Continuous infusion ceftazidime in intensive care: a randomized controlled trial

J. Lipman*, C. D. Gomersall†, T. Gin*, G. M. Joynt* and R. J. Young*

*Royal Brisbane Hospital, Division of Anaesthesiology and Intensive Care, University of Queensland, Brisbane, Australia; †Prince of Wales Hospital, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Hong Kong; Department of Anaesthesia, Christchurch Hospital, Christchurch, New Zealand

We randomized 18 critically ill patients to receive ceftazidime 6 g/day by continuous infusion or bolus dosing (2 g 8 hourly), each with a loading dose of 12 mg/kg ceftazidime. During the first 8 h, plasma ceftazidime concentration fell below 40 mg/L in only one patient (trough 38 mg/L) from the infusion group, compared with eight from the bolus group (2–33 mg/L) for periods ranging from 73 to 369 min. Thereafter all infusion patients remained above 40 mg/L for 40 h of study versus 20–30% of bolus patients. The pharmacokinetic and pharmacodynamic characteristics of ceftazidime suggest that continuous infusions should be clinically investigated in outcome studies.

Introduction

The optimal method for administration of β-lactam antibiotics is under review. Although usually administered in clinical practice as regular intermittent bolus doses according to the manufacturers’ instructions, the administration of β-lactam antibiotics by continuous infusion has been advocated. It has been demonstrated repeatedly that the bactericidal effect of β-lactam antibiotics is determined by the time that antibiotic concentration exceeds a threshold antibiotic concentration.1–3

The most frequent indication for the use of ceftazidime in our ICU is suspected or confirmed Pseudomonas aeruginosa infection. The MIC of ceftazidime for P. aeruginosa is 2–8 mg/L,4 and it would seem logical to maintain the plasma concentration of ceftazidime above 5 × MIC (10–40 mg/L) throughout the dosing interval.

Pharmacokinetic modelling, using published pharmacokinetic data,5 predicts that the normal maximum dose of ceftazidime (2 g every 8 h given in bolus doses) is insufficient to maintain the plasma concentration of ceftazidime above 40 mg/L. This target is maintained most efficiently by giving a loading dose followed by an infusion. For ceftazidime it would be reasonable to calculate the loading dose $D_L$ from the equation:

$$D_L = C_T \times V_{dss}$$

(where $C_T$ is the desired target concentration and $V_{dss}$ is the volume of distribution at steady state) and the subsequent infusion rate $I$ from the equation:

$$I = C_T \times C_l$$

Where $C_l$ is clearance. The aims of this study were to confirm that a plasma concentration of ceftazidime above 40 mg/L could be maintained using a loading dose and infusion regimen, and that this regimen would be superior to the same amount of drug given by the standard intermittent bolus regimen.

Materials and methods

The study was performed in a mixed ICU, approval being obtained from the Clinical Research Ethics Committee of The Chinese University of Hong Kong. Written informed consent was obtained.

Using computer-generated random numbers, we randomized 18 adults with normal renal function, who required ceftazidime according to usual clinical practice, into infusion and bolus groups, given through central venous access. Pharmacokinetic data from critically ill patients were used to derive the bolus dose for the infusion group.5 Taking an extreme estimate of 0.30 mL/kg and a target con-
centration of 40 mg/L, the loading dose was calculated to be 12 mg/kg. To maintain equivalence of dosing between the two regimens, the initial loading dose was given to both groups. We chose a maintenance regimen (2 g every 8 h) because this is the standard maximum dose and it was sufficiently close to the calculated desired infusion rate for the infusion group. Thus the infusion group received 12 mg/kg over 2 min followed immediately by 2 g over 478 min. They then received 2 g given as an infusion every 8 h. The bolus group received 12 mg/kg of ceftazidime over 2 min followed immediately by 2 g infused over 28 min. Subsequently they received 2 g infused over 30 min every 8 h.

