American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 676-681
DOI: 10.12659/AJCR.899080

Received: 2016.04.15
Accepted: 2016.06.29
Published: 2016.09.22

Ciprofloxacin Exposure Leading to Fatal Hepatotoxicity: An Unusual Correlation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Carly Unger
AEFG 2,3 Layth S. Al-Jashaami

1 Bethel University Physician Assistant Program, Paris, TN, U.S.A.
2 Department of Internal Medicine, Banner University Medical Center, Phoenix, AZ, U.S.A.
3 University of Arizona, College of Medicine, Phoenix, AZ, U.S.A.

Corresponding Author: Carly Unger, e-mail: cunger05@bethelu.edu
Conflict of interest: None declared

Patient: Female, 74
Final Diagnosis: Acute drug-induced liver failure
Symptoms: Anorexia • fatigue • nausea • vomiting
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Challenging differential diagnosis

Background: Ciprofloxacin is a commonly used fluoroquinolone antibiotic. It is occasionally associated with benign elevations in liver enzymes. Few reports in the literature correlate ciprofloxacin with significant liver injury. We present a fatal case of ciprofloxacin-induced liver failure.

Case Report: A 74-year-old female was successfully treated with ciprofloxacin for a urinary tract infection (UTI), but immediately began having new-onset symptoms, including fatigue and nausea. This continued for two months, at which time she presented to the hospital; she was found to have elevated liver enzymes and another UTI. She was treated with ciprofloxacin again for UTI and discharged three days later, following mild improvement. One week later, she returned to another hospital and was found to have more significantly elevated liver function tests and jaundice. Extensive viral and autoimmune panels were unremarkable. Liver biopsy showed cholestatic hepatitis of unclear etiology. The patient was discharged again following a mild decline in liver enzymes. Soon after, the patient was admitted to our institution with similar complaints. Serum transaminases remained elevated, with an increase in alkaline phosphatase and bilirubin. The Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scale was found to be 8, outlining a high or definite probability that the ciprofloxacin was the cause of the patient's hepatotoxicity. A one-week course of prednisone for possible hypersensitivity reaction was tried; however, it proved unsuccessful. Palliative care was consulted, and the patient passed away shortly thereafter.

Conclusions: This case demonstrates the potential for liver failure from ciprofloxacin. Clinicians should evaluate the possibility of ciprofloxacin-induced hepatotoxicity in a patient presenting with liver injury of unknown etiology. Similarly, it is important to consider this significant effect when a practitioner considers antibiotic choice.

MeSH Keywords: Ciprofloxacin • Drug-Induced Liver Injury • Liver Failure, Acute

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/899080

Background

Antimicrobials are the most frequently identified cause of drug-induced liver injury [1]. The fluoroquinolone class is a rare offender. In fact, its class is implicated with hepatotoxicity in some 1:100,000 individuals exposed [2]. Ciprofloxacin has been associated with occurrences (1–3%) of mild, temporary elevations in liver enzymes; however, severe hepatic injury is a rare finding. Usually acute liver injury involving ciprofloxacin presents within two days to three weeks of use. Recovery is generally seen within two to four weeks, following cessation of the drug [3]. Herein, we present a different outcome in which the ciprofloxacin-induced hepatotoxicity would prove fatal. To our knowledge, only three reports of death associated with ciprofloxacin-induced liver failure are found in the literature [4–6].

Case Report

A 74-year-old female was treated with ciprofloxacin for a urinary tract infection (UTI). On day 4 of the use of the antibiotic, however, the patient experienced nausea and vomiting. The patient was told it was a "high dose of ciprofloxacin", and it was discontinued on day 5. While the patient had been in relatively good health previously, she continued having symptoms over the following two months including nausea, anorexia, fatigue, and generalized weakness.

