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OPEN JOURNAL OF
Pharmacology and Pharmacotherapeutics

DOI: https://dx.doi.org/10.17352/ojpp

Case Study

A rare case of ciprofloxacin-induced cholestatic hepatits in the newborn

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Received: 03 February, 2021
Accepted: 10 February, 2021
Published: 11 February, 2021

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Keywords: Ciprofloxacin; Cholestasis; Hepatitis; Toxicity

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Abstract

Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic with wide spectrum of activity against Gram-negative, Gram-positive and anerobic organisms. It has greatest utility in the treatment of children hospitalized with serious bacterial infections. The adverse effects on the liver usually range from asymptomatic elevation of liver enzymes to fulminant hepatitis.

Ciprofloxacin has also been linked to rare cases of cholestatic jaundice that usually arises after 1 to 3 weeks of therapy. Most cases are mild and self-limited, but at least one instance of vanishing bile duct syndrome related to Ciprofloxacin therapy has been published.

We report a case of cholestasis in neonate of gestational age 35 weeks who had septicaemia and received ciprofloxacin for 8 days. This infant developed cholestasis and deranged liver transaminases several days after the discontinuation of therapy with ciprofloxacin.

Introduction

Drug-induced liver injury is important in the differential diagnosis in patients with liver injury. A diagnosis of drug-induced liver injury is a challenge and probably one of the most difficult to establish among liver diseases [1]. Antibiotics are the most common drugs reported in major studies of drug-induced liver injury.

Ciprofloxacin is a fluorinated quinolone antimicrobial agent that is widely used to treat a variety of gram positive and gram-negative infections among hospitalized children [2]. However, despite its high effectiveness and relative safety, severe adverse effects associated with its use include gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, skin rashes, photosensitivity, and liver injury [3,4]. Most commonly, liver damage related to ciprofloxacin is limited to an asymptomatic elevation in liver enzymes. Acute fulminant hepatitis and cholestatic hepatitis are reported rarely in the literature [3]. Ciprofloxacin at times causes acute liver injury 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.

In this report, we present the clinico-pathological characteristics of a newborn who developed cholestatic hepatitis after administration of Ciprofloxacin and discuss the current literature.

Case presentation

A premature baby boy with gestational age of 34 weeks was born spontaneously to a G5P4 mother after 6 days of premature rupture of fetal membranes. The mother was seronegative for HIV, Hepatitis B and VDRL. The Apgar scores were 7 and 8 at 1 and 5 minute respectively. He was intubated immediately after his birth because of heavy meconium staining. The infant weight 2.8kg (25th-50th percentile), measured 38 cm (50th-75th percentile), and had a head circumference of 30 cm (50th-

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75th percentile). On clinical exam, the infant was lethargic with a temperature of 38.5°C, blood pressure at 75/46 mm Hg, heart rate at 178 beats/min and capillary blood glucose 58 mg/dl. Other systemic reviews were unremarkable.

Investigation showed marked leukocytosis with neutrophils 17.10×109 /L, moderate anemia and thrombocytosis (Table 1). Procalcitinin (PCT) was 18.22 mg/dL, CRP was 55 mg/l and blood culture was negative. The lumbar puncture was negative. Serum aspartate transferase 33 IU/L, serum alanine transaminase 37 IU/L, serum gamma-glutamyl transferase 121 IU/L.

A diagnosis of newborn sepsis was established. The patient was started on IV fluid on admission and IV antibiotic for 8 days based on Amoxicillin (200mg/kg/day) and Gentallin (5mg/kg/day). The baby was treated for hyperbilirubinemia with phototherapy on the fifth day of life when the Total Serum Bilirubin and Conjugated Serum Bilirubin recorded were 18.9 mg/dl and 3.7 mg/dl respectively. The baby developed fever (peak of 38.7°C) four days after admission, necessitating blood culture and commencement of empirical antibiotic treatment with intravenous Ceftazidime and Amikacin. Blood culture showed significant growth of Klebsiella with sensitivity to Meropenem, Amikacin, and Ciprofloxacin but resistant to Ceftazidime. Subsequently, the antibiotic therapy was changed to Ciprofloxacin on the 17th day of life. On the 25nd day, the baby was noticed to be icteric with the passage of pale stools. The liver transaminases were deranged. TSH was 1.99 mIU/mL. TORCH titers revealed high IgG levels of rubella and cytomegalovirus. A urin analysis did not show any significant abnormality. Abdominal ultrasound was normal and abdominal CT scan revealed gall bladder wall thickening with pericholecystic halo suggestive of cholecystitis. There was gradual resolution of jaundice and normalization of liver transaminases over three months. Abdominal ultrasound repeated at a follow up visit also showed resolution of the pericholecystic halo.

