SUFENTANIL DISPOSITION IN PATIENTS UNDERGOING RENAL TRANSPLANTATION: INFLUENCE OF CHOICE OF KINETIC MODEL†

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There is controversy on the use of opioid drugs in patients with impaired renal function. Prolonged ventilatory depression and sedation have been reported following parenteral administration of morphine or papaveretum [1,2] and plasma concentrations of norpethidine, a metabolite with sedative and convulsant properties, increased when pethidine was given to patients with impaired renal function [3,4].

Studies on the elimination of sufentanil have shown that it has a high hepatic extraction ratio [5] with little involvement of the kidney in native drug clearance; hence the drug should be suitable for use in patients with both normal and impaired renal function. However, there have been reports of prolonged ventilatory depression with altered drug kinetics when sufentanil was given to renal transplant recipients [6,7]. The present study has therefore examined the disposition of sufentanil in such patients, and compared the kinetics with those from a comparable group of healthy anaesthetized patients undergoing lower abdominal surgery.

Studies of drug kinetics during anaesthesia show considerable variability [8,9]. In addition to clearly definable factors (patient age, fitness, choice of anaesthetic agents), different approaches to data handling may affect the estimates for clearance, volumes of distribution, and elimination half-life. Therefore the influence of the kinetic model on derived parameters has been examined also.

SUMMARY

We studied the disposition of sufentanil in 10 patients undergoing renal transplantation, and compared the data with those from eight healthy anaesthetized patients undergoing lower abdominal surgery. Patients received sufentanil 2.5 μg kg⁻¹ as part of a balanced anaesthetic technique. Central venous blood samples were collected at intervals up to 600 min, and plasma sufentanil concentrations assayed by radioimmunoassay. Pharmacokinetic parameters were calculated from drug concentration-time profiles by extended least squares non-linear regression analysis (ELSFIT) and by a model independent (MI) approach using AUC and its first moment, AUMC. There were no differences (based on MI results) between the two groups for elimination half-life (T½) (renal failure: 188 min; anaesthetized controls: 195 min), clearance (Cl) (1030 and 1093 ml min⁻¹) and apparent volume of distribution at steady state (Vss) (223.0 and 215.3 litre). Sufentanil binding to plasma proteins was 91.4% in the renal patients and 92.2% in the healthy group (ns). Comparison of kinetic methods showed significant correlation of the individual estimates for T½, Cl and Vss (P < 0.01). The mean absolute differences between methods were: T½ 2.7 min (95% limits: -26.2 to 31.5), Cl 36.5 ml min⁻¹ (-5.5 to 78.4), Vss -18.4 litre (-47.7 to 10.9). When the mean estimate for the two methods ((ELSFIT + MI)/2) was compared with the difference, there was no correlation for the estimates of Cl and Vss. MI tended to overestimate clearance and underestimate volume of distribution. There was a significant relationship between estimates for elimination half-life, with a slope greater than zero.

PATIENTS AND METHODS

Approval for the study was obtained from the local Hospital Ethics Committee, and all patients gave informed consent. Eighteen patients were studied (table I); 10 had chronic renal failure treated by haemodialysis, and were undergoing cadaveric (n = 3) or living related donor kidney transplantation through an extraperitoneal loin incision. None had received a previous renal transplant. Patients underwent renal dialysis within 6–16 h of transplantation, and maintained concurrent drug therapy up to and including the time of premedication. Patients in the healthy anaesthetized group were undergoing abdominal surgery. No patient in either group had clinical evidence of liver dysfunction or abnormal liver function tests. None of the 18 patients suffered significant intraoperative blood loss.

Premedication comprised diazepam 10 mg given by mouth 90 min before anaesthesia. Sleep was induced with thiopentone 3–4 mg kg⁻¹ and the trachea intubated after vecuronium 0.1 mg kg⁻¹ i.v. Anaesthesia was maintained with 60–67% nitrous oxide in oxygen and controlled ventilation adjusted to provide normocapnia. Volatile supplementation of anaesthesia was given only if patients showed clinical signs of inadequate anaesthesia (heart rate > 90 beat min⁻¹; arterial pressure > 20% greater than pre-induction value; sweating or lacrimation).

When stable anaesthesia had been achieved, sufentanil 2.5 µg kg⁻¹ was administered i.v. over 30 s. After administration of the opioid, venous blood samples (5 ml) were taken into lithium-heparin tubes from a central venous catheter at times 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180 min and then at additional times to 600 min.

