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Disposition of alfentanil in patients receiving a renal transplant

S. BOWER, J. W. SEAR*, *Department of Anaesthetics, University of Newcastle upon Tyne, and *Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford, UK*

Abstract—The disposition of alfentanil has been investigated in 10 anaesthetized patients with chronic renal failure undergoing kidney transplantation and compared with eight age matched anaesthetized patients with normal renal function. Plasma samples were collected to 660 min following intravenous administration of alfentanil 3–5 mg (50 $\mu g\ kg^{-1}$). Drug concentrations were measured by RIA; and alfentanil binding to plasma proteins by equilibrium dialysis against 0·1 M phosphate buffer, pH 7·4. Alfentanil binding to plasma proteins was 87·6% (s.d. 2·0) in the patients with chronic renal failure, and 89·7% (1·2) in patients with normal renal function ($P = 0.025$). There was no correlation between alfentanil binding and plasma albumin, total plasma proteins, plasma urea or plasma creatinine concentrations. In both groups, the drug concentration-time profile decayed in a curvilinear manner; in the chronic renal failure patients, restoration of function did not influence the decay profile. Elimination half life, mean residence time and apparent volume of distribution at steady state were not different in the two groups of patients (mean values: 142·4 and 120·2 min; 128·5 and 136·0 min; and 40·5 and 27·6 L, respectively in chronic renal failure patients and patients with normal renal function). Total drug clearance and Vd area were significantly increased in the chronic renal failure patients: 341·9 vs 211·8 mL min^{-1}; and 69·3 and 35·5 L. There were no differences in intrinsic clearance or apparent volume of distribution at steady state for unbound drug between the two patient groups.

The pharmacokinetics of alfentanil have been described in healthy volunteers, and in patients undergoing surgery (Bower & Hull 1982; Bovill et al 1982; Camu et al 1982; Schuttler & Stoeckel 1982). There are also several reports of the influence of age, surgery or disease state on the disposition of alfentanil showing decreased clearance in the elderly and in the patient with cirrhosis (Bentley et al 1983; Helmers et al 1984; Meistelman et al 1984; Ferrier et al 1985).

Chronic renal failure causes decreased protein binding for many acidic drugs, such as thiopentone (Burch & Stanski 1982); while the binding of basic compounds in patients with renal failure shows more variability. Some drugs show unaltered binding (e.g. propranolol and sufentanil, Bianchetti et al 1976; Sear 1989), while that for morphine and fentanyl was decreased (Olsen et al 1975; Bower 1982). Existing data reporting the disposition of alfentanil in patients with chronic renal failure indicate an increased free fraction (Chauvin et al 1987a) and an unaltered total drug clearance, but a varied effect on elimination half life and volumes of drug distribution (Van Peer et al 1986; Chauvin et al 1987a). The influence of restoration of kidney function through immediate graft function might also affect drug disposition.

This study has therefore examined the binding and disposition of alfentanil when used as analgesic supplementation (in a single dose of approximately 50 $\mu g\ kg^{-1}$) to nitrous oxide in oxygen and enflurane anaesthesia in chronic renal failure patients receiving a transplant. The results were compared with data from anaesthetized, age-matched subjects with normal renal function undergoing lower abdominal or body surface surgery.

Materials and methods

18 patients, ASA I, II or III, were studied whilst undergoing renal transplant surgery (n = 10); or lower abdominal or body surface surgery (n = 8). The studies were approved by the local hospital ethics committee and by the committee for Safety of Medicines; all patients gave informed consent to participation in the studies.

Correspondence to: S. Bower, Department of Anaesthetics, Old Medical School, University of Newcastle upon Tyne, Newcastle NE1 4LP, UK.

Anaesthetic management of the patients undergoing renal transplantation. Patients were dialysed within 6–16 h before induction of anaesthesia. Each patient received diazepam 10 mg orally given 1·0–1·5 h before surgery. Anaesthesia was induced with thiopentone 4 mg kg^{-1}, and the trachea intubated after neuromuscular blockade with vecuronium (0·1 mg kg^{-1}). Patients were ventilated to normocapnia with an inspired gas mixture 67% nitrous oxide in oxygen, supplemented by enflurane (0·6%). Intraoperative analgesia was provided by alfentanil 3–5 mg (approximately 50 $\mu g\ kg^{-1}$) given i.v. over 20 s into the flowing peripheral infusion following the attainment of stable anaesthesia, but before the surgical incision.

