Pharmacokinetic-pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis

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Aims Experimental studies have suggested that constant intravenous infusion would be preferable to conventional intermittent bolus administration of beta-lactam antibiotics for serious Gram-negative infections. Severe melioidosis (*Burkholderia pseudomallei* infection) carries a mortality of 40% despite treatment with high dose ceftazidime. The aim of this study was to measure the pharmacokinetic and pharmacodynamic effects of continuous infusion of ceftazidime *vs* intermittent bolus dosing in septicaemic melioidosis.

Methods Patients with suspected septicaemic melioidosis were randomised to receive ceftazidime 40 mg kg⁻¹ 8 hourly by bolus injection or 4 mg kg⁻¹ h⁻¹ by constant infusion following a 12 mg kg⁻¹ priming dose to perform estimation of pharmacokinetic and pharmacodynamic parameters.

Results Of the 34 patients studied 16 (59%) died. Twenty patients had cultures positive for *B. pseudomallei* of whom 12 (60%) died. The median MIC₉₀ of *B. pseudomallei* was 2 mg l⁻¹, giving a target concentration C_T, of 8 mg l⁻¹. The median (range) estimated total apparent volume of distribution, systemic clearance and terminal elimination half-lives of ceftazidime were 0.468 (0.241–0.573) l kg⁻¹, 0.058 (0.005–0.159) l kg⁻¹ h⁻¹ and 7.74 (1.95–44.71) h, respectively. Clearance of ceftazidime and creatinine clearance were correlated closely ($r=0.71$; $P<0.001$) and there was no evidence of significant nonrenal clearance.

Conclusions Simulations based on these data and the ceftazidime sensitivity of the *B. pseudomallei* isolates indicated that administration by constant infusion would allow significant dose reduction and cost saving. With conventional 8 h intermittent dosing to patients with normal renal function, plasma ceftazidime concentrations could fall below the target concentration but this would be unlikely with a constant infusion. Correction for renal failure which is common in these patients is Clearance = $k \star$ creatinine clearance where $k=0.072$. Calculation of a loading dose gives median (range) values of loading dose, D_L of 3.7 mg kg⁻¹ (1.9–4.6) and infusion rate I = 0.46 mg kg h⁻¹ (0.04–1.3) (which equals 14.8 mg kg⁻¹ day⁻¹). A nomogram for adjustment in renal failure is given.

Keywords: *Burkholderia pseudomallei*, ceftazidime, continuous infusion, melioidosis therapy, pharmacodynamics, pharmacokinetics

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Introduction

Recent appreciation of the differences in pharmacodynamic properties between different classes of antimicrobials has led to revised recommendations on dosing in

severe infections. The aminoglycoside antibiotics have a rapid killing action against Gram-negative bacilli, which is dose-dependent (indicative of a 'flat' concentration effect relationship, i.e. the effect is directly proportional to the dose through the whole of the dose range) and is associated with a prolonged postantibiotic effect (PAE) [1]. In contrast toxicity to the kidney occurs well within the therapeutic range and appears to be related to the duration for which plasma concentrations exceed a toxic threshold. This allows once daily administration compared with traditional twice or thrice daily dosing with gentamicin [2]. In contrast the beta-lactam antibiotics have relatively slower kill-rates sometimes preceded by a lag-phase. They have a relatively steep concentration effect relationship such that concentrations above the minimum bactericidal concentration (MBC) at the site of the infection convey no additional cidal effect. With the exception of the carbapenems, beta-lactam antibiotics also have little or no PAE against Gram negative organisms. Bacterial killing by the beta-lactams depends on the duration for which the serum concentrations exceed the MBC [3, 4]. These data argue in favour of administering the beta-lactam antibiotics either by continuous intravenous infusion or in frequent bolus doses so that the blood concentrations do not fall below the MBC during the dosing interval.