Following increased weakness and near-syncope, she was admitted for hospital evaluation. A thorough history revealed a past medical history of hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), and hypothyroidism. Her only medications included simvastatin (Zocor) 20 mg daily, pantoprazole (Protonix) 20 mg daily, and levothyroxine (Synthroid) 75 mcg daily. She denied any history of herbal supplements, acetaminophen use, or previous liver disease. She also denied any tobacco, alcohol, or illicit drug use. Additionally, her physical examination was essentially unremarkable. Significant labs on admission included: aspartate transaminase (AST) 1,106, alanine transaminase (ALT) 789, alkaline phosphatase (ALP) 338, total bilirubin (TBIL) 2.75, albumin 2.6, hemoglobin 11.6, white blood cells 4,700, and platelets 142,000 (Figure 1). She was also found to have a UTI, and was again treated with three days of ciprofloxacin, as the antibiotic had not yet been considered as a likely cause of the patient's hepatitis. Instead, the patient's abnormal liver transaminases were incorrectly attributed to dehydration and hypoperfusion, as she reported a history of anorexia and poor fluid intake. Following slight improvement in transaminase values, she was discharged on day 3.

Over the course of six days, the patient developed progressive weakness and new-onset vomiting and jaundice, and was subsequently admitted. Her physical examination was remarkable

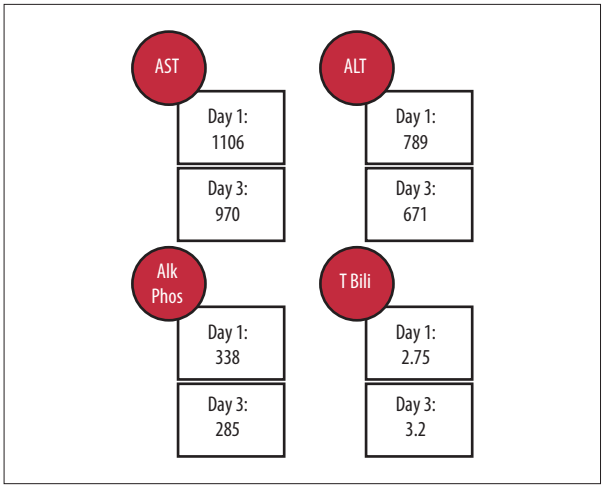

Figure 1. Lab values on the days of admission and discharge, days 1 and 3 respectively, from inpatient stay 1.

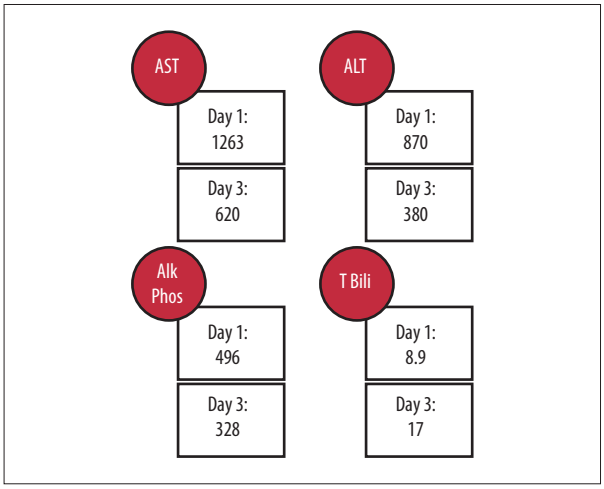

Figure 2. Lab values on the days of admission and discharge, days 1 and 14 respectively, from inpatient stay 2.

for bilateral pedal edema and icterus. Significant labs on admission included: AST 1,263, ALT 870, ALP 496, TBIL 8.9, albumin 2.5, international normalized ratio (INR) 1.2, and platelets 185,000 (Figure 2). Acetaminophen and salicylate levels were obtained, as these drugs are frequent offenders of hepatotoxicity, but were within normal limits. At this time, the patient was taken off of simvastatin as it is a relatively common offender of hepatotoxicity. She also received an extensive workup for liver disease. Serologies for viral hepatitis including antibody screening for hepatitis A, B, C, D and E were all nonreactive. Similarly, serologies for herpes simplex virus (HSV) and cytomegalovirus (CMV) were not suggestive of a cause. Imaging studies including abdominal CT and abdominal ultrasound showed nonspecific heterogeneity of the liver. Similarly, magnetic resonance cholangiopancreatography (MRCP) revealed an atrophic right hepatic lobe. The patient underwent a liver biopsy, which was essentially inconclusive, showing active chronic

