

## Case report

# Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient

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## Abstract

LEVOFLOXACIN IS A FLUOROQUINOLONE ANTIBIOTIC commonly used to treat respiratory, urinary tract, skin and soft-tissue infections. Levofloxacin is generally well tolerated and has fewer reported side effects than other fluoroquinolones. We present a case of levofloxacin-associated severe hepatocellular injury. The hepatitis resolved soon after discontinuation of levofloxacin.

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## Case

A 73-year-old man was admitted to hospital for bilateral above-knee amputations as a result of ischemic gangrene of the lower limbs. His medical history included type 2 diabetes mellitus, chronic renal failure requiring hemodialysis for 4 years, coronary artery disease with 2 previous myocardial infarctions, 2-vessel coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty with stent insertion, peripheral vascular disease and neuropathy. The patient had no history of underlying liver disease.

Three weeks before admission to hospital, cellulitis was diagnosed in both lower extremities, and treatment with levofloxacin, 250 mg/d orally, was initiated. Other chronic medications included captopril, metoprolol, ASA, digoxin, isosorbide dinitrate, erythropoetin, quinine sulfate, vitamins B and C, folic acid, regular insulin and isophane insulin suspension, omeprazole, calcium carbonate and hydromorphone. He was not using ethanol, herbal products or any other over-the-counter medications.

On examination, the patient was found to be confused and drowsy. His blood pressure was 140/80 mm Hg, heart rate 90 beats/min, respiratory rate 18 breaths/min and temperature 37.4°C. The patient had scleral icterus. Cardiovascular and respiratory examination revealed no signs consistent with congestive heart failure or respiratory tract infection. Peripheral pulses were difficult to palpate, especially in the lower limbs. On abdominal examination, there was mild tenderness over the right upper quadrant; otherwise, there was no evidence of abdominal masses, hepatosplenomegaly or stigmata of chronic liver disease.

Laboratory evaluation revealed markedly elevated serum

transaminase levels (Fig. 1): aspartate aminotransferase (AST) 1392 (normally < 35) U/L, alanine aminotransferase (ALT) 857 (normally < 40) U/L and alkaline phosphatase 423 (normally 40–120) U/L. Results of tests assessing hepatic function were also abnormal (Figs. 2 and 3): total bilirubin 70 (normally 2–18)  $\mu$ mol/L and international normalized ratio 2.4 (normally 0.9–1.2). The patient's ALT and AST levels before starting the levofloxacin therapy were 1 and 27 U/L respectively. Hepatitis A IgM, hepatitis B surface antigen, hepatitis B core antibodies and hepatitis C antibody were not detected. Hepatitis B surface antibody was detected, which reflected previous vaccination. Abdominal ultrasonography and portal Doppler study did not reveal any significant abnormality. Specifically, there was no evidence of dilated hepatic veins.

During the first 2 weeks in hospital, the patient remained afebrile and hemodynamically stable, with no episodes of hypotension. The levofloxacin therapy was stopped, and within 1 week the transaminase levels stabilized to near normal values and the patient's confusion resolved. Although there was evidence of biochemical resolution of hepatitis after the levofloxacin therapy was discontinued, long-term follow-up was not possible. Three days after the bilateral above-knee amputations (14 days after admission to hospital), the patient died of causes secondary to a severe postoperative myocardial infarction. No autopsy was performed.

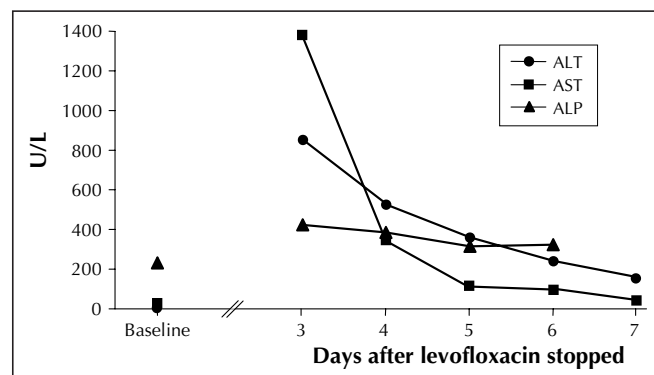


Fig. 1: Liver enzyme levels at baseline (2 months before start of levofloxacin therapy) and days after therapy was stopped. ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase.