Intravenous bolus dosing and constant infusion of ceftazidime have been studied in serious Gram negative infections in animals [5]. Bolus administration produced significantly higher peak concentrations in liver and lung as well as serum, whereas higher concentrations were found in the kidneys during constant infusion. An *in vitro* pharmacokinetic-pharmacodynamic model of ceftazidime killing of *Pseudomonas aeruginosa* has suggested that achievement of sustained concentrations of drug, four times the minimum inhibitory concentration (MIC), by continuous infusion was more efficacious than intermittent dosing [6]. This has also been confirmed *in vivo* in intensive care patients [7]. Further arguments for the theoretical benefits of continuous infusion of beta-lactams have been reviewed recently [8, 9].

Melioidosis is a severe infection caused by the Gram-negative bacillus, *Burkholderia (Pseudomonas) pseudomallei*. Septicaemia is the most common clinical presentation of melioidosis [10]. Despite prolonged courses of high dose, ceftazidime, the current drug of choice, mortality remains high at 40% [11, 12]. *B. pseudomallei* can often be cultured from blood for many days after beginning intravenous treatment with intermittent bolus doses of beta-lactam antibiotics. Although conventional *in vitro* MIC/MBC assessment of ceftazidime indicates good activity against *B. pseudomallei* (MIC₉₀ 2 mg l⁻¹) [13], it was not significantly cidal over a 24 h period in a time-kill kinetic study [14]. As administration of ceftazidime by continuous infusion is preferable theoretically in the treatment of septic

meliodosis, we have conducted a prospective study of the pharmacokinetics and *in vivo* bacterial killing rates (pharmacodynamics) of ceftazidime given either by continuous intravenous infusion or by conventional 8 hourly intravenous injections.

Methods

Patients

Patients or their relatives gave fully informed consent to inclusion in this study, which was approved by the Ethical and Scientific Review subcommittee of the Thai Ministry of Public Health. As in previous studies [11, 12] adults (>14 years of age) admitted to the Department of Medicine, Sappasitprasong Hospital, Ubon Ratchatani, Thailand who were suspected clinically of having septicaemic melioidosis were included provided that they or their relatives gave fully informed consent to the study procedures. Pregnant women, patients who had already received effective antimicrobial therapy and those with known hypersensitivity to beta-lactam antibiotics were excluded.

Clinical and laboratory procedures were as described previously [11, 12]. Patients were weighed and blood was taken for measurement of plasma electrolytes, glucose, lactate, renal and liver function tests and coagulation indices. Arterial blood gases and pH were measured if indicated clinically. Three standard blood cultures (5 ml of blood in 50 ml brain-heart infusion broth (Tissue Culture Services, U.K.) and three pour-plate cultures (1 ml heparinized blood added to 19 ml molten (50°C) Columbia agar) for quantitative bacteriology [15] were taken immediately before administration of ceftazidime. Throat swabs, urine samples, pus from any wound or abscess, and sputum samples, were collected for culture on nonselective and selective media [16]. *B. pseudomallei* was identified as described previously [17].

Treatment

Patients were randomised to receive ceftazidime 120 mg kg⁻¹ day⁻¹ in normal saline; (Fortum[®], Glaxo, Greenford, UK) either by continuous infusion or intermittent bolus injection.

Group A: 40 mg kg⁻¹ every 8 h, i.e. three times daily by intravenous intermittent bolus injection.

Group B: 12 mg kg⁻¹ loading dose, followed by 4 mg kg⁻¹ h⁻¹ by constant rate infusion.

For a typical 50 kg patient Group A received 6 g day⁻¹ and Group B 5.4 g on the first day and thereafter 4.8 g daily. Parenteral treatment was given for a minimum of 10 days. Maintenance oral treatment with amoxycillin/clavulanic acid or the combination of cotrimoxazole,

chloramphenicol and doxycycline was then given as part of studies reported elsewhere [18].

The dose of ceftazidime was reduced in renal failure after the first dose by adjusting for serum creatinine according to the standard prescription information [19]. Other supportive treatment was given as indicated clinically.

