The Pharmacokinetics of Sufentanil in Surgical Patients


The pharmacokinetics of sufentanil, a new thienyl analogue of fentanyl, were studied in 10 surgical patients. Sufentanil, 5 μg/kg, was given intravenously as a bolus injection and plasma concentrations measured at intervals up to 8 h. Plasma sufentanil concentrations decreased rapidly after injection—96% of the administered dose having left the plasma within 30 min. In 9 of the 10 patients, a tri-exponential equation optimally described the sufentanil concentration decay curve, with average (±SEM) half-lives for the rapid (α) and slow (α) distribution phases of 1.4 ± 0.3 min and 17.7 ± 2.6 min, respectively. The average terminal elimination (β) half-life was 164 ± 22 min. The average value for Vdβ was 2.9 ± 0.2 l/kg, Vdα 1.7 ± 0.2 l/kg and total plasma clearance 12.7 ± 0.8 ml·kg⁻¹·min⁻¹ (935 ± 50 ml/min). In one patient, a bi-exponential equation was sufficient to describe the concentration-time data, yielding a distribution half-life of 4.7 min and an elimination half-life of 117 min. (Key words: Analgesics: sufentanil. Anesthetics, intravenous sufentanil. Pharmacokinetics: sufentanil. Surgery.)

SUFENTANIL is a new thienyl analogue of fentanyl currently undergoing clinical evaluation in several countries. It is water soluble and is available as a solution of sufentanil citrate containing 50 μg/ml sufentanil base. Sufentanil is approximately ten times as potent as fentanyl in humans,¹ a ratio that is similar to the affinities of these drugs for opioid receptors.² Large doses of sufentanil (15 to 20 μg/kg) produce surgical anesthesia in patients undergoing coronary artery surgery with minimal hemodynamic disturbances.³⁴ The pharmacokinetics of sufentanil have been investigated in dogs,⁵ but similar data have not been reported previously in humans. We have studied therefore the pharmacokinetics of sufentanil administered intravenously in surgical patients.

Methods

Ten adult patients (ASA classification 1 or 2), undergoing elective surgery expected to last 2 to 4 h, were studied. None had historic or biochemical evidence of hepatic or renal dysfunction. No patient was taking cimetidine or enzyme-inducing drugs at the time of the study. Patients with intraoperative blood loss greater than 15% were excluded from the study. Informed consent was obtained from each patient at the time of the preoperative visit. The study conformed to the ethical standards of the Declaration of Helsinki. Individual patient characteristics and operative procedures are given in table 1.

Premedication was either lorazepam 3 mg or diazepam 10 mg orally 1.5 h before surgery. Anesthesia was induced with a sleep dose of thiopental (3.7 to 5.6 μg/kg) followed by suxamethonium 1 mg/kg to facilitate intubation of the trachea.

The lungs were ventilated with 66% nitrous oxide in oxygen, ventilation being adjusted to maintain end-tidal CO₂ concentration at approximately 4.5%. Pancuronium 0.1 mg/kg was used for muscle relaxation, and anesthesia was supplemented with either halothane 0.5% or enflurane 1–1.5% inspired concentration. A 14-gauge catheter was inserted into the superior vena cava for the withdrawal of blood samples. During surgery, a maintenance infusion of Ringer's lactate solution was given at 7–10 ml·kg⁻¹·h⁻¹. Blood loss in excess of 300 ml was replaced with packed erythrocytes and fresh-frozen plasma. One lung anesthesia was used for a 30-min period in one patient (patient 4) starting 55 min after the administration of sufentanil. Extracorporeal circulation was not used in patient 5 (closed mitral valvotomy). Deliberate hypotension was not used in any patient.

After intubation, a control blood sample was obtained, and then sufentanil 5 μg/kg was injected as a bolus into an arm vein. Blood samples were taken at 1, 2, 3, 5, 10, 15, 30, 45, and 60 min and thereafter every hour until 8 hours after injection. Plasma was separated from blood samples and stored at −26°C until assayed. Sufentanil concentrations were determined in duplicate by radioimmunoassay.⁶ The sensitivity of the assay was 0.06 ng/ml. The intraassay and interassay coefficient of variation was 4.7% and 3.9%, respectively, over a range of 0.14–3.2 ng/ml.