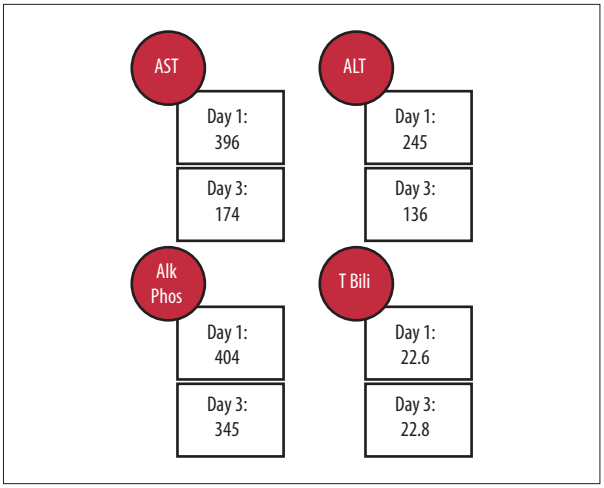

Figure 3. Lab values on the days of admission and final lab draw, days 1 and 5 respectively, from inpatient stay 3.

hepatitis with cholestasis and portal and periportal fibrosis. Additional studies including alpha 1 antitrypsin, ceruloplasmin, antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA), and IgG were of no benefit. CA 19-9 was increased at 187; however, CT and MRCP showed no mass. Additionally, alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were within normal limits. Furthermore, hematology-oncology was consulted and concluded no further workup for malignancy was necessary. Following mild decreases in liver enzymes, despite a rise in bilirubin, the patient was discharged and instructed to follow up with her gastroenterologist.

The patient presented one week later to our facility with worsening fatigue, nausea, anorexia, emesis, and jaundice. Upon our evaluation, the patient was noted to have significant icterus of skin and sclera. Mild ascites and bilateral 2+ pitting, weeping edema were noted. Significant labs on admission included: AST 396, ALT 245, ALP 404, TBIL 22.6, album 2.1, INR 1.8, and platelets 105,000 (Figure 3). Given the extensive workup at the previous hospital, further evaluation of this patient's liver disease included an Epstein-Barr virus (EBV) panel, the results of which were unremarkable. Furthermore, an additional abdominal CT scan showed a small amount of free fluid in the abdomen and an atrophic right hepatic lobe. Additionally, the CIOMS/RUCAM scale was assessed to be 8, defining the suspicion of the ciprofloxacin as the cause of the patient's hepatotoxicity as highly probable. Factors considered in this evaluation included the time of onset between medication use and our patient's symptoms, the course of injury, our patient's risk factors for such a reaction, concomitant drug administration, potential non-drug origins of the hepatic failure, documented information regarding hepatotoxicity and ciprofloxacin, and the response to readministration of the antibiotic.

Treatment over the course of the patient's 12-day hospital stay was mostly limited to supportive measures. On hospital day 1 the patient was given 100 mL of 25% albumin. Additionally, on hospital day 3 the patient was started on prednisone 20 mg daily for probable drug reaction, based on the CIOMS/RUCAM evaluation. She was also treated with lactulose 20 g daily, rifaximin (Xifaxin) 550 mg twice daily, furosemide (Lasix) 40 mg daily and spironolactone (Aldactone) 100 mg daily. Maintenance medications included pantoprazole 40 mg daily, and levothyroxine 75 mcg daily.

Despite such medical treatment, the patient's TBIL continued increasing steadily. Similarly, her ALP remained elevated, at nearly three times the upper limit of normal. The patient continued to show clinical decline over the course of the next several days with increased edema, dyspnea, disorientation, and icterus. Prednisone was discontinued after one week. The patient requested and received palliative care at this time, and she passed away on hospital day 12.