Observations

Vital signs were recorded every 4 h and a detailed clinical examination was performed daily. Patients who did not prove subsequently to have culture-confirmed melioidosis were withdrawn from the study and treated with appropriate antimicrobial therapy. Blood samples (2 ml) for ceftazidime concentrations and pour plates for quantitative assessment of bacteraemia [15] were taken at the following times:

Group A (bolus): 0, 10 min, 30 min, 1 h, 2, 3, 4, 6, 8, 8 h 10 min, 16, 16 h 10 min, 24 h, 24 h 10 min and then daily peak and trough concentrations.

Group B (infusion): 0, 30 min, 1 h, 2, 3, 4, 6, 8, 12, 16, 24 h and then 12 hourly.

Pour-plate blood cultures were repeated at 24 and 72 h. Heparinized blood samples were centrifuged. Plasma was separated and stored at -20°C for 1 month then -70°C until analysis.

Ceftazidime measurement

All sampling was discontinued when blood culture/pour plate became negative after a minimum of 48 h incubation. Patients then continued with standard bolus ceftazidime or another antibiotic regime as appropriate. Plasma concentrations of ceftazidime were measured by h.p.l.c. as described previously with a level of detection of 0.1 mg l^{-1} and a interassay coefficient of variation of 4% at concentrations of 0.5 mg l^{-1} [20].

Analysis

The plasma concentration-time series were analysed using WinNonlin 1.1 (Statistical Consultants Inc., Kentucky, USA 1996) and pharmacokinetic models chosen on the basis of minimization of the Aikake Information Criterion (AIC). Simple one-compartment models provided the best fits to the plasma ceftazidime concentration-time data. Standard pharmacokinetic parameters were generated and the medians, maxima and minima of these derived parameters, total apparent volume of distribution (V_z) and first order elimination rate constants (K_{10}) were then used to model data to explore relationships with the measured MIC of the patients' own *Burkholderia pseudomallei* isolates [13]. Ceftazidime clearance was calculated

from the formula $CL = V_z \star K_{10}$. Creatinine clearance was estimated by the method of Cockcroft & Gault [21]. Although not as reliable as measuring creatinine clearance directly this formula has been validated in an Asian population [22].

Normally distributed continuous data was compared using Student's *t*-test. Data not conforming to a normal distribution were compared using the Mann-Whitney *U*-test and correlations were by the method of Spearman. Proportions were compared using the χ^2 test with Yates' correction. Survival rates were plotted using the Kaplan-Meier method and compared using the log rank test. Linear regression was by the least squares method and a forward and backward stepwise multiple logistic regression model was used to examine the influence of pre-existing patient variables listed in Table 1 upon the derived pharmacokinetic parameters. All analyses were performed using the statistical computing package SPSS for Windows, version 6.1 (SPSS Inc., Chicago, U.S.A.).

Results

Between June and October 1993 34 patients were entered into the study. Data from 21 were suitable for pharmacokinetic analysis. Of these 21, five patients had culture proven melioidosis but were not septicaemic, 15 patients had septicaemic melioidosis of whom seven had positive pour-plate cultures (i.e. $>0.33\text{ cfu ml}^{-1}$ blood), and six did not prove to have melioidosis. Two of the six 'nonmelioidosis' patients had other Gram-negative septicaemia (one *Escherichia coli* and one *Klebsiella pneumoniae*). The other four were blood culture negative, two patients were HIV antibody positive and three patients had culture negative pneumonias. The demographic details of the 15 patients with melioidosis were similar to those with other diagnoses (Table 1). The overall mortality was 59%. Twelve (60%) of the patients with melioidosis and 4 (57%) of the nonmelioidosis patients died. The mortality in the melioidosis pour-plate positive group ($>1\text{ cfu ml}^{-1}$) was 82% ($P < 0.001$). There was no difference between the bolus and infusion groups by survival analysis (log rank $P = 0.89$). All of the 24 isolates of *B. pseudomallei* were sensitive to ceftazidime *in vitro* with a median (range) MIC of 2 mg l^{-1} (0.3–4), i.e. a target concentration of 8 mg l^{-1} would be required to achieve the median $4 \times \text{MIC}$.