The plasma sufentanil concentration–time data from each patient were fitted by computer to bi- and tri-
exponential equations using weighted nonlinear least-squares regression analysis. The weighting factor used was \(1/Ct^2\) (where \(Ct\) = sufentanil concentration at time \(t\)), adjusted so that the sum of weights equaled the number of fitted data points.\(^7\) The choice of a two- or three-compartment model was determined by F-ratio testing.\(^7\) Derived pharmacokinetic parameters were calculated using equations described by Gibaldi and Perrier.\(^9\) The volume of distribution at steady state (\(V_d\)) was calculated using the formula described by Wagner.\(^9\)

Results are expressed as means ± SEM. A value of \(P < 0.05\) was accepted as significant.

Results

There was a rapid decrease in the plasma concentration of sufentanil after injection, 98% of the injected dose having left the plasma within 30 min. The mean change in concentration with time is shown in figure 1.

In 9 of the 10 patients, the best fit to the concentration–time data was by a tri-exponential equation. In the remaining patient (patient 9) the weighted sum of squared deviations was not improved significantly by adding a third exponential to the fitting equation (\(F = 3.054\); degrees of freedom = 2.9; \(P = 0.09\)). However, since the percentage fit of the data with the tri-exponential equation was 98%, compared with 88% with the bi-exponential equation, data from the former has been included in tables 2 and 3, which give details of the derived and calculated pharmacokinetic parameters.

The bi-exponential equation of best fit for patient 9 was as follows:

\[
Ct = 25.8e^{-0.145t} + 1.26e^{-0.0062t}.
\]

From this equation the following parameters were derived: \(T_{1/2\alpha} = 4.8\) min, \(T_{1/3\beta} = 112\) min, volume of the central compartment (\(V_o\)) = 0.18 l/kg, volume of distribution (\(V_d\)) = 2.12 l/kg, \(V_{du}\) = 1.18 l/kg, and clearance (\(Cl\)) = 13.1 ml·min\(^{-1}\)·kg\(^{-1}\).

The average half-lives for the \(\pi\), \(\alpha\), and \(\beta\) phases of the tri-exponential fits were 1.4 ± 0.3 min, 17.1 ± 2.6 min, and 164 ± 22 min, respectively. The apparent volume of the central compartment (\(V_o\)) was 0.164 ± 0.018 l/kg and the apparent volume of distribution (\(V_d\)) was 2.86 ± 0.25 l/kg. The volume of distribution at steady state (\(V_{du}\)) was 1.74 ± 0.19 l/kg. Total plasma clearance was 12.66 ± 0.78 ml·kg\(^{-1}\)·min\(^{-1}\) (935 ± 50 ml/min). Since the plasma/blood concentration ratio for sufentanil is 1.349,\(^10\) total whole blood clearance was 1,200 ± 100 ml/min. Assuming negligible extra-hepatic elimination and an average hepatic blood flow (\(Q\)) of 1,500 ml/min,\(^11\) this corresponds to an hepatic extraction ratio (\(E = Q/V_d\)) of 0.8 and an intrinsic hepatic clearance four times hepatic blood flow, where intrinsic clearance was calculated according to the formula\(^12\),

\[
E = 0.8,\; C_i = 4\times Q.
\]

FIG. 1. Mean (±SEM) plasma concentrations after bolus intravenous injection of sufentanil 5 μg/kg. The tri-exponential equation describes the line of best fit through the points (solid line).
The ratio of the transfer rate constants between the central and deep peripheral compartments (k13/k31) was 8.4. The elimination rate constant (k10) was 9.2 times greater than k31. During the terminal elimination phase, the fraction of the drug present in the central compartment, Fc (=β/k10), was only 5.4%.

The time interval between administration of sufentanil and termination of surgery varied from 1.5 to 9.5 h, the average duration of surgery being 4 ± 0.7 h. No evidence of cardiovascular depression was observed following drug administration. Respiratory depression occurred in one patient (patient 1) at the end of surgery. She had been scheduled for an operation expected to last approximately 3 h but that was completed within 100 min. The plasma sufentanil concentration at that time was 1.02 ng/ml. Adequate ventilation was restored by a single dose of naloxone 0.2 mg intravenously.

Discussion

In 9 of the 10 patients in this study, the pharmacokinetics of sufentanil were described best by a three-compartment open model. In this respect, sufentanil is similar to many other opioids whose plasma disposition after bolus intravenous injection has been characterized by tri-exponential decay, e.g., morphine,15,14 fentanyl,15 and alfentanil.16,17 However other investigators have found that a two-compartment model satisfactorily explained their data with those drugs.18-20 The dispositions of methadone21 and meperidine22,23 also have been characterized most frequently by a bi-exponential equation, although tri-exponential decay has been described for meperidine.24 For drugs administered intravenously, several factors determine whether there will be one or two distribution phases, i.e., a two- or a three-compartment model. These include the physiochemical properties of the drug, distribution organ size, and perfusion. The frequency and site (venous or arterial) of sampling after administration also may be important in determining whether a bi- or tri-exponential equation is required to provide a satisfactory fit to the data. From the evidence available it is impossible to decide which of these factors, i.e., study design or patient characteristic, resulted in bi-exponential decay of sufentanil concentrations in one of our patients.

