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Pharmacokinetics and total removal of fosfomycin in two patients undergoing intermittent haemodialysis and extended dialysis: prescription needs to avoid under-dosing

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Sir,

Fosfomycin, first isolated in 1969 from cultures of *Streptomyces fradiae*, is the single representative of the epoxide family of antimicrobial drugs and shows bactericidal activity against various Gram-positive, Gram-negative and anaerobic pathogens through inhibition of peptidoglycan synthesis destroying the inner bacterial cell wall.[1] The unique properties (molecular weight = 138 Da; protein binding = ~10%; volume of distribution = 0.2–0.4 L/kg) allow easy penetration into soft tissue, bone, muscle, heart, eye, lung, wound fluids and liquor. As fosfomycin is not significantly metabolized but mainly excreted unchanged via the kidneys its half-life is highly dependent on kidney function.[2] Usually, fosfomycin susceptibility is defined by a breakpoint of the MIC of 32 mg/L.[3] Fosfomycin is indicated and most commonly used in urinary tract infections and offers a treatment alternative in soft tissue infections, spondylodiscitis, osteomyelitis and infections of the CNS when systemically administered.[4]

Owing to the emerging increase in infections with antimicrobial drug resistance, old antibiotics such as fosfomycin are increasingly used. The elimination of fosfomycin during haemodialysis was described about 30 years ago using dialysis techniques that have long been considered outdated.[5] Owing to the scarce use of fosfomycin over the last decade, pharmacokinetic data for modern dialysis techniques are almost completely missing. In this report we describe two cases of single-dose pharmacokinetics of fosfomycin during intermittent haemodialysis, as well as during extended dialysis, a prolonged haemodialysis modality commonly used in critically ill patients.[6] To our knowledge, this is the first report that provides data on the total eliminated amount of fosfomycin during an intermittent and an extended dialysis therapy session in the spent collected dialysate.

Written informed consent was obtained from the patients for publication of this article. See Table S1 (available as Supplementary data at *JAC* Online) for the main dialysis and patient characteristics. Both patients were treated at a tertiary care hospital (Hannover Medical School).

Case 1: A female patient in her seventies (158 cm, 49 kg body weight, BMI 19.6 kg/m^2) was admitted to the emergency ward due to distinct dorsalgia denying any trauma. She had been undergoing chronic haemodialysis for 11 years. Owing to former morbid obesity, the patient had undergone bariatric surgery 5 years earlier, which decreased her BMI to 19.6 kg/m^2. A punch biopsy of the lumbar spine was performed, which showed focal osteomyelitis. As the patient was allergic to penicillin, antibiotic therapy with 300 mg of clindamycin thrice daily and 8 g of intravenous fosfomycin sodium on dialysis days was empirically started; while 3 g of the total fosfomycin dosage was administered 4 h prior to the intermittent haemodialysis session the other 5 g was given directly at the end of the intermittent haemodialysis. A 3 h intermittent haemodialysis session was performed with a blood and dialysate flow of 220 mL/min using a polysulfone high-flux dialyser (1.3 m^2 surface) during therapy with the GENIUS dialysis batch system. Details are described elsewhere.[6] Heparin was used for anticoagulation. The maximum plasma concentration (C_{max}) after the 3 g infusion was 496 mg/L. As shown in Figure 1(a) the 3 h dialysis session led to a distinct reduction of fosfomycin plasma levels of 61%, with a dialyser clearance of 75 mL/min. The total amount of fosfomycin in the total collected dialysate was 2430 mg. C_{max} after the additional administration of 5 g of fosfomycin after dialysis treatment was 467 mg/L. Fosfomycin concentrations were measured by LC-MS/MS according to a previously described procedure.[7]

Case 2: A female patient in her twenties (167 cm, 40 kg body weight, BMI 14.3 kg/m^2) with sepsis due to severe osteomyelitis was admitted to the medical ICU. Owing to the severe clinical state of the patient a femur resection was performed and intraoperative swabs showed an infection with multiresistant *Escherichia coli* bacteria susceptible to fosfomycin and therapy with meropenem and fosfomycin was started. Owing to acute kidney injury extended dialysis was performed every other day. A daily dosage of 3 g of fosfomycin was administered intravenously. On the day after initial fosfomycin administration a 6 h extended dialysis treatment with a polysulfone high-flux dialyser (1.3 m^2) was performed. Blood and dialysis flow were set at 240 mL/min. Total ultrafiltration volume during therapy was 3440 mL. Citrate was used for anticoagulation. The fosfomycin peak concentration after administration of 3 g of fosfomycin was 207.4 mg/L after a trough concentration of 106.5 mg/L. The serum concentration declined to 49.5 mg/L after the end of the procedure, resulting in a reduction ratio of 68% (Figure 1b). After the 6 h dialysis treatment a total of 3591 mg of fosfomycin was found in the total spent dialysate. Dialyser plasma clearance was 116 mL/min. Three weeks after the ICU admission the patient died due to multiple septic complications and multi-organ failure.

