

CLINICAL CASE

Acute hepatitis induced by fosfomicin: A case report and review of the literature

Rosa Ferreira^{a,*}, Joana Torres^a, Joana Raposo^b, Margarida Ferreira^a,
Sofia Mendes^a, Cláudia Agostinho^a, Mário Júlio Campos^a

^a Gastroenterology Service, Hospitalar Center of Coimbra, Portugal

^b Anatomic Pathology Service, Hospitalar Center of Coimbra, Portugal

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PALAVRAS-CHAVE

Hepatite aguda;
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Dose única de 3 g;
Efeitos adversos;
Cistite aguda

Abstract Fosfomicin is a broad spectrum antibiotic, belonging to the group of phosphonic acid antibiotics that is active against most urinary tract pathogens. It is an effective and safe antibiotic for the treatment of uncomplicated urinary tract infections, which makes it a frequently used drug in our country in this clinical setting. In general, it is well-tolerated and does not appear to cause serious reactions. Most reactions are gastrointestinal. Hepatotoxicity with this drug has been rarely described. We report a case of acute hepatitis induced by a single 3 g dose of fosfomicin, in a previously healthy female adult.

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Hepatite aguda induzida por fosfomicina: relato de um caso clínico e revisão da literatura

Resumo A fosfomicina é um antibiótico de largo espectro, que pertence ao grupo do ácido fosfónico e é eficaz contra a maioria dos microorganismos do tracto urinário. Pela sua eficácia e segurança no tratamento de infecções do tracto urinário não complicadas é amplamente usado no nosso país nesta situação clínica. É um fármaco geralmente bem tolerado e que não parece causar efeitos adversos graves. A maioria dos efeitos laterais relatada é gastrointestinal. A hepatotoxicidade induzida com a fosfomicina tem sido raramente descrita. Os autores descrevem um caso de hepatite aguda induzida por uma dose única de 3 g de fosfomicina, numa doente adulta previamente saudável.

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* Corresponding author.

E-mail address: rosa.l.ferreira@gmail.com (R. Ferreira).

Introduction

Fosfomycin is an oral antibiotic derived from phosphonic acid that has been widely used in the treatment of uncomplicated urinary tract infections.^{1,2} Its potent and enduring activity against urinary pathogens has been confirmed in Europe³ and USA.⁴ Since 1988 fosfomycin has been extensively used in several European countries for single-dose therapy of uncomplicated urinary tract infections. After a single 3 g dose, fosfomycin exhibits very high and sustained urinary concentrations that rapidly kill pathogens reducing the opportunity for mutant selection. The resistance rates of fosfomycin remain, therefore, extremely low (about 1%) worldwide.⁵ Furthermore, fosfomycin is well tolerated, with a low incidence of adverse events. These consist mainly of gastrointestinal symptoms that are ordinarily transient, mild and self-limiting.^{1,6}

The authors present a case of a 24-year-old woman with acute hepatitis induced by a single 3 g dose of fosfomycin for acute cystitis.

Case report

A 24-year-old woman, with no significant past medical history, presented to the emergency department with nausea, fatigue, increasing muscle weakness, gradually worsening jaundice and dark urine, for four weeks. The symptoms started one week after taking a single 3 g dose of fosfomycin for acute cystitis. She denied any accompanying symptoms, such as rash, arthralgias, fever or adenopathies.

She also denied taken any other medications including over-the counter medications, herbal or traditional medicines. There was no history of drugs or alcohol abuse, past administration of blood products or blood transfusion, or previous hepatitis. She denied recent travels. There was no family history of liver diseases.

On physical examination, the vital signs were normal and there were no remarkable findings except for icteric skin and sclera. Abdominal and neurological examinations were normal.

The hematological data revealed hemoglobin of 12.6 g/dL; total white cell count of $11, 8 \times 10^3/L$ (3.3% of lymphocytes and 0.5% of eosinophils); platelet count of $437 \times 10^3/L$ and prothrombin time of 14 s (INR 1.2). The results of liver tests were: total bilirubin 195 $\mu\text{mol/L}$ (NR: <22) with 124 $\mu\text{mol/L}$ of conjugated, alanine aminotransferase (ALT) 1833 IU/L (NR: 10–66), aspartate aminotransferase 1467 IU/L (NR: 15–46), alkaline phosphatase (ALP) 86 IU/L (NR 38–136), gamma-glutamyl transferase 68 IU/L (NR: 12–58) and LDH 1531 IU/L (NR: 313–618).

Electrolytes, serum albumin, iron and transferrin saturation were normal. IgM anti-HAV, HBsAg, IgM anti-HBc and anti-HCV antibodies were negative. Anti-HIV, anti-CMV, anti-EBV and anti-HSV were also negative. Auto-antibodies (ANA, ANCA, Anti-LKM, AMA and ASMA) were negative. 24 h-urinary copper, ceruloplasmin, α -fetoprotein and α -1 antitrypsin were within normal range. Liver ultrasonography showed no significant abnormality except for increased echogenicity.

