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A Fatal Case of Ciprofloxacin-induced Fulminant Hepatitis

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ABSTRACT

Fatal hepatotoxicity associated with ciprofloxacin is extremely rare. This is the second fully investigated case of fulminant hepatotoxicity due to ciprofloxacin in a male patient previously ciprofloxacin tolerant. The patient's medical history included stable Waldenstrom's macroglobulinaemia, inguinal hernia repair, prostate cancer (radiotherapy in 2006) and idiopathic Parkinson's disease. Extensive investigation for progressive liver failure confirmed drug-induced liver injury.

LEARNING POINTS

- Idiosyncratic drug-induced liver injury is rare, so a history of consumption of any potentially offending drug is vital.
- Exhaustive searches for alternative causes are imperative and a comprehensive history is essential, including a travel history with microbiological investigations if necessary; potential drug-induced liver injury must always be considered.
- The patient's age and past medical history may affect outcome.

KEYWORDS

Ciprofloxacin, hepatitis, adverse drug reaction

BACKGROUND

Ciprofloxacin is widely used. A fatal drug reaction is extremely rare but clinicians should be aware of this possibility.

CASE DESCRIPTION

A 72-year-old man presented to his general practitioner with malaise, fatigue, and signs and symptoms suggestive of right lower zone pneumonia. He was prescribed ciprofloxacin having taken it before without ill-effect. However, 2–3 days later he noted darkening of his urine and appeared jaundiced at a routine outpatient haematology clinic when biochemistry revealed significant hepatitis. Tests revealed ALT 1779 U/l, bilirubin 156 µmol/l and alkaline phosphatase 239 U/l. The patient was admitted for investigation of acute hepatitis.

His medical history included Waldenstrom's macroglobulinaemia, inguinal hernia repair, prostate cancer (radiotherapy with curative intent in 2006) and idiopathic Parkinson's disease. His medications were co-careldopa, sumatriptan, fluticasone and tadalafil, none of which were acute prescriptions. The patient had completed treatment for Waldenstrom's 3 months previously after six cycles of bendamustine/rituximab, with no complications and normal liver function tests.

The patient was retired having worked abroad for many years, and was in good physical health, frequently walking 6–7 km. He was an ex-smoker and consumed 14 units of alcohol per week.

On admission, the patient appeared jaundiced with no other examination findings and no stigmata of chronic liver disease. Liver biochemistry was elevated, prothrombin time was marginally elevated at 15 seconds, and renal function was normal. An abdominal ultrasound was normal except for long-standing, stable, mild splenomegaly.

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A chest radiograph revealed confluent shadowing at the base of the right lung field, which was confirmed to be right/middle lobe collapse/consolidation on a CT scan of the thorax, abdomen and pelvis. No obstructive cause was found for jaundice (normal intra- and extra-hepatic ducts), but there was slight mediastinal and left para-aortic lymphadenopathy.

An extended non-invasive liver screen was unremarkable; testing for hepatitis A, B, C and E was negative, ferritin was 96 ng/ml, the auto-immune profile was normal, IgM kappa paraproteinaemia was detected (long-standing and in keeping with Waldenstrom's – otherwise normal), anti-nuclear antibody was negative, and a1AT was normal. Tests for leptospirosis, influenza A and B, psittacosis, mycoplasma, *Coxiella burnetii*, CMV, EBV, amoebiasis, hydatid disease, strongyloides and fasciola IFAT were all negative. Stool/urine samples were negative. ALT fell to 584 U/l and the patient remained well off antibiotics. Haematological causes of the hepatitis were thought unlikely. The patient was discharged with urgent hepatology follow-up, but deteriorated and was re-admitted with a productive cough. *Streptococcus pneumoniae* was isolated from blood culture and Tazocin (piperacillin plus tazobactam) was commenced.

The patient was regularly discussed with the regional tertiary liver transplant centre where the differential was thought to be drug-induced liver injury or an infiltrative process. As it was felt unlikely that steroids would be of benefit, the patient continued with best supportive treatment. However, bilirubin continued to rise so he was transferred to the regional transplant centre. Liver biopsy revealed 'severe cholestasis without much inflammation or lymphomatous change'. Biopsies were consistent with drug-induced injury thought to be secondary to ciprofloxacin and importantly showed no haematological relapse. Transplantation was not considered suitable so the patient was repatriated to his original referring hospital.

On return from the tertiary centre, the patient deteriorated, experiencing rectal bleeding associated with coagulopathy. He was treated with packed red cells and fresh frozen plasma and reviewed by the local ICU team. A CT angiogram revealed moderate ascites but no source of contrast extravasation. Discussions with his family were on-going but he continued to deteriorate. At this stage, supportive care was considered best. The patient died 49 days after commencing oral ciprofloxacin.

DISCUSSION

Ciprofloxacin is a widely used fluoroquinolone antibiotic with excellent bioavailability and active against a number of Gram-positive and Gram-negative organisms. Severe hepatotoxicity is a rare side effect with only a handful of reported cases of fatal fulminant hepatitis [1–3]. Only one patient had complete work-up and liver biopsy. In the USA, the rate of acute liver failure from ciprofloxacin-induced liver injury is thought to be 2.1 cases per 10 million prescriptions [4].

Mild elevations of transaminases are occasionally (1–3%) seen but typically self-resolve [5]. Severe reactions are much rarer and fulminant hepatitis is very rare. Often presenting with encephalopathy and coagulopathy, the vast majority of patients recover within weeks or months. Liver injury usually occurs within 2–14 days, causing nausea, malaise and abdominal pain which slowly resolve on withdrawal of the drug [3]. Those at most risk of severe drug-induced liver injury tend to have underlying liver disease, excessive alcohol intake or possibly previous ciprofloxacin-associated liver disease [2, 6]. Advancing age has not been shown to increase mortality [6].

The mechanism of ciprofloxacin toxicity is unknown, but could be cellular necrosis, subsequent cholestasis or a hypersensitivity reaction. Liver biopsy in suspected cases has shown a range of histological patterns of injury.

Most patients improve upon withdrawal of the drug with liver enzymes normalising in subsequent months. Steroids, occasionally used, are advocated only if there are convincing signs of hypersensitivity [3]. Treatment options for this condition are limited; supportive therapy with optimal nutritional support is vital, and for some, transplantation may be their only hope.

This patient underwent extensive investigation and, in the absence of an alternative causative factor, ciprofloxacin hepatotoxicity was thought the most likely cause of his acute fulminant liver failure. The clinical course consisted of acute hepatocellular injury occurring in the first few days, with a rapid decline in transaminases and a subsequent prolonged cholestatic phase. The patient had a Rucam score [7] of 11, calculated as follows: hepatocellular type, second exposure 1–15 days previously=2, decrease of ALT to >50% in 8 days=3, alcohol use=1, age >55=1, compatible drug=0, other causes=2, reaction labelled on product=2, re-challenge=0). This was the maximum score without re-challenge with the offending drug, which increases the likelihood of ciprofloxacin causality. Furthermore, there are no reported cases of fulminant hepatitis from bendamustine [8]. Reports of liver injury attributed to rituximab [9] have not been convincing apart from re-activation of hepatitis B. However, this patient had negative serology and liver biopsy inconsistent with this possibility.

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