Pharmacokinetics

Eighteen patients received ceftazidime by constant rate infusion and 14 by intermittent bolus injections. However, in only 10 of the infusion group and 11 of the bolus group could the pharmacokinetic parameters be derived adequately. This was because plasma drug-concentration

Table 1 Clinical features on admission (median/range).

	Bolus (n = 11)	Infusion (n = 10)	Excluded * (n = 13)
Age (years)	43 (27–73)	48 (29–58)	54 (18–67)
Sex F:M	7:4	1:9	10:3
Weight (kg)	50 (45–65)	48 (40–64)	50 (35–75)
Blood culture positive	5	3	6
Pour plate positive	7	4	9
Blood culture negative	0	4	1
Not-melioidosis	4	2	3
Deaths	9 (82%)	3 (30%)	11 (85%)
Time to death (h)	60 (8–240)	34 (20–624)	10 (1–624)
Serum creatinine (mg dl ⁻¹)	2.8 (0.8–10.4)	1.55 (0.9–13)	3.4 (1–7.2)
(Normal range: 0.8–1.7 mg dl ⁻¹)			
Estimated creatinine clearance (ml min ⁻¹)	23 (8–94)	38 (5–69)	21 (8–50)
APACHE II score	21 (9–27)	15 (3–23)	12 (3–24)
Temperature (°C)	39.8 (37.5–41)	40 (36.5–40.5)	40.5 (36.9–39.8)
Duration of previous symptoms (days)	8 (4–30)	14 (5–130)	10 (3–180)

* Eight patients received an infusion and five patients boluses of ceftazidime, exclusion as detailed in methods.

profiles fluctuated considerably, often within dosing intervals, in patients who died within 48 h and derived pharmacokinetic parameters could not be estimated reliably. There was no significant difference in peak and trough plasma ceftazidime concentrations at 8 h between those patients who survived (peak 182 (130–252) mg l⁻¹ trough 44 (2–126) mg l⁻¹) and those who died in the bolus group (peak 187 (72–552) mg l⁻¹ trough 61 (2–343) mg l⁻¹). Similarly there was no significant difference for those given ceftazidime by infusion. (survived 35 (19–43) mg l⁻¹; died 116 (49–136) mg l⁻¹). All of the melioidosis patients in both groups had ceftazidime concentrations above the target concentration C_T throughout the study. The higher concentrations in the fatal cases reflect the greater degree of renal impairment. Two patients without melioidosis had trough levels below the C_T .

Overall in those patients who received bolus administration and whose plasma drug concentration–time data could be analysed, median peak plasma ceftazidime (C_{max}) was 194 mg l⁻¹, and ranged between 553 and 147 mg l⁻¹ at 8.17 h. The median trough (pre dose) value at 8 h was 48 mg l⁻¹ ranging between 1.8 and 344 mg l⁻¹. For the infusion recipients plasma ceftazidime concentrations ranged between 7 and 212 mg l⁻¹. At 30 min after starting the study the ceftazidime concentrations in the infusion group patients were significantly lower than the bolus concentrations ($P=0.006$ for culture positive and $P=0.05$ for culture negative patients) however, by 8 h there was no significant difference. In those patients in whom pharmacokinetic parameters could be estimated reliably there were no significant differences for volume of distribution, systemic clearance, or elimination rate constant when comparing administration methods (bolus

