A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation

Jean Marie Conil,^{1,3} Bernard Georges,^{1,3} Michel Lavit,^{2,3} Jacky Laguerre,⁴ Kamram Samii,¹ Georges Houin^{2,3} & Sylvie Saivin^{2,3}

¹Service de Réanimation, Hôpital de Rangueil, Toulouse, ²Laboratoire de Pharmacocinétique et Toxicologie Clinique, Institut Fédératif de Biologie, 330 Avenue de Grande Bretagne, TSA 40031, 31059 Toulouse Cedex 9, ³Laboratoire de Cinétique des Xénobiotiques, UMR 181 Physiopathologie et Toxicologie Expérimentale (UPTE INRA-ENVIT), Faculté des Sciences Pharmaceutiques, 35 chemin des mara'chers, 31400 Toulouse and ⁴Service des brûlés, Hôpital de Rangueil, Toulouse, France

What is already known about this subject

- There is only one published study of the population pharmacokinetics of ceftazidime in burn patients. Only one covariate (plasma creatinine concentration) was found to contribute to the interindividual variability in the disposition of the drug.

What this study adds

- Three other covariables (creatinine clearance, mechanical ventilation and gender) have been added to a two compartment pharmacokinetic model incorporating multiplicative error, and these are able to explain much of the interindividual variability in ceftazidime disposition in burn patients.

Correspondence

Dr S. Saivin, Laboratoire de Pharmacocinétique et Toxicologie Clinique, Institut Fédératif de Biologie; TSA 40031, 330, avenue de Grande Bretagne, 31059 Toulouse Cedex 9, France.
Tel.: +33 5 6769 0367
Fax: +33 5 6769 0384
E-mail: saivin.s@chu-toulouse.fr

Keywords

burn patients, ceftazidime, population pharmacokinetics

Received

6 July 2006

Accepted

25 October 2006

Published OnlineEarly

23 February 2007

Aims

The aim of this study was to evaluate the disposition of ceftazidime in burn patients using a population pharmacokinetic approach, and to identify the clinical and biological parameters influencing its pharmacokinetics.

Methods

The development of the pharmacokinetic model was based on 237 serum ceftazidime concentrations from 50 burn patients. The determination of the pharmacokinetic parameters and the selection of covariates were performed using a nonlinear mixed-effect modelling method.

Results

A two-compartment model with first order elimination incorporating a proportional error model best fitted the data. Ceftazidime clearance (CL , $l\ h^{-1}$) was significantly correlated with creatinine clearance (CL_{CR}), and the distribution volume of the peripheral compartment (V_2 , l) was correlated with gender, mechanical ventilation and the CL_{CR} . The final model was defined by the following equations:

$$CL = 1.08 + 0.0536 \times CL_{CR}$$

$$Q \text{ (intercompartmental clearance)} = 6.88\ l\ h^{-1}$$

$$V_1 \text{ (distribution volume of the central compartment)} = 18.8\ l$$

$$V_2 = 2.69 \times (1 + 1.43 \times SEX) \times (1 + 2.44 \times VENT) \times (1 + 0.00414 \times CL_{CR})$$

Ceftazidime clearance was 6.1 and 5.7 $l\ h^{-1}$ for mechanically ventilated males and females, respectively, and 7.2 and 6.6 $l\ h^{-1}$ for nonventilated patients. The total volume of distribution was 31.6 and 49.4 l for mechanically ventilated males and females, respectively, and 22.8 and 28.1 $l\ h^{-1}$ for nonventilated patients.

Conclusions

We have shown that gender, mechanical ventilation and CL_{CR} significantly influence the disposition of ceftazidime in burn patients. Interindividual variability in the pharmacokinetics of ceftazidime was significant and emphasizes the need for therapeutic monitoring.

Introduction

Infection by *P. aeruginosa* can seriously jeopardise the prognosis for burn patients and necessitates rapid antibiotic treatment. Among the antibiotics available, ceftazidime remains the drug of choice, but its pharmacokinetics may be modified in such patients. Like other β -lactam antibiotics, the pharmacokinetics of ceftazidime are defined by high renal excretion and a volume of distribution similar to that of the extracellular space [1]. As ceftazidime is completely excreted by the kidneys, following glomerular filtration, 88% of the dose is recovered in the urine over 24 h [2]. Consequently, the changes in the glomerular filtration in the hypermetabolic phase after a burn injury probably affect the pharmacokinetics of ceftazidime [3].