A liver biopsy by percutaneous route was then performed without complications. The biopsy material was fragmented

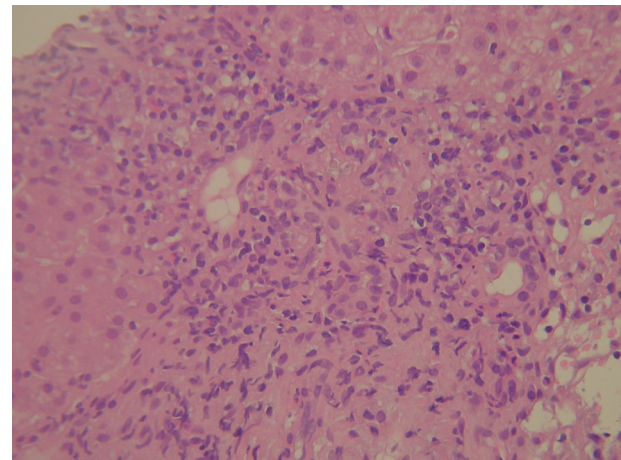


Figure 1 Expanded portal space with discrete fibrosis and intense inflammatory infiltrate (composed by lymphocytes, eosinophils and few neutrophils). There are discrete lesions of interface hepatitis (hematoxylin and eosin, 400 \times).

and had lesions located in the portal spaces and hepatic lobules. The histological examination showed expansion of the portal spaces with scant fibrosis and intense inflammatory infiltrate composed by lymphocytes, eosinophils and few neutrophils. There were also focal lesions of interface hepatitis (Fig. 1). The hepatic lobules showed moderate inflammatory infiltrate, similar to the one noticed in the portal spaces, ballooning degeneration of the hepatocytes (Fig. 2) and isolated apoptotic bodies throughout the entire studied material. It was observed focal hepatic necrosis with collapse of the parenchyma, more severe in the perivenular zone, along with discrete fibrosis. There was also focal hepatic steatosis. No granulomas were detected. These findings were consistent with acute hepatitis and were highly compatible with toxic/pharmacological etiology.

A gradual decrease in liver enzymes was seen; total bilirubin continued to rise and reached a peak 40 days after the intake of fosfomycin, and then it also started to decline (Fig. 3). The patient improved symptomatically, in parallel

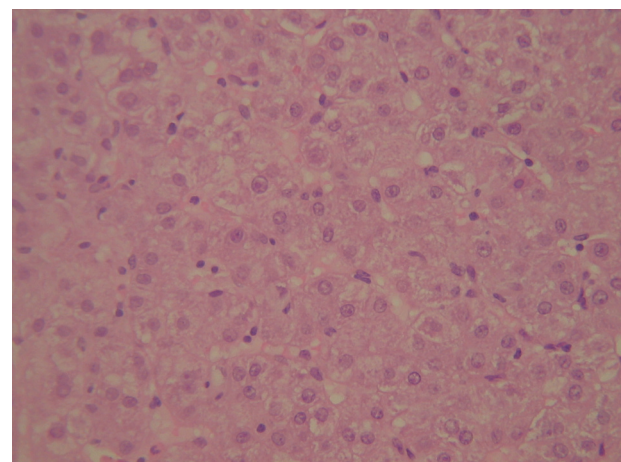


Figure 2 Hepatic lobule with ballooning degeneration of the hepatocytes and sparse inflammatory infiltrate (hematoxylin and eosin, 400 \times).

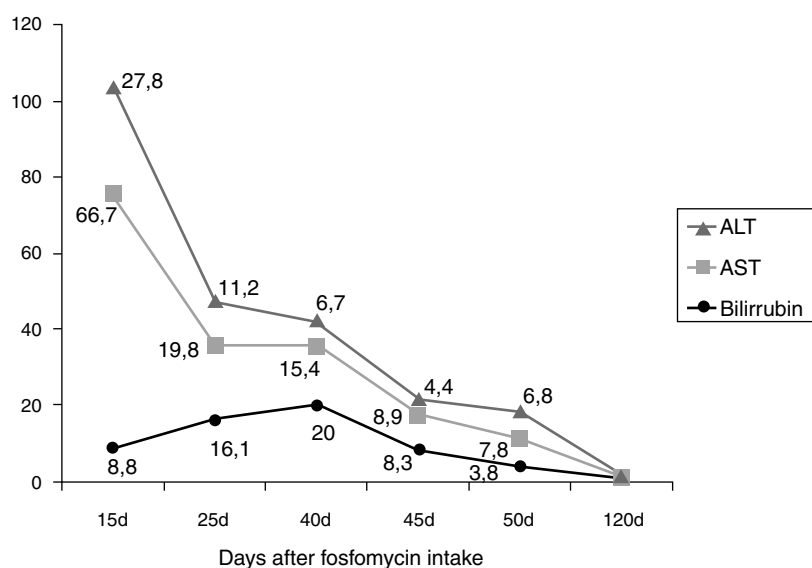


Figure 3 Evolution of aminotransferases and bilirubin after fosfomycin intake.

with the decline in aminotransaminases. Three months after fosfomycin intake, all liver function tests had normalized (Fig. 3).