vs infusion). There was also no significant difference for the values between those patients who had or did not have culture proven melioidosis (Table 2). There was a linear relationship between estimated creatinine clearance and ceftazidime clearance ($r=0.71$) (Figure 1). From the fitted linear regression model the y-intercept of the graph of ceftazidime clearance *vs* creatinine clearance was not significantly greater than zero (intercept mean (95% CI) 0.014 (–2.318–2.345) $P=0.99$; slope 0.072 (0.018–0.126) $P=0.014$) providing no evidence for nonrenal clearance of ceftazidime. In a forward stepwise linear regression model with the admission variables in Table 1 as the independent variables and ceftazidime clearance as the dependent variable, the estimated creatinine clearance accounted for 53% of the variation in ceftazidime clearance in these patients. No other factors contributed significantly. Using the median, maximum and minimum values of the derived parameters the simulated models of infusion and bolus administration were compared (Figure 2). The two patients who had trough concentrations below the median MIC₉₀ of *B. pseudomallei* did not have culture proven melioidosis. The predicted range of plasma concentrations ceftazidime for the intermittent bolus injection regimen fell just below 8 mg l⁻¹ (4 × MIC) before dosing. Reducing the dose interval to 6 hourly did not improve this (data not shown).

Pharmacodynamics

Fourteen patients with melioidosis and bacteraemia >1cfu ml⁻¹ (i.e. who were pour plate positive for *B. pseudomallei*) were studied. Four of these patients did not have a simultaneous pharmacokinetic study. Six patients received bolus injections and eight received infusions. The

Table 2 Pharmacokinetic parameters (median, range) of ceftazidime following bolus injection or constant infusion.

	Overall (n = 21)	Bolus (n = 11)	Infusion (n = 10)
V_z (l kg ⁻¹)	0.468 (0.241–0.573)	0.450 (0.254–0.573)	0.486 (0.241–0.569)
K_{10} (h ⁻¹)	7.53 (0.93–21.3)	3.48 (0.93–21.3)	11.58 (7.2–15.72)
AUC (mg l ⁻¹ h)		1496 (251–8834)	
$t_{1/2,z}$ (h)	7.74 (1.95–44.71)	11.89 (1.95–44.71)	3.59 (2.65–5.78)
C_{ss} (mg l ⁻¹)		75.5 (34–89.5)	
C_{max} (mg l ⁻¹)		89.6 (69.8–157.5)	
CL (l kg ⁻¹ h ⁻¹)	0.058 (0.005–0.159)	0.027* (0.005–0.159)	0.089* (0.038–0.125)

* $P < 0.05$ Mann–Whitney U -test comparing bolus *vs* infusion groups.

original objective of the study to compare bacterial clearance rates between the two regimens could not be fulfilled because the overall mortality was so high in pour plate positive patients; only one patient survived and only three became pour plate negative before death. The median (range) bacteraemia of *B. pseudomallei* at time of entry to the study in this poor prognosis subgroup was 75 (1–2045) cfu ml⁻¹ and the median (range) time to death was 25 (2–480) h. There were no significant differences between the two treatment groups in terms of entry criteria although the continuous infusion group had slightly lower APACHE scores and also lower predicted mortality. The fractional fall in *B. pseudomallei* count (cfu ml⁻¹) at 8 h (i.e. before the second dose of ceftazidime) as a percentage of the initial count was significantly different between the groups. The bolus group increased slightly with a median (range) of 0.5% (19.5% increase to 4% decrease) whereas all of the infusion group patients' counts fell with a median of 7% range (0–13% decrease) $P = 0.025$ (Figure 3).

Discussion

Melioidosis is a major cause of community-acquired septicaemia in south-east Asia. In the province of Ubon Ratchatani in north-eastern Thailand the annual incidence of melioidosis is 4.4 per 100 000, and septicaemic melioidosis accounts for 19% of all community-acquired septicaemias admitted to hospital [10, 23]. The infection is thus a major cause of death in this region. The use of ceftazidime (given in intermittent high-dose boluses) has reduced the mortality of melioidosis from $\approx 80\%$ to 40% [11]. However, the mortality in patients with quantifiable bacteraemias (i.e. > 1 cfu ml⁻¹) remains very high [15] despite prompt and appropriate treatment. Ceftazidime treatment of melioidosis is very expensive (approximately \$100 a day or over 20 times the minimum daily wage in this area) and must be given for at least 10 days, imposing a considerable financial burden on the local health services. The objective of this study was to devise the optimum cost-effective intravenous regimen for ceftazidime admin-

istration in severe melioidosis on the basis of pharmacokinetic and pharmacodynamic measures.

