Original Article

Pharmacokinetics of antimicrobial agents in anuric patients during continuous venovenous haemofiltration

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Abstract

Background. The optimal drug dosing in anuric patients undergoing continuous haemofiltration is a difficult task. More pharmacokinetic data is needed to derive practical guidelines for dosage adjustments.

Methods. Drug elimination of various antimicrobial agents (amikacin, amoxycillin, ceftazidime, ciprofloxacin, flucloxacillin, imipenem, netilmicin, penicillin G, piperacillin, sulphamethoxazole, tobramycin, vancomycin) was studied in 24 patients with acute renal failure treated by pump-assisted continuous venovenous haemofiltration (CVVH). Concentrations of serial blood and ultrafiltrate samples were determined by HPLC or by fluorescence polarization immunoassay. Total body clearance (CL) and haemofilter clearance (CL_f) rates were determined by standard model-independent equations. Data from published literature on fractions not bound to proteins (f_u), non-renal drug clearance fractions (Q_o), and normal clearance values (CL_n) were used to derive a pharmacokinetic model, taking into account drug removal by ultrafiltration and by non-renal clearance.

Results. A total of 37 treatment periods was studied. Blood flow through the haemofilters was 100 ml/min resulting in an average ultrafiltrate flow rate (UFR) of 13.2 ± 4.6 (range 3.2–22.1) ml/min. Acceptable correlations of calculated and measured haemofilter clearances and total body clearances were obtained.

Conclusions. Total body clearance in anuric patients during CVVH is predictable from drug properties, which are generally known. The individual dosage requirements may be calculated by multiplying $Q_o + f_u \cdot UFR/CL_n$ with the dose considered appropriate in the absence of renal impairment.

Key words: acute renal failure; antimicrobial agents; continuous venovenous haemofiltration; drug dosage; pharmacokinetics

Introduction

Continuous haemofiltration is a well-established tool in the treatment of patients with renal failure. However, despite good control of uraemia, acute renal failure is often associated with a high mortality rate [1]. Septicaemia frequently complicates the disease progression, and it has been identified as a major predictor of a poor outcome. Optimal drug dosing is thus essential in this situation but pharmacokinetic data during continuous renal replacement therapy are scarce. Complex mathematical models have been proposed [2,3], but their application in clinical practice is limited. The current methods to estimate drug removal through the haemofilter rely on sieving coefficients, i.e. average filtrate to blood concentration ratios [2–5]. These values, however, must be determined previously for each drug.

The aim of this study is to investigate the pharmacokinetics of various antimicrobial agents in patients with acute renal failure undergoing pump-assisted continuous venovenous haemofiltration (CVVH) and to derive practical guidelines for dosage adjustments.

Subjects and methods

Selection of patients

Anuric patients undergoing continuous renal replacement therapy and receiving antimicrobial chemotherapy were considered eligible for inclusion in the study. Drug clearance rates were measured during the CVVH in a total of 24 patients with acute renal failure due to various causes.

Haemofiltration

Pump-assisted CVVH was performed by a double-lumen subclavian catheter [1]. Blood flow through the polyamide hollow-fibre membrane filters (Gambro FH66) was set at 100 ml/min. The replacement fluid (Ringer's lactate) was administered in pre-dilution or post-dilution mode. The ultrafiltrate flow rate (UFR) was continuously monitored throughout treatment.

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Table 1. Dosage and median pharmacokinetic parameters observed in 24 patients during continuous venovenous haemofiltration

Drug	Number of patients	Number of intervals	Dose (mg)	Interval (h)	Half-life (h)	CL-total (ml/min)	CL-filter (ml/min)
Amikacin	2	2	600–800	24	15.6	26	16
Amoxycillin	3	3	600–1200	6–12	5.8	38	10
Ceftazidime	6	13	500–1000	6–13	13.2	20	5
Ciprofloxacin	2	3	200	6–12	7.5	231	14
Flucloxacillin	3	6	1000–2000	4–39	9.9	27	2
Imipenem	1	2	500	12	3.0	139	4
Netilmicin	6	10	40–200	24–72	13.9	20	12
Penicillin-G	1	2	1198	4	12.6	51	11
Piperacillin	8	16	1000–4000	4–12	10.6	56	10
Sulphamethoxazole	1[a]	1	400	12	9.9	65	10
Tobramycin	1	2	40	24	9.2	13	9
Vancomycin	3	4	500–1000	24–43	23.1	34	17
Total, range	37[b]	64	40–4000	4–72	2.3–139	9–286	1–27