At the end of surgery, residual neuromuscular block was antagonized with atropine 1.2 mg and neostigmine 2.5 mg. In those patients with ventilatory depression (< 10 b.p.m.; tidal volume less than 8 ml kg⁻¹), naloxone 0.2–0.4 mg was administered before tracheal extubation.

Throughout anaesthesia and surgery, heart rate and ECG were monitored continuously; arterial pressure was recorded non-invasively at 5-min intervals.

**Sufentanil assay**

Plasma sufentanil concentrations were measured using a radioimmunoassay with a sensitivity of 0.02 ng ml⁻¹ [10]. This assay does not cross react with any of the known metabolites of sufentanil, with naloxone or with pethidine, which was given i.m. for postoperative analgesia. Plasma protein binding for sufentanil was determined by equilibrium dialysis at pH 7.4 and 37 °C against

| Table I. Details of patients in renal transplant group (n = 10) and healthy anaesthetized group (n = 8). |
|---|---|---|---|---|
| **Age (yr)** | **Sex** | **Weight (kg)** | **Aetiology of RF/surgical procedure** | **Concurrent drug therapy** |
| **Transplant** | | | | |
| 1 | 54 | F | 66.0 | Polycystic kidneys | None |
| 2 | 39 | F | 50.0 | Nephrotic syndrome | Atenolol; nifedipine |
| 3 | 46 | M | 64.1 | Obstructive uropathy | Atenolol; hydralazine |
| 4 | 25 | F | 50.0 | Chronic pyelonephritis | None |
| 5 | 25 | F | 45.0 | Polycystic kidneys | None |
| 6 | 15 | F | 34.0 | Chronic pyelonephritis | Metoprolol; nifedipine |
| 7 | 30 | F | 53.0 | Glomerulonephritis | None |
| 8 | 39 | M | 68.6 | Nephrotic syndrome | a-Methyl DOPA; amiodarone |
| 9 | 30 | M | 53.2 | Unknown; hypertension | Atenolol; hydralazine |
| 10 | 33 | M | 61.3 | Unknown; hypertension | Atenolol; minoxidil |
| **Healthy** | | | | |
| 1 | 59 | F | 60.8 | Abdominal hysterectomy | |
| 2 | 55 | F | 58.8 | Abdominal hysterectomy | |
| 3 | 57 | F | 65.9 | Cholecystectomy | |
| 4 | 62 | F | 54.4 | Anterior resection | |
| 5 | 37 | F | 58.8 | Abdominal hysterectomy | |
| 6 | 60 | M | 85.0 | Ilio-femoral endarterectomy | |
| 7 | 61 | F | 54.6 | Cholecystectomy | |
| 8 | 65 | M | 90.2 | Anterior resection | |
phosphate buffer 1 mol litre\(^{-1}\). The coefficients of variation (intra- and inter-assay) were approximately 5% within the concentration ranges measured.

**Other assays**

Alpha\(_1\)-acid glycoprotein concentrations were determined using commercially available radio-immunodiffusion plates; plasma urea, creatinine, and serum albumin concentrations were measured by routine clinical laboratory methods.

**Kinetic analysis of data**

The plasma drug concentration–time curves for individual patients were analysed by two separate approaches. First, the data were analysed by a model-independent method (MI) with the area under the curve (AUC) and its first moment (AUMC) calculated using the linear trapezoidal method. The terminal or elimination half-life \((t_{1/2})\) was calculated by non-linear regression analysis and the following kinetic parameters derived: apparent volume of distribution at steady state \((V^\infty)\), plasma clearance \((Cl)\) and mean residence time \((MRT)\). Data were analysed also by extended non-linear least squares regression analysis (ELSFIT) with weighting proportional to the reciprocal of the variance of the measured drug concentration \([11]\). The suitability of the compartmental model chosen for each set of data (two- or three-compartment model) was based on evaluation of the residuals between measured and predicted plasma drug concentrations, and the maximum likelihood function.