It was suggestive that the cholestatic hepatits was secondary to use of ciprofloxacin since the symptoms started in the end days following the completion of the antibiotics. Given the onset of symptoms following ciprofloxacin use, the pattern of hepatic enzyme elevation suggestive of liver pathology, and the spontanous resolution of all symptoms all pointed towards the diagnosis of ciprofloxacin induced cholestatic hepatitis.

Discussion

Nosocomial infections are related to neonatal immune immaturity and the frequent use of invasive life sustaining devices mainly in preterm neonates. Also, the injudicious use of broad-spectrum antibiotics in neonatal units has led to high rates of resistance in first line empiric antibiotics like penicillin and cephalosporin [5,6]. As multidrug-resistant organisms become more of a problem in neonatal intensive care units, there is a need to evaluate the use of other available antibiotics to treat serious neonatal infections.

Fluoroquinolones are potent, bactericidal antimicrobials against a broad spectrum of Gram-negative and Gram-positive bacteria. They have been widely used in adult patients because of their excellent tissue penetration, including the cerebrospinal fluid [7].

In neonatology, the use of ciprofloxacin in life-threatening infections, although rare, is justified by the fact that clinical benefits largely overweight the potential risks [8]. In the presence of meningitis, adequate cerebrospinal fluid penetration of ciprofloxacin has been established in adults and older children and available data in infected neonates although limited, showed that cerebrospinal fluid concentrations were comparable to serum ciprofloxacin concentrations

A pharmacokinetic study performed in septic preterm neonates concluded that a dose of 20 mg/kg/d in 2 divided doses would be effective for common gram-negative infections except for Pseudomonas aeruginosa infections and ineffective for Staphylococcus aureus infections. Although this study is well conducted, it does not provide sufficient data to establish the optimal dosing schedule of ciprofloxacin in neonatal sepsis [9,10].

In paediatric patients, diarrhoea and rash are among the most common clinical adverse events and elevation in hepatic transaminases among the most common laboratory adverse events reported with use of ciprofloxacin. Serum aminotransferase elevations have been reported in 1% to 6% of recipients of intravenous ciprofloxacin. These elevations are usually transient, mild and asymptomatic; and rarely require dose adjustment. Ciprofloxacin has also been linked to rare cases of cholestatic jaundice that usually arises after 1 to 3 weeks of therapy [11,12].

Table1: Serial lab investigation results.

	Blood test				Liver function test				
Days	WBC 8.5- 30 (10^9/L)	HgB (14-20G/l)	PLQ 150-450 (10^9/L)	ASAT <40UI/L	ALAT <35UI/L	TBIL 0-0.3 (mg/dl)	DBIL 0-0.2 (mg/dl)	GGT <55UI/l	PAL 30-100 (UI/L)
1	22.5	10.9	66	33	37	-	-	-	-
5	-	-	-	36	42	18.9	3.7		
14	19.1	12	125	-	-	7.2	1.3		
17	20.1	12.2	133	-	-	-	-	-	-
25	17	11.5	156	456	345	10.1	8.1	225.6	456.9
32	16.5	12	255	433	330	9.2	7.6	230	476
48	14.2	12.2	365	256	186	8.5	7.3	212	430

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Ciprofloxacin at times causes acute liver injury within a period of two days to two weeks following the initiation of antibiotic treatment. Although the precise mechanism of ciprofloxacin-induced liver injury remains currently unknown, hepatocellular necrosis leading to elevated liver enzymes has been observed. The pattern of injury can be cholestatic, hepatocellular, or mixed. The more familiar pattern in the acute setting, is hepatocellular, which is associated with markedly elevated alanine transferase levels. The cholestatic pattern of liver injury, such as in our patient,usually occurs after a prolonged course of antibiotic use [13].

