Case Report

Cholestatic hepatitis with ciprofloxacin therapy: A Case Report

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Abstract

Ciprofloxacin has generally been well-tolerated and is the commonly prescribed fluoroquinolone antibiotic for treatment of urinary tract and gastrointestinal infection. The adverse effects on the liver usually range from asymptomatic elevation of liver enzymes to fulminant hepatitis. However, acute fulminant hepatitis and cholestatic hepatitis are reported rarely in literature**.** Here, we report a case of ciprofloxacin induced cholestatic hepatitis in a 52 year old woman following intravenous ciprofloxacin for acute gastroenteritis.

Keywords: Ciprofloxacin, Cholestasis, Hepatitis, Toxicity

Introduction

Ciprofloxacin is a commonly prescribed fluoroquinolone antibiotic that has broad antimicrobial coverage and high oral bioavailability. It is commonly used in the treatment of urinary tract and gastro-intestinal infections due to its activity against both Gram-positive and Gram-negative bacteria.[1] It has associated severe adverse effects including tendon rupture, Stevens-Johnson syndrome, interstitial nephritis, and liver injury. Liver injury is usually limited to an asymptomatic elevation in liver enzymes.[2] However, a broad spectrum of drug-induced liver diseases ranging from an asymptomatic elevation in liver enzymes and hepatitis to fulminant hepatic failure have been reported.[2] Acute fulminant hepatitis and cholestatic hepatitis are reported rarely in the literature.[3] Ciprofloxacin at times causes acute liver injury

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within a period of two days to two weeks following initiation of treatment. Having a high index of suspicion is important for clinicians to recognize and discontinue any medication suspected of producing such reactions. Here, we report a case of cholestasis in a patient treated with ciprofloxacin for acute gastroenteritis. To the best of our knowledge there is no previous report of ciprofloxacin-induced cholestatic hepatitis in Sri Lanka.

Case report

A 52 year old hypertensive woman presented with acute onset of fever and severe watery diarrhea of three days duration. She had not passed urine for 24 hours. She had no other systemic symptoms and no history of substance abuse, herbal medication or drug overdose prior to admission and had no family history of liver cell disease.

On examination, she was severely dehydrated with a pulse rate of 120/min and low volume. Her blood pressure was 70/40mmHg. The rest of the systemic examination was normal. Her complete blood count showed marked leukocytosis (18,000/mm^3) with predominant neutrophils (90%). Her inflammatory markers were high (ESR:80mm/1st hour, CRP:490 mg/dL) suggestive of bacterial gastroenteritis. Her serum creatinine was 610 μmol/L (normal value:79-118 μmol/L) and blood urea was 60mg/dL (normal value:8-25 mg/dL). Her serum electrolytes (serum sodium:135mmol/dL, serum potassium:4.5mmol/dL) and liver function tests (serum aspartate aminotransferase (AST):25 U/L, serum alanine aminotransferase (ALT):35 units/L, total bilirubin:17 μmol/L, and alkaline phosphatase (ALP):49 units/L) were normal. Her blood, urine and stool cultures were negative.

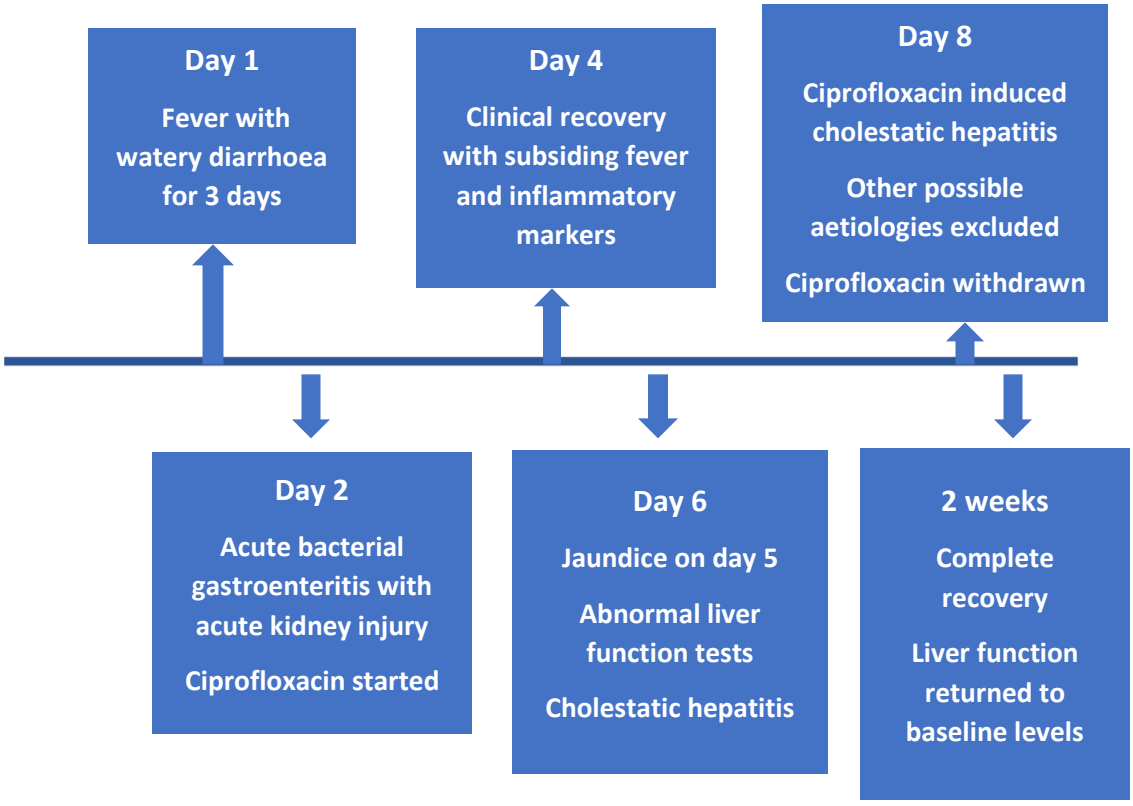
The patient was initially managed with boluses of normal saline, oral rehydration salt and antiemetic and was stabilized with initial treatment. Subsequently she was treated with renal dose of intravenous ciprofloxacin 200mg twice daily following 12 hours of admission due to leucocytosis with high inflammatory markers. She clinically improved with settling of fever and reduction of inflammatory markers. However, she was found to have jaundice on the fifth day of admission without any evidence of obstructive jaundice. She was deeply icteric. Her laboratory investigations showed a total bilirubin of 147 μmol/L, direct bilirubin of 87 μmol/L, AST and ALT of 254 U/L and 566 units/L respectively and ALP of 149 units/L. Other metabolic and hematological parameters were normal on work up.