[a] Trimethoprim concentrations in haemofiltrate were below the limit of detection (<0.2 mg/l) in this patient.
[b] Therapy consisted of 1–3 different drugs in individual patients, resulting in a total of 37 treatment periods.

Dosage and administration

Antibiotics were administered intravenously either alone or in combination (Table 1). The choice of antimicrobial therapy for each patient was based on clinical judgement only. The dosing interval was chosen according to the presumed half-life of the respective drug.

Up to three different drugs were administered to each patient during the study, resulting in a total of 37 evaluable treatment periods. In many cases, several subsequent dosing intervals per drug and patient were studied (64 totally) in order to obtain more reliable data and to ensure that a steady state was reached.

Specimen collection

Serial blood samples and pooled ultrafiltrate were obtained at various time points during the steady state. On the average, 11 ± 7 specimens were collected during each of the 37 treatment periods. The optimal timing of sample collection was determined individually depending on the drug to be studied and on the actual length of the dosing interval. Concentrations of imipenem were determined immediately due to its limited stability, while aminoglycoside and vancomycin levels were assayed within 24 h. All other serum and haemofiltrate samples were stored together with appropriate control standards at $-70°C$ for up to 3 months before being measured in batch.

Assay methods

Concentrations of beta-lactam antibiotics, ciprofloxacin, and sulphamethoxazole were determined by HPLC whereas the aminoglycosides and vancomycin were measured by a fluorescence polarization immunoassay (Abbott TDX).

Pharmacokinetic analysis

The timing of the doses, dosing intervals, duration of infusion, and the volume of the ultrafiltrate produced per time unit were recorded for each patient. A serum concentration versus time profile was plotted for each dosing interval and the area under the curve (AUC) was calculated by the log-

trapezoidal method. The amount of drug excreted through the haemofilter during one dosing interval was calculated from the volume of collected ultrafiltrate and the drug concentration in the ultrafiltrate. Standard model-independent equations were applied to calculate total body clearance (CL = Dose/AUC) and filter clearance (excreted amount/AUC).

Selected drug properties such as protein binding (unbound fraction f_u), non-renal drug clearance fraction (Q_o), and normal clearance values (CL_n) were derived from published literature [6–8] (Table 2).

Statistical methods

The correlations of calculated and measured clearances were determined by standardized principal component analysis [9], and by distribution independent regression analysis according to Passing and Bablok [10,11]. The latter model estimates confidence intervals for slope and intercept and tests for linearity by cusum statistics and by the run test. The performance of the prediction method was determined

Table 2. Selected drug properties used to predict total body clearance and haemofilter clearance [6–8]

Drug	f_u[a]	Q_o[a]	CL_n[a] (ml/min)
Amikacin	0.96	0.02	92
Amoxycillin	0.87	0.06	372
Ceftazidime	0.85	0.05	132
Ciprofloxacin	0.7	0.5	500
Flucloxacillin	0.2	0.3	83
Imipenem	0.75	0.3	233
Netilmicin	0.96	0.01	92
Penicillin-G	0.6	0.08	500
Piperacillin	0.84	0.25	182
Sulphamethoxazole	0.6	0.8	26
Tobramycin	1.0	0.02	77
Vancomycin	0.9	0.05	77
Range	0.2–1.0	0.01–0.8	26–500

[a] f_u, unbound fraction; Q_o, non-renal drug clearance fraction; CL_n, normal clearance.

by calculating bias and precision (root of mean squared differences) according to Sheiner and Beal [12].