The pathogenic events that cause lesions due to the uses of drugs and toxins is either due to their direct toxic effect or an idiosyncratic immunoallergic reaction. The direct toxic effect is likely favoured by the high tissue levels of the drug or its metabolites. Drug-induced liver injury is typically idiosyncratic and is usually unpredictable until the drug is given [14]. Drug-induced liver injury can be differentiated by the level of liver enzymes. The liver injury is termed cholestatic if only alkaline phosphatase is elevated more than two times its upper normal limit or, when both serum alanine aminotransferase and alkaline phoshatase are increased, if the ALT/ALP ratio is less than 2 [15,16].

Discontinuing Fluoroquinolone and symptomatic treatment leads to the resolution of the cholestatic hepatitis within a few months. Based on our computerized literature review, we believe this to be the fourth reported case of cholestatic jaundice induced by ciprofloxacin. Although this reaction occurs infrequently, the consequences can be severe and physicians should be aware of this possible drug response in patients receiving ciprofloxacin.

Conclusions

In conclusion, the practitioners should be aware that Ciprofloxacin is able to induce drug-induced liver injury, including a prolonged symptomatic course of cholestatic hepatitis, in order to recognize early an adverse reaction to the drug thus leading to its immediate withdrawal and avoiding a repeated future exposure.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Disclosure

This clinical case was written based on clinical observation without any funding.

References

1. Watkins PB (2015) How to diagnose and exclude drug-induced liver injury. Dig Dis 33: 472-476. Link: https://bit.ly/2MIUmF7

2. Micromedex Inc. Drug Evaluation Monograph: Ciprofloxacin 86.

3. Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, et al. (2008) Drug Induced Liver Injury Network (DILIN): Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 135: 1924-1934. Link: https://bit.ly/3a2hlng

4. Zimmerman HJ (2000) Drug-induced liver disease. Clin Liver Dis 4: 73-96. Link: https://bit.ly/3jEJpAb

5. Gordon A, Isaacs D (2004) Late-onset infection and the role of antibiotic prescribing policies. Curr Opin Infect Dis 17: 231-236. Link: https://bit.ly/3aUP8hg

6. Lieberman JM (2003) Appropriate antibiotic use and why it is important: the challenges of bacterial resistance. Pediatr Infect Dis J 22: 1143-1151. Link: https://bit.ly/371Efcr

7. Owens RC, Ambrose PG (2000) Clinical use of the fluoroquinolones. Med Clin North Am 84: 1447-1469. Link: https://bit.ly/3d4FXhf

8. Lawn JE, Wilczynska-Ketende K, Cousens SN (2006) Estimating the causes of 4 million neonatal deaths in the year 2000. Int J Epidemiol 35: 706-718. Link: https://bit.ly/3p5jVgv

9. Lipman J, Gous AG, Mathivha LR, Tshukutsoane S, Scribante J, et al. (2002) Ciprofloxacin pharmacokinetic profiles in paediatric sepsis: how much ciprofloxacin is enough? Intensive Care Med 28: 493–500. Link: https://bit.ly/2NhhQRh

10. Rubio TT, Miles MV, Lettieri JT, Kuhn RJ, Echols RM, et al. (1997) Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic Fibrosis patients with acute pulmonary exacerbation. Pediatr Infect Dis J 16: 112-117. Link: https://bit.ly/2NcHxCC

11. Nejjari N, Benomar S, Lahbabi MS (2000) Nosocomial infections in neonatal and pediatric intensive care: the appeal of ciprofloxacin. Arch Pediatr 7: 1268-1273. Link: https://bit.ly/3q8HNBl

12. Wlazlowski J, Krzyzanska-Oberbek A, Sikora JP, Chlebna-Sokół D (2000) Use of the quinolones in treatment of severe bacterial infections in premature infants. Acta Pol Pharm 57: 28-31. Link: https://bit.ly/2Z2d6Sl

13. Ciprofloxacin (2016). Link: https://bit.ly/2Z0Vx4W

14. Schmid DA, Campi P, Pichler WJ (2006) Hypersensitivity reactions to quinolones. Curr Pharm Des 12: 3313-3326. Link: https://bit.ly/2YZDyMu

15. Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, et al. (2005) Spanish Group for the Study of Drug-Induced Liver Disease: Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 129: 512-521. Link: https://bit.ly/3a82VlI

16. Björnsson E, Olsson R (2005) Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 42: 481-489. Link: https://bit.ly/3a6bIEF

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