Preoperatively, patients undergoing transplantation received 10–20 mL $kg^{-1}\ h^{-1}$ normal saline (0·154 M), frusemide 80 mg and mannitol 12 g at the time of renal revascularization. Postoperative fluid input was based on urinary output. Immunosuppression was provided by cyclosporin A, or azathioprine and prednisolone.

Anaesthetic management of patients with normal renal function undergoing lower abdominal or body surface surgery. Premedication and the conduct of anaesthesia were similar to that described for the patients with chronic renal failure undergoing transplantation. Alfentanil was given as a single dose of 3–5 mg i.v. Intra-operative fluid replacement was with Hartmann's solution 4–5 mL $kg^{-1}\ h^{-1}$.

Monitoring. Throughout anaesthesia, the ECG (and derived heart rate) were continuously monitored using leads in the CM_V configuration and the systolic and diastolic blood pressure measured using the DINAMAP automatic blood pressure recorder. In patients receiving a renal transplant, the central venous pressure was measured via a catheter in the internal jugular vein.

Assay of alfentanil in plasma. Blood samples (from central venous catheter or peripheral vein) were taken into lithium heparin tubes, and separated by centrifugation within 2 h of collection. The plasma was stored frozen at −20°C until analysed by a radio-immunoassay method (Bower & Hull 1982), having a sensitivity of 2 pg mL^{-1}. ^{3}[H]Alfentanil and rabbit anti-alfentanil antibody were obtained from Janssen Pharmaceutica BV, Beerse, Belgium. This antibody shows no cross-reactivity with any known metabolite of the parent drug (Michiels et al 1983). Each sample was assayed in duplicate.

Central venous (renal patients) or peripheral venous samples were collected at 0, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 480 and 660 min after drug administration.

Binding of alfentanil to plasma proteins. Alfentanil binding was measured at a concentration of 2 ng mL^{-1} in all 18 patients by equilibrium dialysis against 0·1 M sodium phosphate buffer at pH 7·4 and 37°C using a method similar to that described for fentanyl (Bower 1981).

Data analysis. Individual drug concentration-time profiles were subjected to non-linear least squares regression analysis to determine the terminal half life. The area under the curve (AUC) and its first moment (AUMC) were calculated using the linear trapezoidal method, and the apparent volume of distribution at steady state (Vdss), clearance (CL) and mean residence time (MRT) determined by a model independent method (Benet & Galeazzi 1979). Unbound drug clearance and unbound apparent volume of distribution at steady state were calculated from total drug clearance and volume of distribution divided by the unbound fraction. The results are expressed as mean (±s.d.) except where otherwise indicated. Kinetic variables between patient groups were compared using the two-tailed Mann-Whitney U test; and the relationship between these variables and various biochemical parameters (albumin, total plasma proteins, urea and creatinine concentrations) determined by linear regression.

Results

Demographic details of the 10 patients with chronic renal failure and 8 patients with normal renal functions are shown in Table 1. Preoperative plasma creatinine levels were 784 (s.d. 224) and 97 (23) μmol L^{-1}, respectively ($P < 0.001$) (normal laboratory range 70 to 150 μmol L^{-1}). The corresponding urea concentrations were 19·0 (7·2) (post-dialysis) and 4·3 (1·4) mmol L^{-1} (normal range 2·8 to 6·7 mmol L^{-1}) ($P < 0.001$). Immediate post operative 24 h creatinine clearance in the transplant patients varied between 0·5 and 224 mL min^{-1}; there was no relationship between this and plasma alfentanil clearance.

Table 1. Demographic details of the 18 patients studied (8 with normal renal function and 10 with chronic renal failure undergoing transplantation).