Fosfomycin dosing guidelines in patients undergoing haemodialysis are based on publications from the 1970s and 1980s, when cuprophan membranes were used.[8] These earlier publications indicate a high elimination of fosfomycin during haemodialysis

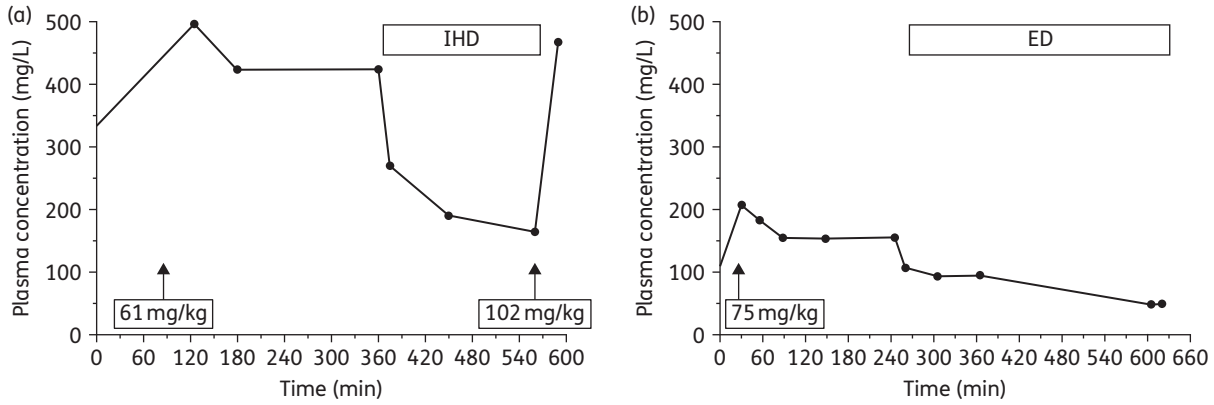

Figure 1. Plasma concentration course of fosfomycin in the described cases. Dialysis treatment duration is depicted by box size. Fosfomycin administration is indicated by black arrows and the dosage (mg/kg of body weight) is indicated in boxes. IHD, intermittent haemodialysis; ED, extended dialysis.

with dialyser clearance rates of about 60 mL/min.[5] Even recent publications recommend a dose of 2–4 g/day fosfomycin on dialysis days,[9] as prescribed in the second case. However, modern dialysis techniques are not well represented in these earlier studies. Much higher doses up to 16 g/day are recommended during continuous renal replacement therapy by Gattringer *et al.*[10] However, the stated study enrolled patients on convection-based continuous venovenous haemofiltration therapy, whereas this case report states the pharmacokinetic courses of diffusion-based haemodialysis patients treated either by intermittent or extended dialysis. Modern dialysis exceeds earlier measured clearance rates, as seen in this case report (75 and 116 mL/min).

The large amount of fosfomycin in the total spent dialysate (80%–120% of the admitted dose) indicates that even with the given efficient tissue penetration, haemodialysis, prescribed in the modality of extended or intermittent dialysis, can decrease fosfomycin serum levels dramatically. Both patients reported were underweight, thus exposed to a rather high dose per kg body weight. Hence, normal weight or even obese patients would be at a higher risk for under-dosing if dosing not based on actual body weight is used. As these anecdotal data are not sufficient to guide dosing, additional pharmacokinetic data regarding fosfomycin dosing in critically ill patients undergoing different dialysis modalities are needed.

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Author contributions

S. M. B.-B. and J. M.-L. conducted the measurement of fosfomycin. J. J. S., M. W., M. O. and J. T. K. were the treating physicians of the reported patients. J. J. S., T. W. and J. T. K. evaluated the test results. All of the authors participated in the discussion and writing of this article.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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