During the hypermetabolic phase, beginning 48 h after the thermal injury, cardiac output increases as long as adequate intensive care has been given. This is accompanied by an increase in blood flow to the kidneys (with a corresponding increase in glomerular filtration rate) and liver [4]. There are few studies on the pharmacokinetics of ceftazidime in burn patients and in most cases only in a small number of patients. Only one study has investigated the pharmacokinetics of ceftazidime in burn patients using a population pharmacokinetic approach [5] in which substantial differences compared with other patients were observed, with high interindividual variability. The aim of our study was to evaluate the disposition of ceftazidime in burn patients who were in the hypermetabolic phase, and to identify clinical and biological determinants of its pharmacokinetics.

Methods

Subjects and sampling

After approval by the local ethics committee (Comité de protection des personnes pour la recherche biomédicale Toulouse I), our study was carried out on 50 patients in the Burns Unit of the University Hospital of Toulouse-Rangueil over a period of 4 years, after they had given their informed consent. Patients were studied during the secondary phase of their burn injuries. The antibiotics were prescribed for local infections or for sepsis either empirically (when the condition required immediate treatment) or following a bacteriological work-up. In patients with a documented infection, the organisms were identified and their sensitivity to antibiotics determined. The administration of ceftazidime was contraindicated in patients showing an allergy to cephalosporin antibiotics.

The patients were randomly divided into two groups. One group initially received a dose of 6 g ceftazidime 24 h⁻¹ given in three separate short perfusions of

2 g each every 8 h. The second group was given six doses of 1 g each every 4 h. The drug was administered as a 20 min infusion using an electric syringe. At the end of the infusion, the syringe was visually inspected to confirm that the correct dose had been administered. Blood was sampled at the troughs and peaks 24 h and 48 h after the start of the treatment. When the dosing regimen was changed for purposes of monitoring, further samples were taken for ceftazidime analysis. Ceftazidime was assayed within 24 h after blood sampling.

Ceftazidime analysis

Total serum concentrations of ceftazidime were measured by reversed-phase HPLC, using an Ultrasep RP 18–6 μ m, 250 $\times$ 4 mm column, a Spectra Physics Model AS 300 automatic injector, an ICS pump, and with UV detection at 260 nm (Shimadzu Model SPD 6 A detector). The mobile phase was 9 : 1 (v : v) 0.005 M KH₂PO₄ : acetonitrile, pH 3.5. The retention time was 20 min. Fifty μ l of internal standard (400 mg l⁻¹ cefepime) were added to 500 μ l of serum and protein was precipitated with 500 μ l of perchloric acid (0.8 M). Samples were centrifuged for 10 min (4000 g), 200 μ l of supernatant were removed and 25 μ l injected onto the HPLC system. The limit of quantification was 1 mg l⁻¹ and the calibration curve was linear from 1 to 100 mg l⁻¹ with a regression coefficient always greater than 0.995. The coefficient of variation at the concentration used to construct the calibration curve, and those in the three quality control samples (3, 25 and 75 mg l⁻¹) analyzed with each series was less than 15%.

Estimation of population parameters

Biological, clinical, and pharmacokinetic data were tabulated by using Excel software (Microsoft system). Creatinine clearance was determined by using the Cockcroft formula for men as follows:

$$CL_{CR} = \frac{(140 - \text{age}) \times \text{Weight}}{0.8 \times P_{CR}}$$

where plasma creatinine is expressed in μ mol l⁻¹, age in years and weight in kg. A correction factor of 0.85 was applied to women [6]. Indices specific to burn patients such as Baux [7], UBS [8], Tobiasen [9] and burn area were also recorded. The population pharmacokinetic analysis [10] was carried out using NONMEM and Visual-NM software. The predictive performance of the tested models was evaluated using the likelihood ratio and the Akaike criteria [11]. Measured concentrations (C_{obs}) were compared with the predicted concentrations (C_{pred}) by the paired *t*-test. Bias and precision were calculated using the method of Sheiner & Beal [12]. Bias

was determined as the mean prediction error, which is the mean difference between measured and predicted concentrations according to the expression:

$$\text{Bias} = \frac{1}{N} \sum_{i=1}^N C_{\text{pred}} - C_{\text{obs}}$$

where i refers to individual concentrations and N is the total number of values. Precision was calculated as the mean squared prediction error, which is equal to the mean of the sum of squared differences between the measured and predicted concentrations according to the expression:

$$\text{Precision} = \sqrt{\frac{1}{N} \sum_{i=1}^N (C_{\text{pred}} - C_{\text{obs}})^2}$$

