Serum pharmacokinetics and sputum penetration of amikacin 30 mg/kg once daily and of ceftazidime 200 mg/kg/day as a continuous infusion in cystic fibrosis patients

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Sir,

Studies in vitro and in animals have shown that killing of bacteria by β-lactams is time dependent and maximal at relatively low concentrations, indicating optimal administration by continuous infusion. Continuous infusion of ceftazidime was recently reported to be well tolerated by children with cystic fibrosis. On the other hand, the bacterial activity of aminoglycosides is concentration dependent in vitro and animal models. Meta-analysis of efficacy in patients’ administration indicates that single daily dosing of aminoglycosides is as effective as conventional dosing, with similar or lower toxicity. However, there is scant information about the safety of single daily dose of aminoglycosides given as repeat courses in cystic fibrosis patients. The aim of this study was to provide pharmacokinetic data in cystic fibrosis patients on administration of ceftazidime by continuous infusion and amikacin by single daily dosing.

Twelve patients [eight males, four females, mean age (range) 19 (10–32) years, mean weight (range) 49 (27–65) kg] admitted for treatment of acute pulmonary exacerbation of cystic fibrosis were included in the study, which was approved by the Ethics Committee of Erasme Hospital. Informed consent was obtained from each patient or their legal guardian. Two days before the sampling day, each patient was given ceftazidime 65 mg/kg (Glaxo Wellcome, Brussels, Belgium) iv over 30 min as a loading dose, followed by a continuous infusion of 200 mg/kg/day in 500 mL dextrose 5% administered via an infusion pump. Amikacin 30 mg/kg (Bristol-Myers Squibb, Brussels, Belgium) was administered iv over 30 min once daily. Antimicrobial therapy was continued for 14 days, and blood and sputum samples were taken on the third day of treatment. Timed serum (pre-dose, 30 min, 2, 4, 6, 8, 24 h post-dose) and bronchial (pre-dose, and 1–3, 3–5, 5–7, 7–9 and 22–24 h intervals post-dose) secretion samples were collected after amikacin dosing. Sputum and separated serum were stored at −70°C within 1 h of sampling. Defrosted sputum was sonicated in a circulating water bath (4°C) (Sonicator W-225 R; Heat Systems-Ultrasound, New York, NY, USA) (2 min, 100 W) and then centrifuged (12 000g, 3 min). Assays were performed on supernatant.

Amikacin was assayed using fluorescence polarization immunoassay (TDx; Abbott Diagnostics, Ottignies, Belgium) according to the manufacturer’s recommendations. The manufacturer’s published limit of detection for amikacin is 0.25 mg/L. Ceftazidime was assayed by HPLC. Calibrators and samples were prepared by mixing with an equal volume of 0.72% perchloric acid containing cefadroxil (0.5 mg/mL) as internal standard. This mixture was centrifuged at 1000g, 3 min). The eluate was monitored at 257 nm. The limits of detection for ceftazidime were 0.20 and 0.25 mg/L for serum and sputum supernatant, respectively.

Amikacin pharmacokinetic parameters were calculated using a two compartment open model (Siphar 4.0; Simed, Créteuil, France). The area under the serum concentration–time curve (AUC) was determined by the trapezoidal rule up to the last concentrations determined. Amikacin clearance was determined by multiplying the elimination rate constant by the distribution volume. Ceftazidime clearance was calculated by dividing the dose by the AUC. The values are reported as mean ± S.D. (range).

Concentrations of ceftazidime and amikacin in serum and sputum are presented in the Figure (a and b). The mean peak and trough values of amikacin in serum were 116 ± 37 (82–192) mg/L and 0.3 ± 0.4 (<0.25–9.2) mg/L, respectively. The T1/2 β was 2.6 ± 1.3 h, with a distribution volume of 20.0 ± 7.9 L (0.40 ± 0.16 L/kg), and a total clearance of 5.26 ± 1.42 L/h. The peak sputum concentration 2 h post-dose was 5.9 ± 2.7 (2.4–9) mg/L and the trough 1.4 ± 0.8 (<0.25–2.4) mg/L. The mean serum and sputum AUCs for amikacin were 235 ± 110 and 83.7 ± 43.4 mg·h/L, respectively. The steady-state blood concentration of ceftazidime was 56.1 ± 23.3 mg/L (23.9–96) and the sputum penetration of amikacin 30 mg/kg once daily and of ceftazidime 200 mg/kg/day as a continuous infusion in cystic fibrosis patients.
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concentration was 1.7 ± 2.2 (<0.2–10.5) mg/L. The mean serum and sputum AUCs for ceftazidime were 1387 ± 346 and 22.3 ± 18.3 mg·h/L, respectively. The mean ratios AUC_{sputum}:AUC_{serum} for amikacin and ceftazidime were 25 ± 1.5% and 1.4 ± 1.4%, respectively. The overall clinical results were favourable and all the patients were discharged after 2 weeks of treatment without any adverse events (data not shown).

The administration of amikacin 30 mg/kg once daily achieved sputum antibiotic concentrations higher than those obtained with lower doses of amikacin or when multiple-daily dosing regimens were used.\textsuperscript{2,3} With respect to ceftazidime, the serum concentrations of the drug during continuous infusion of 200 mg/kg/day in cystic fibrosis patients reached c. 50 mg/L, but the concentration in the bronchial secretions remained very low. These low concentrations might be explained by poor penetration of ceftazidime through the blood–bronchial barrier as a result of a saturable transport mechanism, as suggested by others.\textsuperscript{4} However, the low concentrations in sputum might be due, in part at least, to the high levels of β-lactamase activity produced by Pseudomonas aeruginosa in the sputum of cystic fibrosis patients.\textsuperscript{5}

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References