Arterial blood samples were collected at 0, 5, 15, 30 and 60 min and at 2, 4, 8, 16, 24 and 48 h after the start of antibiotic administration. The samples were centrifuged and plasma stored at -70°C until analysis. Ceftazidime concentrations were measured by HPLC. The calibration curve for the assay was linear over the range 1–500 mg/L (r = 0.9984). The within-day coefficient of variation at 50 mg/L was 1.76%.

Pharmacokinetic modelling was performed using a two-compartment model and standard noncompartmental methods (Kinetica Simed SA, Creteil, France). From the individually fitted concentration–time curves, we calculated the total time at which plasma ceftazidime concentrations were <40 mg/L. Data were analysed by Student’s t-test, Mann–Whitney U-test or Fisher’s exact test as appropriate. P values of <0.05 were considered significant.

Results

The groups were evenly matched as regards demographic data with no difference in creatinine clearances, but members of the infusion group were older (64 ± 9 vs 53 ± 14 years; P < 0.05) and had higher APACHE II scores (20.5 vs 15.5; P < 0.05). The fitted curves for plasma ceftazidime concentrations in the first 8 h are given in the Figure. The mean time for which serum ceftazidime concentrations decreased below 40 mg/L was 0 min (range 0–65) for the infusion group and 194 (range 0–363) for the bolus group (P < 0.01). Only one patient in the infusion group had a serum ceftazidime concentration below 40 mg/L and even then the lowest concentration was only 38 mg/L. In contrast, the lowest concentrations in the bolus group ranged from 2 to 48 mg/L.

At 16, 24 and 48 h, all patients in the infusion group had concentrations of >40 mg/L while in the bolus group this was only achieved in two of ten patients at 16 h, three of ten at 24 h and two of nine at 48 h.

No ceftazidime-related adverse reactions were noted.

Discussion

Ceftazidime has no significant post-antibiotic effect, and it is not important to achieve high peak serum concentrations. Instead, concentrations should be maintained above 4–5 × MIC. A n in-vitro pharmacokinetic model, using resistant pseudomonas stains, demonstrated the need for sustained high concentrations of ceftazidime. More specifically, this study showed the need for sustained ceftazidime concentrations above 4–5 × MIC. Our study demonstrates that a loading dose and infusion regimen maintained the desired concentration throughout the dosing interval and eliminated the variation in antibiotic concentration resulting from bolus dosing, demonstrated in this and previous work. Virtually all patients in the infusion group maintained target levels.

It may be argued that, in patients with highly resistant Gram-negative organisms (which may have MICs higher than those quoted above), antibiotic concentrations achieved during infusions would never result in bactericidal or even bacteriostatic activity. To avoid this potential clinical problem it would be prudent to establish the range of MICs for the Gram-negative organisms in individual

Figure. Ceftazidime serum concentrations vs time (logarithmic scale) for the bolus group (a) and continuous infusion group (b) over 8 h. Broken lines are at 8 mg/L (high MIC for P. aeruginosa) and five times that, i.e. 40 mg/L.
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... in order to calculate appropriate loading and infusion doses. Equipment such as infusion pumps is readily available in modern ICUs. The drawbacks of continuous infusions are therefore largely theoretical. Although β-lactam antibiotics work best on dividing organisms, their mode of action is diverse.

We have compared the plasma concentrations of ceftazidime during infusions (6 g/day) with standard intermittent dosing (2 g every 8 h), in critically ill patients. Bolus dosing produces variable concentrations, frequently below the desired threshold concentration towards the end of the dosing interval. Infusions consistently maintain concentrations above this threshold. In conclusion, we believe that infusions may be the preferred method of administration of ceftazidime in the ICU because of the kill characteristics of β-lactams and the suggestion of improved efficacy in animal studies. ICU patients are often immunocompromised and are in an environment that often has potential to develop resident resistant flora. This makes optimal antibiotic use essential. We believe that continuous infusions of β-lactams go a long way towards this. Our findings suggest prospective studies comparing bolus and infusion regimes with clinical outcome in critically ill patients are necessary.

References


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