Results

Twenty-four patients were included in the study. Approximately 50% of the patients experienced an acute renal failure due to various internal medical causes, e.g. septic shock, pneumonia, ARDS, pancreatitis, hepatorenal syndrome. One-third of the patients suffered from postoperative acute renal failure following either renal transplantation, combined renal and pancreas transplantation, or cardiac surgery. The remaining patients had multiple traumatic lesions or traumatic brain injury. Half of the patients were on the internal and half on the surgical intensive care unit. All patients were attended by a nephrologist.

The antimicrobial therapy used consisted of 12 different antimicrobial agents given in a wide variety of dosages either alone or in combination (Table 1). Serum and filtrate kinetics were studied during a total of 37 treatments (64 dosing intervals). The average ultrafiltrate flow rate was 13.2 ± 4.6 ml/min (mean $\pm$ SD, range 3.2–22.1).

Using the fundamental pharmacokinetic drug parameters observed in individuals without renal failure (Table 2), a theoretical model was derived which could be used to predict the clearance values. The measured haemofilter clearances and total body clearances were in good agreement with $f_u \cdot UFR$ and with $f_u \cdot UFR + Q_o \cdot Cl_n$ respectively. Figures 1 and 2 illustrate the distribution of the observed values. The quantity $f_u \cdot UFR$ was a good predictor of filter clearance (Table 3). The majority of the measurements deviated by less than 15%. Total body clearance was underestimated by $f_u \cdot UFR + Q_o \cdot Cl_n$ by an average of 7.6 ml/min. Deviations were <33%, however, in the majority of the 37 treatment periods.
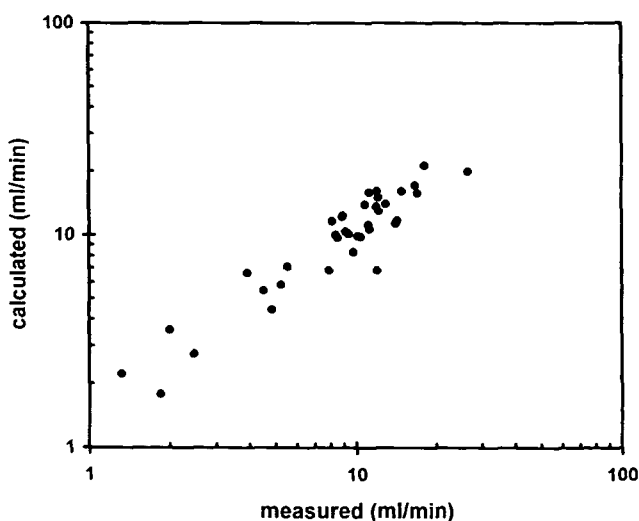

Fig. 1. Measured and calculated haemofilter clearance rates of 12 different drugs during continuous venovenous haemofiltration (calculated values were obtained from $f_u \cdot UFR$).
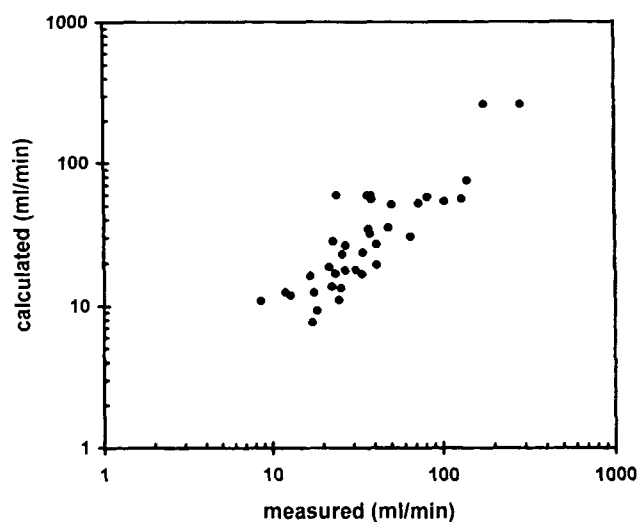

Fig. 2. Measured and calculated total body clearance rates of 12 different drugs during continuous venovenous haemofiltration (calculated values were obtained from $f_u \cdot UFR + Q_o \cdot CL_n$).