## Comments

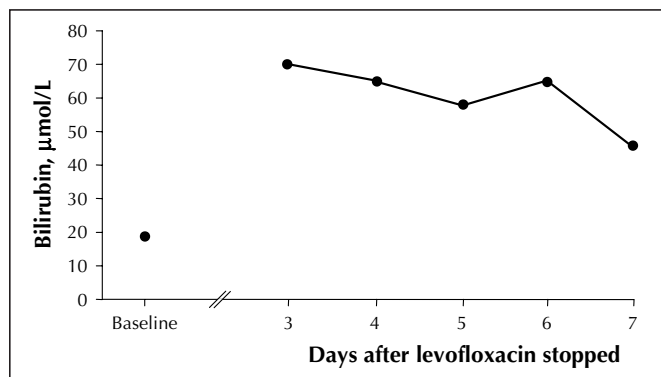
The case we have reported is similar to the first reported case of levofloxacin-associated hepatocellular injury.<sup>1</sup> In both cases, the patients were elderly (73 and 74 years old) and had underlying comorbid conditions, including kidney impairment. The renal insufficiency of both patients may have contributed to the antibiotic-associated hepatocellular damage, because 87% of levofloxacin is excreted as unchanged drug through the kidneys.<sup>2,3</sup> Both patients' serum transaminases levels improved shortly after the levofloxacin therapy was stopped (after 5 and 11 days respectively). Unfortunately, both patients died shortly after the event, because of underlying comorbid conditions and not as a direct result of the levofloxacin-associated hepatotoxicity, and therefore the long-term sequelae of the levofloxacin-associated liver injury remain unknown.

The patient in our case had been taking captopril and omeprazole, which have rarely been associated with hepatotoxicity; however, it is important to note that the patient had been taking them for more than 18 months before the development of hepatocellular injury. The negative viral hepatitis serology results and the absence of sepsis or hypotensive shock point to levofloxacin as a possible cause of the hepatitis. In addition, the association between the de-

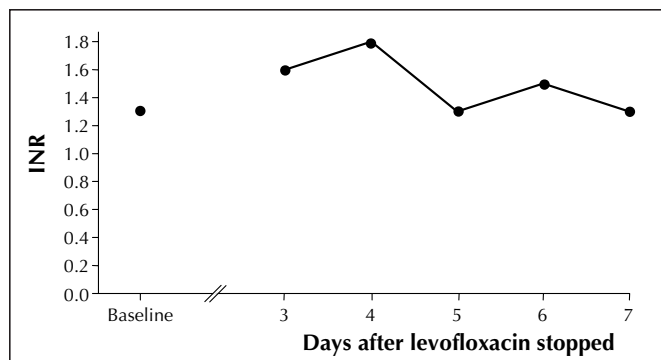
velopment and resolution of hepatitis and the initiation and discontinuation of the levofloxacin therapy while no other specific medical interventions were performed supports the possibility that levofloxacin was the causative agent.

Since its introduction in 1993, levofloxacin has been prescribed to more than 200 million patients worldwide. The drug is widely used because it has a broad spectrum of antimicrobial activity and a favourable risk-to-benefit ratio. The most common side effects are nausea (1% to 3% of cases) and diarrhea (1% to 2%), with an overall rate of adverse events of 6.2%.<sup>4-6</sup> The rate of reversible liver enzyme abnormalities due to fluoroquinolones as a class is 2% to 3%.<sup>6,7</sup> The association between trovafloxacin and severe hepatocellular damage causing morbidity and mortality is well known. There are only a few reports of severe hepatocellular injury related to other fluoroquinolones.<sup>6-12</sup>

Physicians should be aware of levofloxacin-associated hepatocellular injury, which, although rare, can be severe. Our case and the previously reported one<sup>1</sup> suggest that the injury is reversible after discontinuation of the medication. Because this condition is rare, we do not suggest routine monitoring of the liver enzymes with administration of levofloxacin. However, physicians should be aware of possible liver injury associated with the drug, especially when it is administered to patients with significant renal impairment.



**Fig. 2:** Bilirubin levels at baseline (2 months before start of levofloxacin therapy) and days after therapy was stopped.



**Fig. 3:** International normalized ratio (INR) at baseline (2 months before start of levofloxacin therapy) and days after therapy was stopped.

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