The half-life of the terminal elimination phase (T1/2b) for sufentanil (164 min) is intermediate between

### Table 2. Sufentanil Pharmacokinetic Parameters in 10 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Vc (L/kg)</th>
<th>Vdβ (L/kg)</th>
<th>Vdα (L/kg)</th>
<th>CL (ml·kg⁻¹·min⁻¹)</th>
<th>K10 (min⁻¹)</th>
<th>K12 (min⁻¹)</th>
<th>K13 (min⁻¹)</th>
<th>K21 (min⁻¹)</th>
<th>K31 (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.204</td>
<td>3.77</td>
<td>2.78</td>
<td>7.68</td>
<td>0.038</td>
<td>0.333</td>
<td>0.056</td>
<td>0.102</td>
<td>0.006</td>
</tr>
<tr>
<td>2</td>
<td>0.187</td>
<td>2.95</td>
<td>2.04</td>
<td>12.16</td>
<td>0.065</td>
<td>0.219</td>
<td>0.085</td>
<td>0.104</td>
<td>0.011</td>
</tr>
<tr>
<td>3</td>
<td>0.099</td>
<td>1.53</td>
<td>1.09</td>
<td>10.03</td>
<td>0.101</td>
<td>0.537</td>
<td>0.154</td>
<td>0.303</td>
<td>0.019</td>
</tr>
<tr>
<td>4</td>
<td>0.195</td>
<td>3.27</td>
<td>2.03</td>
<td>15.41</td>
<td>0.069</td>
<td>0.149</td>
<td>0.075</td>
<td>0.099</td>
<td>0.009</td>
</tr>
<tr>
<td>5</td>
<td>0.122</td>
<td>2.10</td>
<td>1.12</td>
<td>15.44</td>
<td>0.126</td>
<td>0.783</td>
<td>0.056</td>
<td>0.232</td>
<td>0.012</td>
</tr>
<tr>
<td>6</td>
<td>0.111</td>
<td>2.71</td>
<td>1.44</td>
<td>15.58</td>
<td>0.140</td>
<td>0.479</td>
<td>0.102</td>
<td>0.201</td>
<td>0.010</td>
</tr>
<tr>
<td>7</td>
<td>0.180</td>
<td>3.58</td>
<td>1.99</td>
<td>14.76</td>
<td>0.081</td>
<td>0.291</td>
<td>0.057</td>
<td>0.173</td>
<td>0.008</td>
</tr>
<tr>
<td>8</td>
<td>0.202</td>
<td>2.54</td>
<td>1.48</td>
<td>11.75</td>
<td>0.058</td>
<td>0.292</td>
<td>0.036</td>
<td>0.143</td>
<td>0.008</td>
</tr>
<tr>
<td>9</td>
<td>0.076</td>
<td>2.22</td>
<td>1.08</td>
<td>12.29</td>
<td>0.162</td>
<td>0.335</td>
<td>0.113</td>
<td>0.202</td>
<td>0.010</td>
</tr>
<tr>
<td>10</td>
<td>0.260</td>
<td>3.88</td>
<td>2.34</td>
<td>13.54</td>
<td>0.052</td>
<td>0.078</td>
<td>0.026</td>
<td>0.050</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean</td>
<td>0.164</td>
<td>2.86</td>
<td>1.74</td>
<td>12.66</td>
<td>0.089</td>
<td>0.350</td>
<td>0.077</td>
<td>0.161</td>
<td>0.010</td>
</tr>
<tr>
<td>±SEM</td>
<td>0.018</td>
<td>0.25</td>
<td>0.19</td>
<td>0.78</td>
<td>0.013</td>
<td>0.065</td>
<td>0.012</td>
<td>0.024</td>
<td>0.001</td>
</tr>
</tbody>
</table>
that of fentanyl (T½β 185\(10\) to 219\(15\) min) and alfentanil (T½β 70\(20\) to 98\(10\) min). The very short half-life of alfentanil can be explained by a small apparent volume of distribution (Vdβ = 0.86 l/kg) and moderate plasma clearance.\(^6\) Whereas the plasma clearance of sufentanil in this study (935 ml/min) is similar to that of fentanyl (956 ml/min\(^6\)), the volume of distribution (2.86 l/kg) is less (4 l/kg\(^5\)). This can explain the more rapid elimination of sufentanil.