One- and two-compartment models were evaluated on their ability to describe the pharmacokinetics of ceftazidime. Proportional and additive error models were assessed on their ability to describe the interindividual variability in pharmacokinetic parameters and the residual error, and a pharmacostatistical model was chosen. This was fitted to the data to obtain the population values (mean and variance), of total body clearance in l h^{-1} , and the distribution volumes of the central and peripheral compartments in l . Individual pharmacokinetic parameters were obtained by using the Bayesian maximum *a posteriori* estimator. NONMEM computed the objective function, which is proportional to twice the log-likelihood maximum. The influence of each covariate was then examined in the structural model. A decrease in the objective function value of more than 3.84 (corresponding to a χ^2 with 1 degree of freedom for a P value lower than 0.05) was required to identify a

covariate as being significant. A multivariate intermediate model was constructed with all the significant covariates. The final pharmacostatistical model was assessed by the independent deletion of each covariate from the previous model. A change in the objective function value of more than 10.83 (corresponding to a χ^2 with 1 degree of freedom for a P value lower than 0.0001) was required to retain a covariate.

Results

Fifty burn patients, with a total of 237 serum ceftazidime concentrations were included in the analysis, corresponding to a mean of 4.7 measurements per patient. Figure 1 shows the individual concentrations normalized to the mean daily dose kg^{-1} over time. The population characteristics are presented in Table 1. The patients were relatively old (age 52 ± 21 years) and badly injured (UBS = 65 ± 50), with mechanical ventilation being required in 32% of cases. Mean $\pm$ SD serum creatinine was in the normal range ($76.5 \pm 21.8 \mu\text{mol l}^{-1}$) as was the mean creatinine clearance ($105 \pm 39.3 \text{ ml min}^{-1}$) which showed considerable interindividual variability (range 33–191).

The initial values of the pharmacokinetic parameters that were used to initiate iteration algorithms were obtained from the work of Walstad *et al.* [13] on the pharmacokinetics of ceftazidime in burn patients.

Two models, a one-compartment model (ADVAN1-TRANS2) and a two-compartment model (ADVAN3-TRANS4), were studied.

The one-compartment model incorporating an error model showed a marked bias (-11.7 mg l^{-1}) described by the equation:

Figure 1

Ceftazidime concentrations vs. time in 50 burn patients. Concentrations were normalized to the mean daily dose per kg

Table 1Characteristics of the burn patients studied ($n = 50$)

	Mean $\pm$ SD	Range	CODE
<i>Quantitative variables</i>			
Age (years)	52.3 $\pm$ 20.7	15–90	AGE
Body weight (kg)	71.3 $\pm$ 13.5	50–108	WT
Burned surface area (% of the total body surface)	23.0 $\pm$ 13.5	10–62	BSA
Baux index	75.6 $\pm$ 22.4	30–122	BAUX
UBS index	64.8 $\pm$ 50.0	10–233	UBS
Tobiasen index	7.0 $\pm$ 1.8	4–11	TOBI
Serum creatinine ($\mu\text{mol l}^{-1}$)	76.5 $\pm$ 21.8	35–141	CREA
Creatinine clearance (ml min^{-1})	105.3 $\pm$ 39.3	33–191	CLCR
Proteinaemia (g l^{-1})	56.8 $\pm$ 7.1	38–69	PROT
BUN (mmol l^{-1})	7.3 $\pm$ 3.6	2–19	BUN
<i>Qualitative variables</i>			
Gender			
Men = 0; women = 1	38	12	SEX
Mechanical ventilation			
Without = 0; with = 1	34	16	VENT

$$\text{PRED} = 0.56 \times \text{DV} + 26.36 \quad (r^2 = 0.57)$$

where DV is the observed concentrations and PRED the predicted concentrations. The relationship between individual predicted concentrations (IPRED) and the observed concentrations follows the equation:

$$\text{IPRED} = 0.66 \times \text{DV} + 14.57 \quad (r^2 = 0.79)$$

with a bias of -2.93 mg l^{-1} . This model had an objective function of 1824.628.