	Normal patients (n = 8)	Renal failure patients (n = 10)
Age (years)	44·0 (9·0)	34·6 (12·4)
M:F	3:5	6:4
Weight (kg)	66·4 (6·5)	64·7 (14·3)
Albumin (g L^{-1})	41·8 (5·3)	38·5 (4·2)
Total proteins (g L^{-1})	68·1 (7·2)	66·2 (6·7)

Data shown as mean (s.d.).

Table 2. Derived pharmacokinetic parameters for 8 anaesthetized patients with normal renal function, and 10 anaesthetized patients with chronic renal failure undergoing transplantation. Both groups received alfentanil 3–5 mg. i.v. over 20 s. Mean (s.d.).

	Healthy patients	Renal failure patients
Total drug kinetics:		
Elimination half life	120·2 (28·2)	142·4 (49·5)
Clearance	211·8 (55·6)	341·9 (159·5)*
Vdss	27·6 (5·2)	40·5 (18·1)
Vd area	35·5 (8·8)	69·3 (48·3)**
MRT	136·0 (31·9)	128·5 (42·4)
Free drug kinetics:		
Free fraction	10·3 (1·2)	12·4 (2·0)**
Clearance	2089 (614)	2556 (1123)
Vdss	272·9 (74·4)	323·7 (114·6)

Elimination half life—min; clearance—mL min^{-1}; Vdss and Vd area—litres; MRT—min; Free fraction—%.
** $P < 0.025$; and * $P < 0.05$.

There was a significant ($P = 0.025$) increase in the unbound fraction in the patients with renal failure (12·4% vs 10·3% in the anaesthetized patients with normal renal function). On combining the data from the uraemic patients and the patients with normal renal function, no significant correlations were found between albumin, or total protein and drug binding ($r = 0.08$ and 0·373, respectively); nor with the preoperative urea and creatinine concentrations ($r = 0.313$ and 0·488). For the renal failure patients alone, there was also no correlation between albumin or total proteins and alfentanil binding ($r = 0.404$ and 0·667).

In all patients, the drug concentration-time profile declined in a curvilinear manner. The transplanted kidneys were reperfused by between 1·25 and 5·5 h (median: 1·5) after the bolus dose of alfentanil. There was no change in the decay profile of the alfentanil with revascularization. No patient showed secondary peaks in the plasma alfentanil concentration. The derived kinetic parameters are shown in Table 2. There were no significant differences between the groups with respect to the elimination half life, mean residence time and Vdss when calculated using total drug concentrations. However, there was a greater total drug clearance ($P = 0.025$) and Vd area ($P < 0.05$) in the renal failure patients.

When Vdss and clearance were calculated in terms of unbound drug, there were no significances between the two patient groups. There were no correlations between any parameter and the plasma creatinine, urea, total proteins, or albumin.

Discussion

The disposition of opioid drugs such as morphine and pethidine may be altered in patients with chronic renal failure (Szeto et al 1977; Chauvin et al 1987b; Sear et al 1989). Because of the associated pathology, changes may be observed in protein binding, volumes of drug distribution, rates of drug elimination, or rates of metabolite excretion.

The plasma protein binding of alfentanil in renal failure patients pre-transplantation was less than that found in age-matched patients with normal renal function. As a result, total drug clearance and Vd area were increased, and there was a tendency towards a greater apparent volume of distribution at steady state.

The increased unbound drug cannot be explained by hypoproteinaemia, as albumin and total protein concentrations were unaltered in the renal failure group. As suggested by Chauvin et al (1987a), it is probable that accumulation of endogenous compounds or drug metabolites are responsible for the higher unbound drug fraction (Sjoholm et al 1976; Verbeeck et al 1981). Decreased plasma protein binding has also been demonstrated for other anaesthetic drugs in patients with renal failure (eg. thiopentone, diazepam, midazolam, morphine) (Ghoneim & Pandya 1975; Olsen et al 1975; Ochs et al 1981; Burch & Stanski 1982; Christensen et al 1983; Vinik et al 1983).