Discussion

Acute hepatic failure is most commonly drug-induced in Western society. This is of particular importance today, with an aging population and the growing concern of polypharmacy [1]. The mechanism by which drug-induced liver injury occurs is poorly understood. Most such injuries are thought to be idiosyncratic in nature. Rarer findings include dose-dependent reactions. Additionally, research shows no specific pattern of enzyme elevations; however, the majority of cases in which a mixed pattern is seen tend to be less severe [6–8]. Our patient showed a hepatocellular enzyme pattern of injury, while the findings on liver biopsy were consistent with cholestatic hepatitis.

Despite research limitations, there are characteristic signs and symptoms involving drug-induced hepatic failure of which a clinician should be aware. Our patient had many classical symptoms, including fatigue, nausea, encephalopathy, and jaundice. Other symptoms a patient may present with include abdominal pain and pruritus [1,3].

Of course, transaminitis supports the diagnosis. As stated previously, fluoroquinolones have been associated with benign, temporary elevations in transaminases. Literature supporting an association between fluoroquinolones, particularly ciprofloxacin, and significant liver injury, however, is limited. To our knowledge, we describe one of the few reported cases of death from ciprofloxacin [4–6].

Other potential sources of the patient's liver failure were evaluated at length. Our patient's case was complicated by her use

Table 1. Table representing the scores of our patient using the Naranjo scale, determining the relationship between an adverse clinical event and a drug.

Question	Yes	No	Don't know
Are there previous conclusive reports on this recation?	1		
Did the adverse event appear after the suspected drug was admnistered?	2		
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	1		
Did the adverse event reappear when drug was re-admnistered?	2		
Are there alternate causes, other than the drug, that could solely have caused the reaction?		2	
Did the reaction reappear when a placebo was given?			0
Was the drug detected in the blood (or other fluids) in a concentration know to be toxic?		0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?			0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1		
Was the adverse event confirmed by objective evidence?			0

Total: 9: (≥9=definite, 5–8=probable, 1–4=possible, ≥0=doubtful).

of other medications, yet each was relatively easily ruled out as the likely offending drug. She had been taking simvastatin, pantoprazole, and levothyroxine for many years without any elevation of aminotransferases or other consequence. While simvastatin is the most noted of her medication history to be associated with hepatotoxicity, it did not correlate with our patient's clinical picture, as it classically shows a mild course, with an onset of symptoms within the first one to six months of use [9]. Similarly, evidence is limited regarding aminotransferase levels during levothyroxine use; however, its use has been associated with rare occurrences of hypersensitivity reactions, with symptoms noted within eight weeks of use. Classical symptoms include fever and fatigue [10]. Again, the timeframe poorly correlates with this patient's presentation, as she had been taking levothyroxine for many years. Likewise, fever was not part of her symptomatology. Lastly, the patient's history of pantoprazole was not suspicious for a relationship to her hepatic injury. Pantoprazole has been associated with increases in ALT in less than 1% of patients. Additionally, clinically apparent injury has been shown to appear within four weeks of use [11]. Once more, this medication was easily excluded as a likely cause of this patient's hepatitis, given her use of the medication for many years without any sequelae. Moreover, this patient received an extensive liver workup that eliminated other potential etiologies of her hepatic failure. Her workup included multiple imaging studies, including abdominal ultrasound, CT, MRCP, and liver biopsy. While none of these diagnostic measures established a clear origin of the patient's injury, they did help to narrow the differential diagnosis, excluding an obstructive source or malignancy. Viral serologies, including hepatitis A, B, C, D, E, CMV, EBV, and HSV were unremarkable. Additional studies, including alpha 1 antitrypsin, ceruloplasmin, ANA, and AMA, were similarly without diagnostic benefit.