Figure 2 represents the regression lines between the observed concentrations (DV or dependant variable) and predicted concentrations (PRED) starting from the population and individual (IPRED) parameters using a two-compartment model. The following equations describe this second model:

$$\text{TVCL} = \theta(1) \quad (1)$$

$$\text{TVV1} = \theta(2) \quad (2)$$

$$\text{TVQ} = \theta(3) \quad (3)$$

$$\text{TVV2} = \theta(4) \quad (4)$$

where CL = total body clearance in l h^{-1} , V1 = the distribution volume of the central compartment in l, V2 = the distribution volume of the peripheral compartment in l and Q = the distribution clearance describing ceftazidime exchange between the central and peripheral compartments.

Figure 2

Correlations between the predicted concentrations starting from the population (PRED) (A) and the individual predicted concentrations (IPRED) (B) and the observed concentrations (DV) based on a two-compartment model

The two-compartment model showed a less marked bias (-5.97 mg l^{-1}) of the adjustment than the preceding model, and is described by the equation:

$$\text{PRED} = 0.61 \times \text{DV} + 19.20 \quad (r^2 = 0.63).$$

The two-compartment model based on the individual predicted concentrations is described by the equation:

$$\text{IPRED} = 0.73 \times \text{DV} + 10.97 \quad (r^2 = 0.83)$$

with a bias of -1.88 mg l^{-1} . This model had an objective function of 1749.280 and showed a greater homogeneity in the distribution of the concentrations about the identity line. Overall, the two-compartment model gave the best fit to the data.

For this model, two tests of modelling of the error were carried out. The additive error model was described by the following equation:

$$\text{CL} = \text{TVCL} + \text{EXP}(\eta(1))$$

where η is the interindividual variance. In this model $\text{IPRED} = 0.6498 \times \text{DV} + 10.057 \quad (r^2 = 0.7829)$ with a bias of $+1.91 \text{ mg l}^{-1}$. However, the additive error model described the variability in the concentrations poorly.

The proportional error model was described by the equation:

$$\text{CL} = \text{TVCL} \times \text{EXP}(\eta(1))$$

The distribution of the residues (RES) (Figure 3A) and the weighted residues (WRES) (Figure 3B) according to the predicted concentrations (PRED) from the two-compartment model incorporating a proportional error model, is shown in Figure 3. In this model $\text{IPRED} = 0.7141 \times \text{DV} + 10.968 \quad (r^2 = 0.8362)$. The residues show a horizontal funnel-shaped distribution, typical of a multiplicative variability. The respective precisions were 20.5 for the additive model and 17.6 for the multiplicative model. The objective function was lower and the proportional error model was more accurate in describing residual and interpatient variability.

Our basic pharmaco-statistical model is a two-compartment model with a proportional error. It is characterized by the parameters given in Table 2. Mean clearance was 4.03 l h^{-1} with an interindividual variability of 27%, the distribution volume of the central compartment was 20.7 l (interindividual variability of 23%), intercompartmental clearance was 3.57 l h^{-1} (interindividual variability: 363%), and the distribution volume of the peripheral compartment was 128 l (interindividual variability: 190%). The residual variability including intraindividual variability and errors of measurement (sampling time, measured concentrations.) was 38%.

In a preliminary screening, the influence of covariates was examined one by one in this structural model. Many

covariates decreased the objective function and the inter-individual variability in the pharmacokinetic parameter. These were age, Baux index, creatinine clearance, serum creatinine, Na, pCO_2 , SaO_2 , alkaline phosphatases, body weight, proteinaemia, BUN, alkaline reserve, gender, transaminase, burned area, Tobiasen index and mechanical ventilation.