In healthy volunteers the mean total apparent volume of distribution of ceftazidime is between 15 and 20 l (i.e. 0.2–0.3 l kg⁻¹) [24], and with normal renal function, the elimination half-life is usually between 1 and 3 h. Women have a slightly smaller total apparent volume of distribution for ceftazidime than men [25], and systemic clearance is reduced with age, partly as a result of decreased renal function [26]. In this study of severe melioidosis, as in other studies, the predominant route of ceftazidime clearance found to be renal elimination accounting for between 52% and 96% of total plasma clearance [27, 28]. Ceftazidime is a widely used antibiotic particularly for the treatment of *Pseudomonas* infections in patients with cystic fibrosis [29]. In this group of patients both volume of distribution and renal clearance are increased. This has been attributed to fever-induced increases in renal blood flow. However, in more severely ill patients who do not have cystic fibrosis renal blood flow [30], as a fraction of cardiac index, is not increased.

Previous studies of ceftazidime pharmacokinetics in severely ill patients show a wide variation in estimated clearance and volume of distribution [31–33] although in

Figure 1 Ceftazidime clearance *vs* estimated creatinine clearance.

Figure 2 Models derived using derived pharmacokinetic parameters. (Maxima, minima and median values from bolus (dotted lines) and infusion (dashed lines) groups in the simulation modules in Winnonlin. Also shown is minimum inhibitory concentration (MIC).

every study, including the present one, renal function remains the major determinant of ceftazidime clearance. The pharmacokinetic properties of ceftazidime in Thai patients with septicaemic melioidosis were similar to those reported previously in patients with other causes of shock and renal failure. Total apparent volume of distribution was larger than in healthy subjects, and systemic clearance was reduced – largely as a result of renal impairment which is very common in septicaemic melioidosis. The difference in clearance between the bolus and the infusion groups probably results from the slight difference in creatinine clearance at randomization. The ratios of estimated ceftazidime to creatinine clearance were similar. In a multiple regression model of the factors influencing ceftazidime clearance, estimated creatinine clearance contributed most to the variation seen in this patient group. The APACHE scoring system does take into account creatinine clearance but also other measures of severity of illness [34]. In this series the APACHE score consistently underestimated the risk of death of these patients. This may be due to differences in the availability of intensive support available in this area. Approximately 1% of ceftazidime clearance is through biliary excretion. Previous studies in chronic liver failure and in cirrhosis have shown changes in volume of distribution resulting in

shortened elimination half-times with no overall change in total body clearance [35, 36]. There was no evidence for significant nonrenal clearance in this study [37]. Although the patients in the study with severe melioidosis were hypoalbuminaemic, this is unlikely to have affected the disposition of ceftazidime as plasma protein binding is low ($\approx 17\%$) [38, 39].

There has been debate recently about optimization of ceftazidime delivery in critically ill septic patients. It is generally considered that continuous infusion is superior to intermittent bolus dosage in terms of a more favourable time concentration profile. Young *et al.* [40] found trough concentrations of ceftazidime below the median MIC for *P. aeruginosa* given intermittent bolus dosing in over half of 7 critically ill patients studied. All had normal renal function. In our study only 2 patients, neither of whom had melioidosis, had plasma ceftazidime concentration below the MIC for *B. pseudomallei*. The renal failure associated with melioidosis ‘protects’ against low trough concentrations. Benko *et al.* [41] also found continuous infusion always maintained serum concentrations over the MIC whereas with the bolus administration concentrations fell below MIC for 8% of the time. The present study had similar findings. Modelling these data it can be predicted that large bolus dosing will give plasma

Table 3 Nomogram for reduction of ceftazidime dose in renal failure.