A complete work up of investigations to exclude other possible causes of acute viral hepatitis (Hepatitis A antibody, Hepatitis B surface antigen, Hepatitis C antibody, Hepatitis E antibody), urine toxicology screening and autoimmune markers (antinuclear antibody) were negative. Her radiological imaging was negative.

The liver injury secondary to use of ciprofloxacin was made because her symptoms started on the 5th day of ciprofloxacin therapy. Therefore, ciprofloxacin was stopped. The patient was treated with supportive therapy with hydration and anti-emetics as needed. Subsequently the patient's symptoms resolved over the next five

days with improvement of her liver enzyme levels. Her liver function tests normalized gradually with cessation of ciprofloxacin and completely recovered with normal limits within two weeks time (total bilirubin:15 µmol/L, AST:34 U/L, ALT:26 units/L, and ALP:59 units/L). Timeline of the clinical course is given below.

Timeline for progression of disease



The onset of symptoms following ciprofloxacin use coupled with the pattern of cholestatic picture of liver pathology and the normalization of liver function tests following withdrawal of ciprofloxacin therapy all pointed towards the diagnosis of ciprofloxacin induced acute hepatitis.

Discussion

Ciprofloxacin related liver injury ranges from asymptomatic elevation of liver enzymes to fulminant hepatitis.[2] Ciprofloxacin is absorbed well in the gastrointestinal tract and metabolized in the liver and then excreted by the kidneys. It causes 1-3% self-limited transient elevation of liver enzymes. Jaundice with hepatomegaly may be noted on clinical examination. Cholestatic hepatitis is rarely reported in the literature.[3] The pathogenesis related to liver injury is unknown. However, an idiosyncratic reaction resulting in hepatocellular necrosis has been described.[3] The type of liver injury could be differentiated from the pattern of

elevation of liver enzymes. The elevation of ALP more than two times or ALT/ALP ratio less than 2 indicates cholestatic hepatitis.[4]

The cholestatic hepatitis associated with markedly elevated liver enzymes was described in our patient. There are no specific tests to establish the diagnosis of drug induced hepatitis which is usually a diagnosis of exclusion. The onset of symptoms following ciprofloxacin therapy should alert the clinician and needs prompt discontinuation of the drug and suggest further evaluation. Ciprofloxacin induced hepatitis is usually nonfatal and self-limiting following discontinuation. One fatal case has been reported in the literature.[5] A high clinical suspicion of a drug reaction is important to discontinue the drug immediately and prevent further adverse reactions. Prerenal acute kidney injury due to gastroenteritis had no impact on the hepatic outcome because the initial liver function tests were normal.

Our patient developed ciprofloxacin induced liver injury on the 5th day of initiation of drug therapy. The patient's liver biochemical profile returned to normal in 2 weeks following the stopping of ciprofloxacin. A complete negative work up for the possible causes of acute viral hepatitis, urine toxicology screening, autoimmune markers and radiological imaging favored the diagnosis of ciprofloxacin induced hepatitis in our patient.

This case provides evidence that ciprofloxacin can cause liver injury at therapeutic doses. Ciprofloxacin can cause severe hepatitis and physicians should be aware of this possible drug reaction.

Conflicts of interest: There are no conflicts of interest.

Ethics: Informed written consent was obtained from the patient for publication of this case report.

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