In the forward multivariate model-building, CL was mainly influenced by age, Baux index, creatinine clearance, gender, Tobiasen index, and mechanical ventilation. Age and gender were excluded because they were correlated with the creatinine clearance for which the best estimates were obtained. V1 was influenced by age, Baux index and alkaline reserve and V2 by creatinine clearance, serum creatinine, gender, mechanical ventilation, burned surface area and alkaline reserve. Q did not seem to be influenced by any of the covariates. In the backward elimination phase, only creatinine clearance influenced ceftazidime clearance, exceeding the objective function cut-off value of 10.83, when it was omitted individually from the model. V2 was influenced by gender, mechanical ventilation and creatinine clearance. The final model had an objective function of 1618.37 and is described by the following equations:

$$\text{TVCL} = \theta_1 + \theta_5 \times \text{CL}_{\text{CR}}$$

$$\text{TVV1} = \theta_2$$

$$\text{TVQ} = \theta_3$$

$$\text{TVV2} = \theta_4 \times (1 + \theta_6 \times \text{SEX}) \times (1 - \theta_7 \times \text{VENT}) \\ \times (1 + \theta_8 \times \text{CL}_{\text{CR}})$$

These equations can be transformed to:

$$\text{TVCL} = 1.08 + 0.0536 \times \text{CL}_{\text{CR}}$$

$$\text{TVV1} = 18.8$$

$$\text{TVQ} = 6.88$$

$$\text{TVV2} = 2.69 \times (1 + 1.43 \times \text{SEX}) \times (1 + 2.44 \times \text{VENT}) \\ \times (1 + 0.00414 \times \text{CL}_{\text{CR}})$$

with $\text{SEX} = 0$ for men and 1 for women, $\text{VENT} = 1$ if the burn patient was mechanically ventilated and $=0$ if not.

Interindividual variability in the clearance was decreased to 16% and that of the central volume of distribution to 13%. Mean values for the pharmacokinetic parameters based on creatinine clearance are shown in Table 3.

Figure 3

Distributions of the residues (A) and weighted residues (B) according to the predicted concentrations (PRED) based on a two-compartmental model incorporating a proportional error model

Pharmacokinetic parameters	Mean	Interindividual variability	Confidence interval
Clearance (L h^{-1})	4.03	27%	2.89–5.17
Distribution volume of the central compartment (l)	20.7	23%	17.4–24.0
Inter-compartmental clearance (L h^{-1})	3.57	363%	1.05–6.09
Distribution volume of the peripheral compartment (l)	128	190%	35–221

Table 2

Pharmacokinetic parameters obtained from the basic pharmaco-statistical model

Table 3

Mean pharmacokinetic parameters calculated from creatinine clearance data in ventilated and nonventilated patients

Parameters	Without mechanical ventilation		With mechanical ventilation	
	Males	Females	Males	Females
<i>n</i>	27	7	11	5
Creatinine clearance (ml min ⁻¹)	114	103	93	87
Clearance (l h ⁻¹)	7.2	6.6	6.1	5.7
Distribution volume of the central compartment (l)	18.8	18.8	18.8	18.8
Inter-compartmental clearance (l h ⁻¹)	6.9	6.9	6.9	6.9
Distribution volume of the peripheral compartment (l)	4.0	9.3	12.8	30.6
Volume of distribution (l)	22.8	28.1	31.6	49.4
Elimination rate (h ⁻¹)	0.384	0.350	0.323	0.305
Half-life (h)	1.81	1.98	2.15	2.27

Discussion

The data collected in this study over the dosing interval were best described by a two-compartment model, which is in agreement with previous observations [14].

Like Dailly *et al.* [5], we showed that a one proportional error model was the best predictor of residual and interpatient variability. A multiplicative model is usually better adapted when the variation in the concentrations is greater than a factor of 10. In the present study, the measured concentrations were between 1 mg l⁻¹, the limit of quantification of the method, and 214.7 mg l⁻¹.