Bower (1982) has previously shown differences in fentanyl binding to plasma proteins in patients with uraemia. Increases in pre-B-lipoprotein and B-lipoprotein in hyperlipidaemic patients resulted in a significant increase in fentanyl binding. Multiple regression analysis also indicated significant correlations between % binding and serum albumin and total protein minus albumin concentrations. Plasma concentrations of urea and creatinine did not affect fentanyl binding. The binding of fentanyl in healthy volunteers was also unaltered over a wide concentration range (0·6 ng mL^{-1} to 10 mg mL^{-1}) (Bower 1981).

Although alfentanil binding was carried out on samples subjected to storage at −20°C, the formation of any precipitate would seem unlikely to significantly affect the percentage binding in either patient group—as the main precipitated

protein will be fibrinogen. This has not been shown to play an important role in the binding of drugs to plasma proteins.

In the present study, preoperative creatinine and urea concentrations did not influence alfentanil binding. In contrast to fentanyl, alfentanil showed no correlation (in all 18 patients or in the 10 chronic renal failure patients) between albumin and total plasma proteins and percentage binding. This is readily explainable as the main binding protein for alfentanil is not albumin, but rather α_1-acid glycoprotein (AAG) (Meuldermans et al 1982). Drug binding may also be affected by blood pH. Bower (1981) showed a decrease in fentanyl binding to both whole plasma and albumin under acidotic conditions, as a result of increased drug ionization. This has been confirmed by Meuldermans et al (1982), who have shown that a change in pH from 7·5 to 7·0 will result in a 52% increase in the free fraction for fentanyl. A similar pH change would only increase the free fraction for alfentanil by 6%. However, haemodialysis will tend to restore the acidotic renal patient back towards pH 7·4.

Most studies to-date in conscious volunteers and anaesthetized patients with normal renal function have indicated kinetic parameters similar to those in our control patient population. The differences for the patients with renal failure between our results and those of Van Peer et al (1986) and Chauvin et al (1987a) can be explained by alterations in pathophysiology.

The patient populations in this study and those of Chauvin et al (1987a) differ in respect of our patients having all been dialysed pre-anaesthesia and surgery, compared with only two of the nine in the French study. In renal failure, there is accumulation of endogenous inhibitors which compete with drugs for plasma protein binding sites, so resulting in decreased drug binding. These inhibitors include creatine-creatinine, methylguanidine, guanidinosuccinate, uric acid and some phenolic compounds—all of which will be removed by dialysis (Bowmer & Lindup 1982). Thus the unbound alfentanil fraction in the uraemic patients reported by Chauvin might be expected therefore to be significantly greater than that in the present study (19% as against 12·4%); the free fraction in the two healthy patient groups was similar (11% and 10·3%). In addition, use of heparin at the time of dialysis increases plasma free fatty acid levels. These acids act to decrease drug binding during dialysis, while a lower unbound fraction will be measured on inter-dialysis days.

In comparison, the data by Van Peer et al (1986) demonstrated a shorter half life in uraemic patients compared with controls, and smaller volumes of distribution (Vdss and $V\beta$). Plasma clearance was not significantly altered. These authors suggest that increased alfentanil binding in uraemic patients AAG may have been partly responsible for the smaller distribution volume of the drug; however, this has not been supported by binding studies. Henriksen et al (1982) have reported increased AAG concentrations in patients on chronic haemodialysis; although a previous study examining the disposition of sufentanil in patients undergoing renal transplantation did not find significantly increased AAG levels (Sear 1989). Our own plasma protein binding data has similarly not shown any increase in binding in the renal failure patients; rather renal failure was associated with an approximate 20% increase in the free drug fraction. Lack of any significant change in unbound drug clearance indicates intrinsic hepatic metabolizing capacity to be unaltered in renal failure, the kidney only playing a minor role in excretion of unchanged alfentanil from the body. Both Schuttler & Stoeckel (1982), and Meuldemans et al (1988) have shown less than 0·5% of an i.v. dose to undergo renal elimination. Hence the restoration of renal function during the sampling period in the chronic renal failure group would be unlikely to affect the plasma drug concentration-time profile or the derived kinetic parameters.