Given the unremarkable findings of the extensive liver workup and the clinical presentation of our patient, the focus increasingly shifted towards evaluating ciprofloxacin as the most likely offender of her hepatotoxicity. Our patient's symptom onset on day 4 of ciprofloxacin use was comparable to other reports, in which symptoms began within one day to three weeks of exposure [4–6,12–14]. Similarly, she had taken no other new medications during this time. Also taken into consideration was our patient's CIOMS/RUCAM scale of 8, relating her ciprofloxacin use and hepatic failure as a highly probable causation. Several factors are taken into consideration in this scale, as stated previously. Our patient's R ratio was 6; therefore, the enzyme pattern is regarded as hepatocellular in nature. In addition, she began having symptoms four days into use of ciprofloxacin, thus one point was added for the time of onset. Two points were added for the course, as her ALT decreased more than 50% from the peak value in less than 30 days. The patient was greater than 55 years old, thus one point was given for this risk factor. Zero points were calculated for concomitant drug administration, as the patient had been taking her other medications for many years, far outside the typical window of time for hepatic injury [9–11]. Two points were given for non-drug causes, as the patient received a negative workup extensively evaluating other potential causes, including numerous viral sources of hepatitis,

biliary obstruction, alcoholic liver disease, and autoimmune diseases. Similarly, one point was added for noted cases of ciprofloxacin causing hepatic injury, but without indication of such adverse effect on the drug's label. Finally, an additional point was given as the patient's bilirubin increased by more than 50% following readminstration of ciprofloxacin [15–18]. Additional scales evaluating adverse drug reactions include the WHO-UMC (World Health Organization-Uppsala Monitoring Centre) Causality Assessment, Naranjo scale, and preventability assessment. According to the WHO-UMC assessment, the causal link between ciprofloxacin use and this patient's hepatotoxicity is probable/likely, based on its four categories involving laboratory abnormality and time frame, the unlikelihood that such hepatic failure was from another drug or disease, the clinical change following our patient's cessation of ciprofloxacin, and the fact that rechallenge with the drug was inadvertently performed but not required [19]. In addition, according to the Naranjo scale, our patient had a value of 9, indicative of a definite adverse drug reaction (Table 1) [17,19,20]. Finally, the adverse drug reaction in our case was assessed as "not preventable" using the Shumock and Thornton scale of preventability [21,22]. Such findings supported the rationale of a one week treatment with prednisone for a possible hypersensitivity reaction to ciprofloxacin in our patient. Unfortunately, this proved unsuccessful and our patient passed away on hospital day 12.

As stated previously, our patient received an additional course of ciprofloxacin, despite her symptoms following receipt of her first course. It is unclear if this patient's outcome would have been different if multiple courses of ciprofloxacin had not been administered. Reports outlining significant dose-dependent reactions to ciprofloxacin are limited [23]. Further research in this field is implicated to ensure quicker recognition and better understanding of such injury in the future.

Conclusions

Hepatotoxicity with ciprofloxacin warrants further investigation. Better understanding of the mechanisms of disease, including individual variations in drug response, could lead to improved outcomes and even prevention. Clinicians should be aware of the potential for significant liver injury involving ciprofloxacin. Indeed, this patient's outcome may have been different had ciprofloxacin been evaluated earlier in her course of care as a potential source of her hepatotoxicity. Similarly, it is unclear if the patient's prognosis would have been changed had she not been given an additional course of the drug. In conclusion, the benefit of this study is two-fold: both in the evaluation of ciprofloxacin as a possible cause of liver failure, and in increasing consideration of appropriate antibiotic choice for a given patient.

Conflicts of interest

None.