In a previous study [15] we reported high interindividual variability in the trough concentrations of ceftazidime and its influence on glomerular filtration. In the current study, we found a total clearance and a volume of distribution close to that observed by Walstad *et al.* [13], corresponding to an increase in these parameters compared with healthy subjects. In the pharmacokinetic study of Walstad *et al.* [13], eight burn patients were studied at the beginning of the hypermetabolic phase. It found a linear relationship between creatinine clearance and renal clearance of ceftazidime, but not between creatinine clearance and the total ceftazidime clearance, indicating an enhanced extra-renal clearance of the drug (32%). We found no relationship between ceftazidime clearance and the burned area and the depth of burn injury. In the study of Walstad *et al.*, blood samples were taken during surgical procedures and in four of the patients, blood loss was considerable (more than 5 l replacement liquid was required) which may have led to a loss of drug and perturbation of renal function. The authors noted that the blood loss could have distorted the interpretation of the results.

The *trans*-burned area clearance described in burn patients [16–19] does not seem sufficiently important in

our study to be statistically significant. Zong *et al.* [16] demonstrated that concentrations of ceftazidime (1 to 21 mg l⁻¹) are well distributed in the exudates from the burn injury and are generally comparable with the blood concentrations. Whatever the fluid loss from these burned areas, the excretion of ceftazidime through exudates is numerically negligible compared with a clearance from 4 to 8 l h⁻¹.

Values for pharmacokinetic parameters obtained in the present study are different from those obtained from a population pharmacokinetic approach in 41 burn patients by Dailly *et al.* [5]. These authors showed an inverse linear relationship between the total clearance of ceftazidime and serum creatinine concentration. Such findings raise the question of the validity of using plasma creatinine concentrations in burn patients [20, 21]. In our study, the Bayesian approach showed a clear and significant relationship between ceftazidime clearance and creatinine clearance, which emphasizes the importance of renal function.

An elevated volume of distribution has also been reported in burns patients [5] and explained by an increase in the extracellular fluid volume. However, in the work of Dailly *et al.* [5], the average time between the burn injury and the administration of ceftazidime was 31.7 days, i.e. during the hypermetabolic phase. Extracellular fluid volume is significantly increased during the acute phase of the injury (the first 48 h) and decreases over the whole hypermetabolic phase. Our values of volume of distribution are in agreement with those in the literature [13, 16] in burn patients, corresponding to a two fold increase, compared with healthy subjects.

Moreover, it appears that mechanical ventilation also has an influence on the pharmacokinetics of ceftazidime. Such changes in the pharmacokinetics have been

described [22], particularly by Triginer during the use of gentamycin in critically ill adults without burn injuries [23]. The consequence of mechanical ventilation on ceftazidime disposition can be attributed to its effect on positive expiratory pressure (PEP), which could lead to a decrease in glomerular filtration rate [24] and an increase in the secretion of antidiuretic hormone responsible for the formation of oedema. This could also explain the variation in the volume of distribution. Mechanical ventilation increased the peripheral volume of distribution by a factor of 2.5 in both males and females. Mechanically ventilated patients are severely injured, and therefore the severity of the burn injury may be a confounding factor.

The distribution of the female population as a function of the area of the burn was homogenous; whereas the males were less badly injured than the females and were not similarly distributed according to the burned area. Even if gender is included in the Cockcroft formula, these parameters are poorly related ($r = 0.38$). The deletion of the covariable SEX led to a loss of information since it increased the objective function by 22.5, which correspond to a probability of 2×10^{-6} . As shown in Table 3, an influence of gender on the volume of distribution was found in all groups of burned patients in that the value was 1.2 times higher in females than males in nonmechanically ventilated patients, and 1.5 times higher in mechanically ventilated patients.

The maximum variation in half-life (22%) was observed between the nonmechanically ventilated women and men, whereas mechanical ventilation increased the half-life by 15% on average for both genders. Since the time necessary to reach steady state was only slightly altered and the half-life of ceftazidime was short, these differences are not clinically relevant.

This study highlights the complexity of ceftazidime pharmacokinetics in burn patients. We have shown that gender, mechanical ventilation and creatinine clearance significantly influence ceftazidime disposition in these patients.

These easily measurable covariates should be used to establish an optimal dosage regimen for ceftazidime. In particular, glomerular filtration rate is increased in burn patients, exposing them to the risk of plasma concentrations that are insufficient to exceed the MIC of many pathogens. In burn patients, the interindividual variability in ceftazidime pharmacokinetic parameters is significant, emphasizing the need for therapeutic monitoring.