Ideally the blood sampling in both groups should have been from an arterial site—as this is the physiological driving force to drug distribution and elimination. However, ethical considerations precluded this. By the first sampling time point (2 min), adequate drug mixing and distribution will have occurred with no significant difference between central venous, peripheral venous and arterial drug concentrations (Major et al 1983). There are few data for first pass pulmonary uptake of opioids; although Taeger et al (1988) have shown a median first-pass uptake of 58% for alfentanil. However, by 2–3 min after injection, there was no significant mixed venous to arterial difference.

What are the clinical implications and consequences of our findings? There were no clinically significant alterations in total drug plasma clearance, elimination half life or apparent volume of distribution at steady state in patients with renal failure undergoing transplantation. The increased unbound drug presenting to the receptor sites may, however, increase the clinical efficacy of a given drug dose. Thus, as with all other opioids, dosage regimens titrating dose-to-effect rather than rigid regimens should be employed, to avoid overdosage and adverse side effects, when alfentanil is given to the patient with renal dysfunction.

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Bioavailability of isradipine in young and old rats: effect of mode of administration

F. L. S. TSE, J. M. JAFFE, A. E. HASSELL, H. F. SCHRAN, *Department of Drug Metabolism, Sandoz Research Institute, East Hanover, New Jersey 07936, USA*

Abstract—The bioavailability of isradipine has been examined in 7- and 52-week-old rats after oral (12·5 mg kg^{-1}) or intravenous (2·5 mg kg^{-1}) doses as a solution and administration of various doses (1·8–85·5 mg kg^{-1}) in the diet. Serial plasma samples were obtained from each rat and the drug concentration was determined by radioimmunoassay. Absorption from the dose given by gavage was rapid but when administered in a drug-diet mixture, isradipine appeared in the plasma slowly and in a manner reflecting the feeding pattern. Its absolute bioavailability from the drug-diet mixture averaged 3% over the dose range tested. By gavage its bioavailability was enhanced to 5% of dose with peak plasma values approximately 7 times higher than from a comparable dose in the diet. The low oral bioavailability of isradipine in the rat was most likely due to extensive first-pass metabolism. The decline in plasma concentrations was biexponential, with a mean terminal half-life of 3·6–3·7 h after oral or intravenous dosing. The pharmacokinetic characteristics of isradipine examined were independent of the age of the rat, except that its volume of distribution decreased with age. The older rats also showed a greater inter-animal variability in isradipine bioavailability from the drug-diet mixture.

In most toxicological studies in the rat, the test drug is administered either by gavage or by incorporation into the diet. There is ample evidence to show that the absorption and/or metabolism of some drugs may be affected by the mode of oral administration used. For example, while the absorption and bioavailability of captopril were greater after gavage than given in the diet (Singhvi et al 1981), continuous dietary administration of cefatrizine yielded higher, albeit later, peak plasma concentrations and greater overall bioavailability than the same single daily dose by gavage (Van Harken & Hottendorf 1978). In contrast, the bioavailability of *N*-acetylprocainamide (Kamath et al 1981) and the extent of absorption of fluperlapine (Dain & Jaffe 1988) were unaffected when administered in the diet compared with gavage.

Correspondence to: F. L. S. Tse, Department of Drug Metabolism, Sandoz Research Institute, East Hanover, New Jersey 07936, USA.

Isradipine is a dihydropyridine derivative with a potent calcium channel blocking activity (Cortes et al 1983; Hof & Rüegg 1988). In the present study, its bioavailability in the rat has been evaluated after oral and intravenous dosing as a solution, as well as various doses mixed in with the diet. The study was intended to provide pharmacokinetic information in support of the toxicity trials in this species. Because of the subchronic or chronic nature of the toxicity studies, and the potential effect of age on the absorption and disposition of some drugs (Kapetanovic et al 1982a, b; Yacobi et al 1983), both 7- and 52-week-old rats were used.

Materials and method

Animals. Male Sprague-Dawley rats (Charles River) of two different age groups (49–50 days, ca 250 g and 52 weeks, ca 500 g) were housed individually in metabolism cages at room temperature (25°C) and allowed free access to water and food (Purina rat chow) or a drug-diet mixture.

Dosing and plasma collection. i) *Drug-diet mixture.* The intended