Table 3. Comparison of measured and calculated haemofilter clearance and total body clearance values during 37 treatment periods

Method	Filter clearance[a]	Total clearance[a]
Predictive performance [12]:		
bias (ml/min)	0.6 (−0.2, 1.4)	−7.6 (−16.4, 1.1)
precision (rmse[b])	2.4 (1.7, 3.0)	27.0 (14.0, 35.6)
Standardized principal component analysis [9]:		
slope	0.94	1.03
y-intercept (ml/min)	1.3	−8.9
Distribution-independent regression analysis [10, 11]:		
slope[c]	1.04 (0.87, 1.24)	0.81 (0.57, 1.05)
y-intercept[c] (ml/min)	0.56 (−1.3, 2.0)	−2.0 (−9.9, 5.7)

[a] 95% confidence intervals are indicated in parentheses.
[b] Root of mean squared prediction error.
[c] No statistically significant differences of slopes from 1 or of intercepts from 0 ($P<0.05$) and no significant deviation from linearity as determined by the cusum and run tests ($P>0.1$).

Comparison of the measured and calculated values for both haemofilter and total body clearance by distribution-independent linear regression analysis yielded slopes of approximately 1 and y-intercepts near 0 ml/min (Table 3). No significant deviation from linearity was found by the cusum and run tests ($P>0.1$).

Discussion

The existing mathematical models used to estimate drug elimination during continuous renal replacement therapy have recently been reviewed by Reetze-Bonorden *et al.* [5]. Sieving coefficients are frequently used to characterize the ability of a drug to pass through the haemofilter membrane. These values, how-

ever, have not been measured for all drugs used in patients with acute renal failure.

The approach presented in this study has the advantage that all parameters needed to estimate drug clearance are readily available. The convective transport from blood to ultrafiltrate was calculated from ultrafiltrate flow rate and unbound fraction alone, and the non-renal clearance was assumed to be the same as in patients without renal impairment. This simple model is far from being perfect. It is evident that protein binding may be altered in anuric patients and non-renal elimination may be impaired in these severely ill patients. Moreover, possible interactions due to multiple drug therapy may be responsible for pharmacokinetic alterations. It is conceivable also that a reduced hepatic clearance may be in part compensated by lower protein binding and consequently increased haemofilter clearance and vice versa.

Various statistical methods were used to compare predicted with measured haemofilter and total body clearances. Evaluation of predictive performance [12] has become usual practice; however, this method demands an independent variable presumed to be free of experimental error. Standardized principal component analysis [9] is a multivariate procedure, but normal distribution of the values is required. Regression analysis, according to Passing and Bablok [10,11], may overcome these drawbacks since it does not depend on an error-free variable or on rigid distributional requirements. In addition, this procedure tests for a linear relationship between the two variables, confidence limits are given for the slope and the intercept, and the influence of outliers is minimized.

The 12 drugs studied exhibited marked differences in their protein binding as well as in their non-renal contribution to total clearance. In addition wide ranges of dose, dosing intervals, and ultrafiltration rates were covered. Nevertheless in most patients the proposed formula $f_u \cdot UFR + Q_o \cdot CL_n$ provided a reliable estimate of the total drug clearance. The individual dosage requirements may be calculated in proportion to the ratio of total body clearance observed during CVVH and the normal clearance rate found in patients without renal impairment. Consequently the following formula may be used to predict the maintenance dose during renal replacement therapy.

$$Dose = D_n \cdot (Q_o + f_u \cdot UFR/CL_n)$$

where D_n denotes normal dose, CL_n normal clearance, Q_o non-renal clearance fraction, f_u unbound fraction, and UFR ultrafiltrate flow rate.

In conclusion, the results of the present study allow practical dosage recommendations to be made for anuric patients undergoing CVVH. Most drugs used in clinical practice have relatively low molecular weights, so that similar mechanisms of clearance during CVVH would be expected. It is therefore anticipated that the same dosage calculations will also be appropriate for the majority of other therapeutic agents. Monitoring serum concentrations, however, remains mandatory when using drugs which possess a narrow therapeutic range. Prospective studies are needed to evaluate the efficiency of these dosage guidelines and to study specifically whether the desired drug concentrations are achieved.

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