The authors thank Professor J. Woodley for help with the English language.

References

- 1 Rains CP, Bryson HM, Peters DH. Ceftazidime. An update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1995; 49: 577–617.
- 2 Ljungberg B, Nilsson-Ehle I. Comparative pharmacokinetics of ceftazidime in young, healthy and elderly, acutely ill males. *Eur J Clin Pharmacol* 1988; 34: 179–86.
- 3 Weinbren MJ. Pharmacokinetics of antibiotics in burns patients. *J Antimicrob Chemother* 2001; 47: 720.
- 4 Loirat P, Rohan J, Baillet A, Beauvils F, David R, Chapman A. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. *N Engl J Med* 1978; 299: 915–9.
- 5 Dailly E, Pannier M, Jolliet P, Bourin M. Population pharmacokinetics of ceftazidime in burn patients. *Br J Clin Pharmacol* 2003; 56: 629–34.
- 6 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16 (1): 31–41.
- 7 Baux S. Thèse de Médecine. Paris; 1955.
- 8 Sachs A, Watson J. Four years' experience at a specialised burns centre. The McIndoe Burns Centre 1965–68. *Lancet* 1969; 1: 718–21.
- 9 Tobiasen J, Hiebert JH, Edlich RF. Prediction of burn mortality. *Surg Gynecol Obstet* 1982; 154: 711–4.
- 10 Beal SL, Sheiner LB. Estimating population kinetics. *Crit Rev Biomed Eng* 1982; 8: 195–222.
- 11 Ludden TM, Beal SL, Sheiner LB. Comparison of the Akaike Information Criterion, the Schwarz criterion and the F test as guides to model selection. *J Pharmacokinet Biopharm* 1994; 22: 431–45.
- 12 Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm* 1981; 9: 503–12.
- 13 Walstad RA, Aanderud L, Thurmann-Nielsen E. Pharmacokinetics and tissue concentrations of ceftazidime in burn patients. *Eur J Clin Pharmacol* 1988; 35: 543–9.
- 14 Richards DM, Brogden RN. Ceftazidime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985; 29: 105–61.
- 15 Conil J, Georges B, Fourcade O, Seguin T, Houin G, Saivin S. Intermittent administration of ceftazidime in burns patients: influence of glomerular filtration. *Int J Clin Pharmacol Ther* 2006; in press.
- 16 Zong G, Xiao G, Zhang Y. [The pharmacokinetics of ceftazidime in the burned patients]. *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi* 1994; 10: 385–8.
- 17 Lesne-Hulin A, Bourget P, Le Bever H, Ainaud P, Carsin H. [Therapeutic monitoring of teicoplanin in a severely burned patient]. *Ann Fr Anesth Reanim* 1997; 16: 374–7.
- 18 Lesne-Hulin A, Bourget P, Ravat F, Goudin C, Latarjet J. Clinical pharmacokinetics of ciprofloxacin in patients with major burns. *Eur J Clin Pharmacol* 1999; 55: 515–9.
- 19 Bourget P, Lesne-Hulin A, Le Reveille R, Le Bever H, Carsin H. Clinical pharmacokinetics of piperacillin-tazobactam combination

- in patients with major burns and signs of infection. *Antimicrob Agents Chemother* 1996; 40: 139–45.
- 20 Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, Colardyn FA. Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. *Nephrol Dial Transplant* 2005; 20: 747–53.
 - 21 Kellen M, Aronson S, Roizen MF, Barnard J, Thisted RA. Predictive and diagnostic tests of renal failure: a review. *Anesth Analg* 1994; 78: 134–42.
 - 22 Perkins MW, Dasta JF, DeHaven B. Physiologic implications of mechanical ventilation on pharmacokinetics. *Dicp* 1989; 23: 316–23.
 - 23 Triginer C, Izquierdo I, Fernandez R, Torrent J, Benito S, Net A, Jane F. Changes in gentamicin pharmacokinetic profiles induced by mechanical ventilation. *Eur J Clin Pharmacol* 1991; 40: 297–302.
 - 24 Annat G, Viale JP, Bui Xuan B, Hadj Aissa O, Benzoni D, Vincent M, Gharib C, Motin J. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. *Anesthesiology* 1983; 58 : 136–41.