgesia should be enhanced by the administration of a larger dose or more frequent doses or both. From the results of the current study, it is not possible to postulate whether an intrathecal dose larger than 15 µg would enhance duration of analgesia, since the patients were under general anesthesia. However, according to clinical experience, 75 µg sufentanil seems to be a maximal bolus dose given epidurally, and the CSF concentrations seen after this dose are in the range of those seen after 15 µg sufentanil given intrathecall.\textsuperscript{§} Consequently, until proper dose–response studies have been performed, extra care should be taken with intrathecal sufentanil doses greater than 15 µg. Alternatively, a sustained effect may be obtained by frequent intrathecal administration of sufentanil, consistent with its rapid clearance from CSF. However, with that option, one should be aware of the difference in persistence times of sufentanil in CSF and plasma, as found in the current study. Therefore, before an intrathecal infusion technique of sufentanil can be recommended, the pharmacokinetics of intrathecal sufentanil, including its pharmacokinetics under steady-state conditions, must be determined.

No serious side effects of intrathecal sufentanil were observed, but urinary retention and sedation was a common finding. In our experience, these effects occur normally after thoracotomy under general anesthesia and therefore are not necessarily related to the intrathecal administration of sufentanil in these patients.

In conclusion, we showed that 15 μg intrathecal sufentanil results in a disposition in CSF that is more rapid compared than that of meperidine and morphine. This indicates that the disposition in CSF of these drugs is related to their lipophlic properties. Moreover, in contrast to morphine and meperidine, the disposition of sufentanil was more rapid in CSF than in plasma. This property suggests that intrathecal sufentanil is less likely to accumulate in CSF than in plasma after multiple doses. However, an intrathecal dose of 15 μg sufentanil results in postoperative analgesia of short duration but with few side effects, possibly as a result of its rapid disposition in CSF rather than from a small dose size.

References