**Statistical analysis**

Data are presented as the mean (SD) or range. Statistical significance between patient groups was determined using the Mann–Whitney \(U\) test. Kinetic parameters derived by the MI and ELSFIT analyses were compared using methods described by Bland and Altman \([12]\).

| Table II. Pharmacokinetic variables determined by extended non-linear least squares regression analysis (ELSFIT) and model independent method (MI) in 10 patients with endstage renal failure undergoing transplantation, and eight healthy anaesthetized patients undergoing abdominal surgery, and sufentanil binding to plasma proteins at concentration of 0.5 ng ml\(^{-1}\) (mean values (SD)). MRT = Mean residence time; \(FF = \text{free (unbound) fraction of sufentanil in plasma}\). |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | ELSFIT analysis   | MI analysis       |                   |
|                   | \(T_f\) (min)     | \(MRT\) (min)    | \(Cl\) (ml min\(^{-1}\)) | \(V^\infty\) (litre)   | \(T_f\) (min)     | \(MRT\) (min)    | \(Cl\) (ml min\(^{-1}\)) | \(V^\infty\) (litre) | \(FF\) (%) |
| Transplant        |                   |                   |                   |                   |
| 1                 | 80               | 87               | 1703              | 147.6             | 86               | 100             | 1710              | 170.6             | 8.0       |
| 2                 | 228              | 161              | 555               | 89.5              | 162              | 141             | 563               | 79.4              | 5.8       |
| 3                 | 178              | 186              | 859               | 160.3             | 172              | 185             | 830               | 153.0             | 8.0       |
| 4                 | 148              | 139              | 845               | 117.6             | 207              | 201             | 804               | 163.4             | 8.3       |
| 5                 | 163              | 159              | 720               | 114.2             | 143              | 163             | 609               | 99.4              | 9.9       |
| 6                 | 74               | 75               | 852               | 63.8              | 81               | 88              | 820               | 72.0              | 10.4      |
| 7                 | 190              | 178              | 1214              | 216.3             | 186              | 212             | 1097              | 232.7             | 9.5       |
| 8                 | 153              | 144              | 1242              | 179.6             | 182              | 215             | 1100              | 236.4             | 7.6       |
| 9                 | 190              | 185              | 1963              | 362.7             | 221              | 286             | 1742              | 497.5             | 9.2       |
| 10                | 608              | 635              | 950               | 605.1             | 437              | 528             | 1003              | 529.0             | 9.3       |
| Mean              | 201              | 195              | 1090              | 205.7             | 188              | 212             | 1030              | 223.0             | 8.6       |
| SD                | 151              | 159              | 446               | 163.4             | 99               | 125             | 410               | 163.0             | 1.3       |
| Healthy           |                   |                   |                   |                   |
| 1                 | 106              | 91               | 1088              | 99.3              | 227              | 262             | 988               | 258.5             | 10.7      |
| 2                 | 355              | 315              | 841               | 264.3             | 321              | 322             | 876               | 281.8             | 7.8       |
| 3                 | 188              | 212              | 1015              | 215.9             | 223              | 233             | 1040              | 241.6             | 6.7       |
| 4                 | 141              | 136              | 1371              | 186.5             | 133              | 134             | 1375              | 184.7             | 9.2       |
| 5                 | 72               | 73               | 1887              | 137.9             | 80               | 79              | 1958              | 154.3             | 9.7       |
| 6                 | 235              | 261              | 1020              | 266.1             | 214              | 206             | 871               | 179.4             | 5.9       |
| 7                 | 238              | 220              | 666               | 146.1             | 218              | 229             | 726               | 165.9             | 5.8       |
| 8                 | 147              | 150              | 1687              | 252.3             | 152              | 150             | 1710              | 256.1             | 6.3       |
| Mean              | 185              | 182              | 1196              | 196.0             | 195              | 202             | 1093              | 215.3             | 7.8       |
| SD                | 90               | 84               | 420               | 63.8              | 73               | 78              | 443               | 49.3              | 1.9       |
RESULTS

Anaesthesia was uneventful in all patients, and lasted 179.2 (37.6) min in the renal transplant group and 123.1 (43.2) min in the healthy patients. Preoperative plasma concentrations of urea and creatinine were 4.0 (1.1) mmol litre$^{-1}$ and 92 (14) μmol litre$^{-1}$ in the healthy patients; and 18.6 (10.5) mmol litre$^{-1}$ and 714 (197) μmol litre$^{-1}$ in the renal transplant patients ($P < 0.005$). In both groups, administration of sufentanil 2.5 μg kg$^{-1}$ resulted in decreases in systemic arterial pressure (mean systolic pressure $-25.3\%$; mean diastolic pressure $-29.0\%$) and heart rate (mean $-20.2\%$). There were no differences between the groups, and all patients responded promptly to the infusion of crystalloid.

