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This study was carried out as part of our routine work.

Transparency declarations
M. J. R. has received speaking honoraria from Cubist, Forest, Novartis and Sunovion, consulting fees from Durata, Cubist, Forest, Cepheid and Theravance, and research grant support from Cubist, Forest and Cerexa Pharmaceuticals. G. S. has received speaking honoraria from Cubist, Forest and Novartis Pharmaceuticals, consulting fees from Cubist and Forest Pharmaceuticals, and research grant support from Forest Pharmaceuticals. K. E. B.: none to declare.

References

Prolonged treatment with large doses of fosfomycin plus vancomycin and amikacin in a case of bacteraemia due to methicillin-resistant Staphylococcus epidermidis and IMP-8 metallo-β-lactamase-producing Klebsiella oxytoca

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Sir,
Fosfomycin is an old, but potent, antibiotic in the current global fight against antibiotic resistance, mainly for carbapenem-resistant Enterobacteriaceae,1 but also for Gram-positive bacteria, such as MRSA.2 However, information about the effectiveness and safety of the drug in severe systemic infections is scarce. We present a case of systemic infection in which methicillin-resistant Staphylococcus epidermidis and carbapenem-resistant Klebsiella oxytoca were isolated.

A 68-year-old Caucasian man was admitted to La Merced Hospital (Osuna, Seville, Spain) for elective colectomy in July 2011. A written consent to publish this case was obtained. His medical history included arterial hypertension, dyslipidaemia, cerebrovascular disease (a frontal ischaemic stroke 2 years earlier) and benign prostate hyperplasia. In 1998, he had undergone an abdominoperineal resection, radiotherapy and chemotherapy due to a rectal cancer. Since then, he had suffered radiation cystitis. In June 2011, he was diagnosed with cancer recurrence and a total colectomy was performed. Forty-eight hours later, an intra-abdominal infection forced the performance of a wide small bowel resection. As a result, the patient developed short bowel syndrome, for which he had to receive prolonged total parenteral nutrition. A three-way Foley catheter had to be maintained because of a protracted haematuria. On day 114 of hospitalization, the patient developed fever with no evident source. Physical examination revealed conjunctival haemorrhages. Imipenem (1 g/8 h intravenously), vancomycin (1 g/12 h intravenously) and amikacin (1 g/24 h intravenously) were initiated. Methicillin-resistant S. epidermidis

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and carbapenem-resistant *K. oxytoca* were isolated from all three sets of blood cultures. The central catheter was removed, but it could not be cultured and none of the implicated microorganisms was isolated from urine. Since the *K. oxytoca* were only susceptible to fosfomycin (MIC $\leq 16$ mg/L), colistin (MIC $<0.5$ mg/L) and amikacin (MIC $<2$ mg/L), imipenem was switched to fosfomycin (4 g/6 h intravenously). *S. epidermidis* was susceptible to vancomycin (MIC 1 mg/L) and fosfomycin (MIC $<8$ mg/L). A transesophageal echocardiogram revealed signs of possible infectious endocarditis, which was subsequently confirmed by the visualization of a 10 mm vegetation on the coronary sinus of the aortic valve through a transesophageal echocardiogram. The patient became afebrile after 72 h of treatment, but on day 126 (day 12 of treatment) he developed a fever again. A blood culture was negative and the markers of infection were improving, so a non-infectious cause of fever was suspected and a non-steroidal anti-inflammatory drug was added to the treatment. He remained afebrile subsequently. A total of 28 days of treatment were completed. No heart complications were noted. The most significant event was a self-limited hypokalaemia, which is the most frequently described fosfomycin-related adverse event.10 Our patient’s only remarkable adverse effect was a self-limited hypokalaemia, which is the most frequently described fosfomycin-related adverse event.10

In conclusion, our case showed that the prolonged use of high doses of fosfomycin in combination with other antibiotics could be useful for severe systemic infections due to multidrug-resistant bacteria, with an apparently excellent safety profile. The promising clinical application that our data suggest should be confirmed in future prospective studies.

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Intrahepatic antiviral quantification in a patient undergoing orthotopic cadaveric liver transplantation

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Sir,

Patients with end-stage liver disease (ESLD) have lower rates of sustained virological response to hepatitis C virus (HCV) treatment compared with those without significant hepatic impairment.1 There may be pathophysiological alterations associated with ESLD, which may alter drug penetration or drug activation in the liver.2 Comparing the concentrations of antiviral drugs in liver versus blood may inform drug selection in ESLD. The objective of this work was to quantify antiviral drugs in liver tissue and the active, phosphorylated forms of nucleos(t)ide analogues (NAs) in hepatocytes obtained from a fresh liver explant and to compare these values with drug concentrations in paired plasma and PBMCs.

A 50-year-old male with HIV/HCV coinfection on the liver transplant list was transferred to our hospital with acute kidney injury (serum creatinine 4.11 mg/dL) with a Model for ESLD score of 40. In the year prior to hospitalization, the patient’s antiretroviral regimen included 300 mg of tenofovir disoproxil fumarate once daily plus 200 mg of emtricitabine once daily, 800 mg of darunavir once daily, 100 mg of ritonavir once daily and 400 mg of raltegravir twice daily. The patient had an HIV-1 RNA of <20 copies/mL and a CD4 count of 420 cells/μL. On day 1, tenofovir disoproxil fumarate/emtricitabine was discontinued. On day 2, emtricitabine was initiated and dose adjusted based on renal function. Darunavir was discontinued and replaced with atazanavir on day 3. Raltegravir and ritonavir doses remained unchanged.

The patient provided written informed consent for quantification of antiviral drugs in blood, PBMCs and hepatic tissue from his explant liver and publication of study findings. Six days following transfer to our hospital, the patient underwent orthotopic cadaveric liver transplantation. In the operating room, whole blood was obtained for quantification of antiviral drugs in plasma and PBMCs. Forty-five minutes later, the cirrhotic liver was removed. An 18-gauge needle biopsy was used to extract tissue cores from the liver explant for isolation of hepatocytes and quantification of antiviral drugs in blood, PBMCs and hepatic tissue from his explant liver and publication of study findings. Six days following transfer to our hospital, the patient underwent orthotopic cadaveric liver transplantation. In the operating room, whole blood was obtained for quantification of antiviral drugs in plasma and PBMCs. Forty-five minutes later, the cirrhotic liver was removed. An 18-gauge needle biopsy was used to extract tissue cores from the liver explant for isolation of hepatocytes and quantification of phosphorylated nucleotides. Small liver tissue samples were also collected from scalpel cuts of the explant for quantification of parent drugs.

Liver tissue samples were weighed and homogenized with an electro-homogenizer and frozen at −80°C until quantification of parent drugs. Hepatocytes were isolated from core biopsies for quantification of phosphorylated metabolites. Briefly, the core biopsy samples were soaked in warm perfusion medium. Digestion medium was added and samples were shaken. Dissociated cell aggregates were filtered through a 100 μm cell strainer and rinsed with wash medium. Samples were centrifuged, the supernatant discarded and the pellet re-suspended in wash medium and counted. The isolated hepatocytes were lysed with 70:30 methanol/water then stored at −80°C until intracellular drug level analysis.

Tenofovir diphosphate, emtricitabine triphosphate and lamivudine triphosphate were quantified in PBMCs and isolated hepatocytes using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method.3 Tenofovir, emtricitabine, raltegravir, atazanavir and ritonavir were measured in plasma and liver tissue homogenate using validated LC/MS or HPLC/UV methods.4–6

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