Two years after, the patient remains asymptomatic and without alteration of the liver enzymes.

Discussion

Fosfomycin is a widely used, broad-spectrum antibiotic, which exhibits a rapid bactericidal activity against a large number of aerobic Gram positive and Gram-negative bacteria.^{1,2} It is approved as a single-dose therapy (3-g oral dose) for the treatment of uncomplicated urinary tract infections (acute cystitis) in women.⁷

Usually, it is a well-tolerated drug and does not appear to cause serious reactions.

Reported adverse events are usually mild and last only 1–2 days, resolving without treatment. The overall incidence of side-effects is 6% with oral therapeutic dosing and 17% with parenteral administration. Gastrointestinal complaints, mostly diarrhea, are the most frequent. Dizziness, headache and vaginitis have also been reported.⁶ In terms of liver adverse events, only rare cases of asymptomatic and mild liver enzyme abnormalities have been described.⁸

To our knowledge there are three cases in the literature of fosfomycin induced-liver injury: a case of recurrent fosfomycin-induced hepatic toxicity with drug rechallenge in a 30-year-old woman with cystic fibrosis in France,⁹ a case of acute severe hepatitis in Japan¹⁰ and a case of fosfomycin-induced liver disease in a 50-year-old woman in China.¹¹ The authors have no additional information about the case reported in Japan because this article was published in Japanese. In the other two cases, liver enzymes increased 3–4 days after fosfomycin administration and returned to normal levels within a week to a month after the withdrawal of the drug. In our patient, the normalization of all liver function tests took three months to occur. In these cases, fosfomycin induced hepatotoxicity was observed with

higher doses during a longer period of time than in our patient (3g single dose), suggesting that its hepatotoxic effect may be dose independent. While the liver injury observed in our case can be classified as hepatocellular (ALT >2 upper limits of normal (ULN) or ALT/ALP ratio ≥ 5), in the Chinese case it was mixed (ALT >2 ULN and 2 < ALT/ALP ratio >5) and in the French case it cannot be classified because, despite the elevation of ALT, the ALP value was not mentioned.

In our patient, acute hepatitis appears to be causally related to the administration of fosfomycin, based on a temporal relationship, negative serology for acute viral infection, negative autoantibody markers, exclusion of other drugs or other potentially hepatotoxic agents, and suggestive histological alterations in the biopsy. Liver biopsy was not performed in none of the two previously reported cases, and so these histological findings cannot be compared. Proof is not possible in the absence of a second exposition to the drug for ethical reasons.

Based on the "Roussel Uclaf Causality Assessment Method (RUCAM)" scale,¹² a score of 9 was obtained in our patient, indicating that the association between fosfomycin and the liver injury was "highly probable". According to the Maria and Vitorino scale,¹³ this causality was considered to be "possible" (score of 11).

Drug-induced liver injury (DILI) diagnosis remains a challenge for physicians and it is usually based on exclusion of other possible causes of hepatic dysfunction and on the temporal association between drug administration and the onset of liver disease.^{14,15} In our case, hepatic biopsy was a helpful tool to establish the diagnosis.

Although not performed in our institution, the drug lymphocyte stimulation test (DLST) is a laboratory test that can be useful to ascertain the diagnosis of DILI and to identify a single causative drug. It consists in culturing a patient's lymphocytes in the presence of the suspected drug. Lymphocyte proliferative response is determined by monitoring ³H-thymidine uptake.¹⁶ It is most frequently positive on immune mediated liver injury.¹⁷ However, recent findings of

associations between specific HLA haplotypes and DILI,^{18–20} which does not have hypersensitivity features, have highlighted the DLST's potential value.²¹ In fact, a recent diagnostic scale, the Digestive Disease Week–Japan, already includes DLST.¹⁷ Nevertheless, low sensitivity (around 50%), lack of causality between a positive result and liver injury, lack of standardization and restricted availability outside Japan limit its use.^{21,22} And so, some authors advocate that it should be considered in selected cases, such as those in which a single causative agent cannot be determined.²² We considered that DSLT was not mandatory in our patient since fosfomycin was the only drug used.

In a prospective study, drug-induced liver injury was caused by a single prescription medication in 73% of the cases and antibiotics were the single largest class of hepatotoxic agents.¹⁵

In summary, we report a potential case of acute hepatocellular lesion caused by fosfomycin. Being a commonly used antibiotic, physicians should be aware of this rare but potentially serious adverse drug reaction.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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