Mean concentrations of sufentanil at incision were 1.40 (0.58) ng ml$^{-1}$ in the healthy anaesthetized group and 1.06 (0.75) ng ml$^{-1}$ in the transplant patients (ns). No patient showed somatic or autonomic response to the surgical incision. During surgery, five of 10 patients in the transplant group and one of eight healthy anaesthetized patients received volatile supplementation of anaesthesia ($\leq 0.6\%$ enflurane) at plasma concentrations of sufentanil between 0.20 and 0.78 ng ml$^{-1}$. At the end of surgery, extubation of the trachea was achieved uneventfully in 15 of the 18 patients (plasma sufentanil concentration 0.05–0.51 ng ml$^{-1}$). Three patients in the healthy group received naloxone 0.2 mg i.v. to initiate adequate spontaneous ventilation. Plasma concentrations of sufentanil at tracheal extubation in these patients were 0.22–0.31 ng ml$^{-1}$.

Table II lists the derived parameters calculated by the two methods of kinetic modelling, with the percentage binding of sufentanil to plasma proteins at a drug concentration of 0.5 ng ml$^{-1}$. The free fraction of sufentanil did not differ between the two groups. No correlation was observed between the sufentanil free fraction or binding ratio (bound/free fraction) and the alpha$_1$-acid glycoprotein (α$_1$-AGP) concentration ($r = 0.318$ and 0.386, respectively). Concentrations of α$_1$-AGP were slightly greater in the renal failure group (1.25 (0.84) v. 0.89 (0.24) g litre$^{-1}$), although this did not achieve significance. Despite the increased concentrations of α$_1$-AGP

![Correction plots comparing elimination half-life ($T_{1/2}$), clearance (Cl) and apparent volume of distribution at steady state ($V_{ss}$) determined by model independent method (M1) and extended non-linear least squares regression analysis (ELSFIT) for 18 patients. —— = Regression line; ——— = line of identity. Regression equations: $T_{1/2}$: ELSFIT = 1.231 M1 - 44.58; $r = 0.871$; $P < 0.01$. Cl: ELSFIT = 0.991 M1 + 46.38; $r = 0.981$; $P < 0.01$. $V_{ss}$: ELSFIT = 0.921 M1 - 2.34; $r = 0.897$; $P < 0.01$.](image)
in some patients in the renal transplant group, there was no correlation between \( \alpha_1 \)-AGP concentration and \( V_{ss} \) (total) for sufentanil. Serum albumin concentrations were similar in the two groups: 37.8 (4.3) and 41.7 (4.2) g litre\(^{-1}\), respectively.

Kinetic values for elimination half-life, clearance, apparent volume of distribution at steady state and mean residence time were similar in both groups. Based on the parameter estimates determined from the total drug concentrations by the model-dependent method (ELSFIT), there were also no differences in free (unbound) drug clearance or free drug apparent volume of distribution at steady state between the two groups (table III).

As there were no significant differences in data for the two groups, these have been combined to allow comparison of the two methods of kinetic analysis (table IV).

Although there were differences between the calculated values for the three main kinetic parameters, none achieved statistical significance and the slopes of the MI vs. ELSFIT plots (fig. 1) were not different from unity (the line of identity). This suggests good agreement between the two kinetic methods.

To examine if bias might exist between the two approaches, the difference between methods was compared with the average of the two methods (fig. 2). For all three parameters, there was wide dispersion of the values about the zero (ELSFIT–MI) intercept. For clearance and apparent volume of distribution, there was no
significant correlation between average value and difference, and the slope of the correlation lines was not different from zero. MI kinetic methods resulted in an overestimation of clearance and underestimate of the apparent volume of distribution at steady state. This indicates fixed bias between the kinetic methods. For elimination half-life, a significant correlation was observed between the methods ($r = 0.583; P < 0.02$), with the slope significantly different from the zero (ELSFIT–MI) intercept, indicating a variable bias between the two kinetic methods. However, this correlation was influenced by a single data set.

DISCUSSION

In this study, the kinetics of sufentanil did not differ between healthy anaesthetized patients and those with chronic renal failure. This conflicts with the clinical report of Wiggum and colleagues [6]. Although polymorphic drug oxidation has been proposed as a mechanism for altered drug metabolism in some patients receiving alfentanil [13,14], this is unproven, and there are no data to support such polymorphism for sufentanil metabolism. The variability of sufentanil clearance in the present study (37%, $n = 18$) is similar to that cited for other opioids [8, 9, 15]. The range of sufentanil concentrations at tracheal extubation (0.05–0.51 ng ml$^{-1}$) was similar to those reported previously [16–18]. There were no apparent differences in the concentration–effect relationship between healthy anaesthetized patients and those with chronic renal failure.

