Cefazolin serum concentrations with fixed intravenous dosing in patients on chronic hemodialysis treatment

Sir,

Staphylococcus aureus and coagulase-negative staphylococci are the most frequent causes of sepsis in chronic haemodialysis patients. Due to the emergence of vancomycin-resistant enterococci (VRE) and staphylococci, the use of vancomycin as empirical treatment for sepsis or because of dose convenience in patients with renal failure has been discouraged.

The spectrum of anti-bacterial activity of cefazolin, a first-generation cephalosporin, offers an attractive alternative for vancomycin (with or without aminoglycoside) as treatment for sepsis in patients on chronic haemodialysis, however data about cefazolin pharmacokinetics and efficacy in this population are sparse. Recently it was shown that a titrated dose of cefazolin 20 mg/kg given i.v. after dialysis was effective for achieving therapeutic serum concentrations with resolution of clinical infections [5].

We conducted a study with a fixed cefazolin dose of 2 g i.v. in our chronic haemodialysis patients to establish whether this more convenient dosing strategy would also be effective.

Methods. Fifteen stable chronic ambulatory haemodialysis patients from our low-care dialysis centre (14 male patients) gave informed consent to participate in the pharmacokinetic part of the study. They were free of infection for at least 4 weeks at the time of inclusion. Patients known to be allergic to penicillins or cephalosporins were excluded. Fourteen patients were on haemodialysis (4 h sessions) and one on haemodiafiltration (4 h sessions); 14 patients used high-flux membranes and the remaining one a medium-flux membrane. Patients age ranged from 41 to 77 years (mean 64.5 years); the mean body weight for this group was 72 kg (range
53–104 kg). Etiology of chronic renal insufficiency was diabetic nephropathy (two patients), chronic glomerulonephritis (four), adult dominant polycystic kidney disease (three), renal vascular disease (one) and unknown (five).

Residual renal function was calculated from measured 44-h urine collections and ranged from 0 to 1 ml/min; eight patients were completely anuric.

Two grams cefazolin was administered i.v. to these 15 patients at the end of each dialysis treatment (over 15 min) for three consecutive dialysis sessions (on day 0, 2 and 4). Cefazolin trough serum levels were measured just before each next dialysis session, 44 or 68 h after the previous dose (on day 2, 4 and 7).

Blood samples were collected on heparin from the dialysis access line. Cefazolin serum concentrations were randomly determined by high-performance liquid chromatography and blinded to the investigator. Data are expressed as mean ± standard deviation unless otherwise stated.

Results. The dose of cefazolin expressed in milligram per kilogram of body weight for our patients ranged from 37.7 mg/kg to 19.2 mg/kg with a mean of 28.7 ± 5.22 mg/kg. The mean cefazolin serum trough levels for these 15 patients measured on day 2, 4 and 7 were 84 ± 24 µg/ml (range 47–130 µg/ml); 97 ± 27 µg/ml (range 52–145 µg/ml) and 61 ± 22 µg/ml (range 26–99 µg/ml) respectively. Minimum inhibitory concentration (MIC) for cefazolin susceptible bacteria was ≤8 µg/ml, according to the 1998 NCCLS guidelines [1].

Clinical signs and symptoms occurring during the study period and interpreted as probably related to cefazolin administration were: urticaria (one patient) not recurring on subsequent dosing, superficial mouth ulcers (one patient), Clostridium difficile colitis requiring oral vancomycin therapy (one patient) and vomiting (one patient), although the latter patient was subsequently diagnosed with reflux oesophagitis grade IV.

Discussion. The emergence of VRE not only in intensive care units but also in haemodialysis and nephrology wards is responsible for large hospital VRE outbreaks [2]. The Hospital Infection Control Practices Advisory Committee (HICPAC) published recommendations for preventing the spread of VRE in the hospital setting [3].

Using vancomycin for the treatment of infections due to β-lactam-sensitive Gram-positive bacteria in patients with renal failure should be discouraged and reserved only for β-lactam-resistant Gram-positive isolates or patients with β-lactam allergy. The International Society for Peritoneal Dialysis also recommended not to use vancomycin plus aminoglycosides as first choice therapy for initial empiric treatment of peritoneal dialysis-related peritonitis, but to treat with cefazolin and gentamicin [4].

Our results show that administration of a fixed dose of 2 g cefazolin i.v. to stable chronic haemodialysis patients at the end of each consecutive dialysis session produces predialysis trough serum concentrations of cefazolin 3–18 times the MIC for susceptible microorganisms.

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