The apparent volume of distribution (Vdβ) of sufentanil exceeds total body water by a factor of three. Volume of distribution is dependent on protein and tissue binding.\(^25\) Sufentanil is very highly protein bound: -92.5% compared with 84% for fentanyl.\(^10\) The combination of high plasma protein binding and a large volume of distribution suggests extensive uptake of the drug into tissues. A high tissue affinity is in keeping with the very lipophilic nature of sufentanil—the partition coefficient between n-octanol and water is 1,754, that for fentanyl being 816.\(^10\) This very high lipid solubility of sufentanil, will allow the drug to penetrate membranes, including the blood–brain barrier, rapidly. The onset of action of the central nervous effects of sufentanil therefore should be rapid, a prediction confirmed by clinical experience.\(^4,26,27\)

Extensive tissue uptake and high lipid solubility play a role in prolonging elimination of a drug. This is reflected, in the case of sufentanil, by the high ratio of the transfer rate constants into and out of the third (deep peripheral) compartment (k13/k31 = 8.4). The elimination rate constant (k10) was 9.2 times greater than k31. The third peripheral compartment thus acts as a reservoir, limiting return of drug to the central compartment, from which elimination is assumed to occur.

The total body clearance of sufentanil, related to whole blood, was large (1,200 ml/min) and corresponded to a hepatic extraction ratio of 0.8, assuming a hepatic blood flow of 1,500 ml/min and negligible extrahepatic elimination. This latter assumption is reasonable in view of the highly lipophilic nature of sufentanil that results in extensive renal tubular reabsorption of the free drug. Our assumption about normal hepatic blood flow is perhaps less well founded. General anesthesia causes a decrease in hepatic blood flow—approximately 20% in the case of halothane in nitrous oxide.\(^58\) It is thus likely that our calculations of the hepatic extraction ratio for sufentanil is an underestimation and that the true value is closer to unity. Since the extraction ratio is greater than the fraction of free drug in plasma, hepatic extraction is nonrestrictive. The total intrinsic clearance of sufentanil was calculated as four times hepatic blood flow. Total intrinsic clearance gives an indication of the maximum ability of the liver to metabolically remove drug in the absence of flow limitations. For drugs such as sufentanil with high intrinsic clearance, hepatic elimination will be sensitive to changes in liver blood-flow but not to alterations in the drug-metabolizing capacity of the liver.

Because of the high hepatic extraction, sufentanil will be subjected to extensive presystemic (first-pass) metabolism after oral dosing. Accumulation of fentanyl in the stomach has been demonstrated,\(^29\) and this is also likely to occur with sufentanil, which, like fentanyl, is a weak base (pK = 8.01\(^10\)). It has been postulated that subsequent enterohepatic recycling of fentanyl could explain the observed secondary increases in plasma concentration. Because of the large first-pass effect with fentanyl, this is unlikely. It would be just as unlikely in the case of sufentanil.

The variability in kinetic parameters among the patients in this study is greater than normally observed in pharmacokinetic studies involving healthy adult subjects under standardized conditions. This variability was not unexpected, considering that our subjects were patients undergoing a variety of surgical procedures under general anesthesia. Data from this group of patients are more likely to reflect the variability that will be presented to the clinical anesthesiologist in his everyday practice than data from volunteers. It is likely that most of the variability that we observed results from physiologic changes associated with anesthesia and surgery. It is known that changes in plasma and extra cellular volume, plasma protein concentration, and tissue blood flow occur during surgery and these can influence drug distribution.\(^29,30,31\) Binding to the "acute phase" protein, alpha-1-acid glycoprotein constitutes a significant proportion of the total plasma protein binding of sufentanil.\(^10\) Levels of alpha-1-acid glycoprotein vary over a threefold range in healthy volunteers\(^30\) and are increased after surgery.\(^31\) This would result in a decrease in the free fraction of sufentanil in the plasma. Changes in pH during surgery also would influence the free fraction of drug, although the influence of pH on protein binding is less for sufentanil than for fentanyl.\(^10\) Because of its high intrinsic clearance, sufentanil elimination also will be sensitive to changes in liver blood flow occurring during anesthesia and surgery.

In conclusion, we have shown that sufentanil has pharmacokinetic properties intermediate between those of fentanyl and alfentanil. These findings are in keeping with the clinical profile of the drug.

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References

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