Although other studies have investigated the influence of renal failure on disposition of sufentanil, there are few data from within-study, between-group comparisons. Differences in sampling times and sites, assay methodology and data analysis render comparisons between separate studies less than satisfactory. Data from most studies in the healthy anaesthetized patient have indicated an elimination half-life of 140–200 min [19–23]; thus the shortened sampling time (180 min) of Davis and colleagues [24] tended to underestimate half-life and overestimate clearance. In addition, Davis investigated adolescent subjects (aged 10–15 yr); the age range of the patients in the present study was 13–65 yr. Within our population there was no observed age-related influence on drug kinetics.

Renal failure alters the plasma protein binding of many drugs [25, 26]. For acidic compounds, there is frequently a decrease in binding, although the binding of basic drugs shows greater variability. Thus for the anilino–piperidine opioids, Bower found no influence of uraemia on the binding of fentanyl [27], while others reported an increase in the alfentanil free fraction [28,29]. No effect of renal failure on sufentanil binding was seen in the present study, and hence no difference between patient groups in either free drug clearance or free drug apparent volume of distribution at steady state. It is unlikely, therefore, that chronic renal failure has a significant effect on drug dynamics.

In the present study, all transplanted kidneys showed immediate graft function. However, it is unlikely that this influenced significantly the disposition of drug in the renal failure group, as only 5–10% of the parent drug is excreted unchanged via the kidney [5].

Sufentanil, in common with fentanyl and alfentanil, binds to $\alpha_2$-AGP. However, there was no significant increase in the concentration of this acute phase protein in the patients with renal failure, and hence no relationship between the sufentanil free fraction and $\alpha_2$-AGP.

There have been many observations on factors influencing drug disposition during anaesthesia [30,31]. However, in comparing anaesthetic studies from healthy patients and those with renal failure or other diseases, little attention has been paid to the kinetic model from which parameters have been derived. The present data show no significant effect of the method of modelling on mean derived parameters. This is in agreement with other data [32,33]. However, the wide 95% confidence intervals of the means show the variation which may be introduced when comparing different methods.

Use of time-invariant mammillary modelling to define the behaviour of drug within a system depends on appropriate and adequate blood sampling to allow accurate derivation of the various micro-constants, in addition to presupposing the nature of drug distribution and metabolism. For any drug, distribution within the body may be considered in a number of different compartments. For a drug showing a biexponential decline in the concentration–time profile, a two-compartment kinetic model is assumed. There are, however, three possible and different models that may be defined for a given decay profile [34]. The advantages and inherent prob-
lems in compartmental modelling have been discussed elsewhere [35, 36].

Compartment independent analysis is a more robust method, as the parameter estimates are based on determination of the AUC and are therefore not sensitive to small fluctuations in the concentration–drug profile [37]; also there is an absence of need to define the various inter-compartmental rate constants, each dependent on the other, with progressively increasing errors and greater standard deviations [38]. These errors may be compensated for by use of advanced mathematical techniques, such as that described by Bower and Hull [39], but this involves significant computation. MI analysis is not dependent on such constraints, although one limitation of the method necessitates previous knowledge of the terminal rate constant (for calculation of the additional AUC and AUMC from the last data point to infinity), its calculation by the method of residuals (curve stripping), or its determination by linear regression analysis, with the analyst consigning the concentration–time point at which the terminal phase commences following visual inspection of the data.

Thus although there were only small differences between the mean parameter estimates calculated by the two kinetic methods, there was considerable variability when data were expressed as the 95% limits. When data from separate studies are compared, use of different methods of data handling may increase inter-individual variability above that produced by other factors (age, fitness, disease states, etc.), and lead to erroneous conclusions. If adequate sampling regimens have been adopted and the correct kinetic model defined, the use of compartmental approaches may be preferred—otherwise, model independent analysis should be used to define drug disposition.

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REFERENCES


BRITISH JOURNAL OF ANAESTHESIA

21. Gregoretti S, Vinik HR. Sufentanil pharmacokinetics in
burn patients undergoing skin grafting. *Anesthesia and Analgesia* 1986; 65: S64.


