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CLINICAL CASE

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

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Abstract Fosfomycin 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 fosfomycin, in a previously healthy female adult.

PALAVRAS-CHAVE
Hepatite aguda;
Fosfomicina;
Dose única de 3 g;
Efeitos adversos;
Cistite aguda

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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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 Europe[3] 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, 8×10^3/L (3.3% of lymphocytes and 0.5% of eosinophils); platelet count of 437×10^3/L and prothrombin time of 14 s (INR 1.2). The results of liver tests were: total bilirubin 195 μmol/L (NR: <22) with 124 μmol/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 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

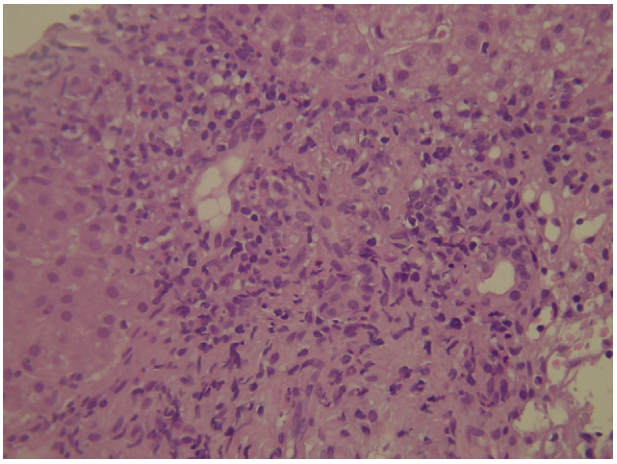

Figure 1 Expanded portal space with discrete fibrosis and intense inflammatory infilltrate (composed by lymphocytes, eosinophils and few neutrophils). There are discrete lesions of interface hepatitis (hematoxilin and eosin, 400×).

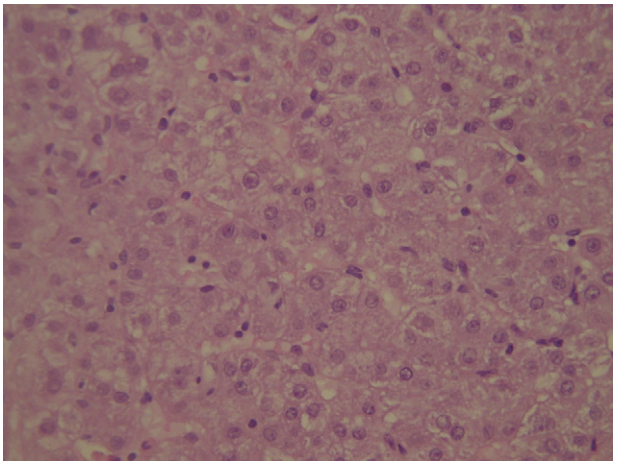

Figure 2 Hepatic lobule with balloning degeneration of the hepatocytes and sparse inflammatory infiltrate (hematoxilin and eosin, 400×).