References:

1. Haque T, Sasatomi E, Hayashi PH: Drug-induced liver injury: Pattern recognition and future directions. Gut Liver, 2016; 10: 27–36
2. Andrade RJ, Tulkens PM: Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother, 2011; 66: 1431–46
3. NIH: National Institutes of Health and LiverTox [Internet]. Bethesda (MD): Ciprofloxacin. [(accessed on 29 January 2015)]. Available from: *URL:http://livertox.nlm.nih.gov/Ciprofloxacin.htm*
4. Fuchs S, Simon Z, Brezis M: Fatal hepatic failure associated with ciprofloxacin. Lancet, 1994; 343: 738–39
5. Grassmick BK, Lehr VT, Sundareson AS: Fulminant hepatic failure possibly related to ciprofloxacin. Ann Pharmacother, 1992; 26: 636–39
6. Zimpfer A, Propst A, Mikuz G et al: Ciprofloxacin-induced acute liver injury: case report and review of literature. Virchows Arch, 2004; 444: 87–89
7. Orman ES, Conjeevaram HS, Vuppalanchi R et al: Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol, 2011; 9: 517–523.e3
8. NIH: National Institutes of Health and LiverTox: Cholestatic Hepatitis [(accessed on 2 February 2016)]. Available from: URL: *http://livertox.nih.gov/Phenotypes_chol.html*
9. NIH: National Institutes of Health and LiverTox: Simvastatin [(accessed on 10 February 2016)]. Available from: URL: *http://livertox.nlm.nih.gov/Simvastatin.htm*
10. NIH: National Institutes of Health and LiverTox [Internet]. Bethesda (MD): Levothyroxine [(accessed on 6 June 2016)]. Available from: URL: *http://livertox.nlm.nih.gov/levothyroxine.htm*
11. NIH: National Institutes of Health and LiverTox [Internet]. Bethesda (MD): Pantoprazole [(accessed on 6 June 2016)]. Available from: URL: *http://livertox.nlm.nih.gov/Pantoprazole.htm*
12. Dichiara AJ, Atkinson M, Goodman Z, Sherman KE: Ciprofloxacin-induced acute cholestatic liver injury and associated renal failure. Case report and review. Minerva Gastroenterol Dietol, 2008; 54(3): 307–15
13. Goetz M, Galle PR, Schwarting A: Non-fatal acute liver injury possibly related to high-dose ciprofloxacin. Eur J Clin Microbiol Infect Dis, 2003; 22(5): 294–96
14. Villeneuve JP, Davies C, Cote J: Suspected ciprofloxacin-induced hepatotoxicity. Ann Pharmacother, 1995; 29(3): 257–59
15. Danan G, Teschke R: RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci, 2015; 17: 14
16. NIH: National Institutes of Health and LiverTox [Internet]. Bethesda (MD): Roussel Uclaf Causality Assessment Method (RUCAM) in Drug Induced Liver Injury [(accessed on 29 May 2016)]. Available from: URL: *http://www.livertox.nih.gov/rucam.html*
17. NIH: National Institutes of Health and LiverTox [Internet]. Bethesda (MD): Causality. [(accessed on 29 May 2016)]. Available from: URL: *http://livertox.nih.gov/Causality.html*
18. García-Cortés M, Stephens C, Lucena MI et al., Spanish Group for the Study of Drug-Induced Liver Disease (Grupo de Estudio para las Hepatopatías Asociadas a Medicamentos GEHAM): Causality assessment methods in drug induced liver injury: strengths and weaknesses. J Hepatol, 2011; 55(3): 683–91
19. Zaki S: A. Adverse drug reaction and causality assessment scales. Lung India, 2011; 28(2), 152–53
20. Naranjo CA, Busto U, Sellers EM et al: A method for estimating the probability of adverse drug reactions. Clin Pharacol Ther, 1981; 30: 239–45

21. Raut A, Patel P, Patel C, Pawar A: Preventability, predictability and seriousness of adverse drug reactions amongst medicine inpatients in a teaching hospital: A prospective observational study. International Journal of Pharmaceutical and Chemical Sciences, 2012; 1(3): 1293–99

22. Schumock GT, Thornton JP: Focusing on the preventability of adverse drug reactions. Hosp Pharm, 1992; 27: 538

23. Bataille L, Rahier J, Geubel A: Delayed and prolonged cholestatic hepatitis with ductopenia after long-term ciprofloxacin therapy for Crohn's disease. J Hepatol, 2002; 37(5): 696–99