Estimated creatinine clearance (ml min^{-1})	Bolus dosage (total in 24 h)	Loading dose for infusion (mg kg^{-1})	Infusion rate ($\text{mg kg}^{-1} \text{ h}^{-1}$) (total over 24 h)
50	40 mg kg^{-1} every 8 h (120)	4	3.6 (90.4)
31–50	20 mg kg^{-1} every 12 h (80)	4	1.8 (47.2)
15–30	20 mg kg^{-1} every 24 h (20)	4	1.1 (30.4)
< 15	10 mg kg^{-1} every 24 h (10)	4	0.8 (23.2)

Bolus dosage (loading dose in mg kg^{-1} and dose interval, total dose (mg kg^{-1}) over 24 h in brackets). Infusion dosage (loading dose in mg kg^{-1} and infusion rate, total dose (mg kg^{-1}) over 24 h in brackets).

concentrations below the median MIC for *Burkholderia pseudomallei* for of a small fraction the dosing interval when renal function is normal (Figure 2). It remains unclear whether would have an adverse effect on outcome, since although the original objective of these studies was to relate pharmacokinetic parameters to pharmacodynamic measures, this could not be achieved because of the high mortality in patients with quantifiable bacteraemias. Previous studies with *P. aeruginosa* [6, 42] have suggested that sustained achievement of plasma concentrations at or above four times the MIC for the infecting organism provides optimum therapeutic effect, but there are no comparable data for *B. pseudomallei* – a bacterium which is genetically much closer to *B. cepacia* than to *P. aeruginosa*. *B. pseudomallei* is intrinsically resistant to many antibiotics and even relatively resistant to those antibiotics that do have *in vitro* activity.

Since creatinine clearance is the major determinant of ceftazidime clearance dose reduction is recommended when renal function is impaired. Although the therapeutic ratio is very wide neurotoxicity (seizures) has been reported in patients with renal failure [43]. Calculation of the dose reduction for a continuous infusion necessary in renal impairment is relatively simple (see Appendix). At very low values of renal clearance the nonrenal component may become significant.

Perhaps the main advantage of giving ceftazidime by a constant infusion, provided that equipment such as infusion pumps or infusion chambers are available, is a significant cost saving. Simple infusion devices have already been used successfully to deliver continuous infusions of ceftazidime in the United States [44] and in Northern Australia where melioidosis is also endemic. (B. Currie, personal communication). The average saving in a 14 day course of intravenous treatment of melioidosis in patients with unimpaired renal function would be 16.2 g of ceftazidime or 19% of the overall dose. This would amount to a cost saving per patient of 8800 Thai baht or \$220 at current prices while still maintaining blood antibiotic concentrations well above four times the MIC. There would also be savings in nursing staff time and costs for preparation and administration of a single infusion rather than three doses of drug. Drug administration by a single simple intravenous infusion set such as that used in Australia would not add to the costs since there would only be one used per day as opposed to three.

We thank the medical and nursing staff of the Department of Medicine, Sappasitprasong Hospital for their help in performing this study and Mr S. Langla for technical assistance. This study was part of the Wellcome-Mahidol University, Oxford Tropical Medicine Research Programme, funded by the Wellcome Trust for Great Britain.

Appendix

Calculation of a loading dose, infusion rate and dose reductions in renal failure

Calculation of the loading dose (mg kg^{-1}) is from the equation: $D_L = C_T \star V_{z,ss}$ (where C_T is the target concentration (mg l^{-1}) and $V_{z,ss}$ the volume of distribution at steady state (l kg^{-1})). Calculation of the infusion rate is: $I = C_T \star CL$ (where CL is ceftazidime clearance which equals $0.072 \star \text{estimated creatinine clearance} + 0.014$). This gives median (range) values of $D_L = 8 \star 0.468 = 3.7 \text{ mg kg}^{-1}$ (1.9–4.6) and $I = 8 \star (0.072 \text{ CL}_{Cr} + 0.014) = 3.6 \text{ mg kg}^{-1} \text{ h}^{-1}$ (0.4–13) for a creatinine clearance of 100 ml min^{-1} . This equals a total infusion dose of 90 as compared with $120 \text{ mg kg}^{-1} \text{ day}^{-1}$. This is shown as a nomogram in Table 3.

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