Cefixime-induced hepatotoxicity and acute renal failure: a case report

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ABSTRACT

Background: Cefixime is widely used in treating infections in children, and it can commonly cause minor gastrointestinal adverse effects. However, hepatotoxicity and acute renal failure are among the rarely reported serious adverse drug reactions of cefixime and other cephalosporins.

Case Presentation: We report the case of a 7-month-old infant who was previously well but was admitted to the pediatric intensive care unit (PICU) as she developed acute onset hepatic and renal failure 2 days after cefixime treatment. Her liver enzymes were more than five-times the upper normal limit and her kidney function deteriorated acutely and rapidly over a short period, with evident acute renal parenchymal disease on abdominal ultrasound.

Conclusion: Given the nature of rapid resolution of all organ-related insults and no other confirmed diagnosis and with the support of Naranjo and Roussel Uclaf Causality Assessment Method scales, this is probably the first case of cefixime-induced hepatotoxicity and acute renal failure.

Keywords: Cefixime, cephalosporin, hepatotoxicity, renal failure.

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Background

Cefixime is a third-generation cephalosporin that is indicated for the treatment of infections caused by various pathogens, especially gram-negative bacteria. It is generally a well-tolerated and safe antibiotic. Its common adverse effects are gastrointestinal disturbances such as abdominal pain and indigestion (3%), diarrhea (16%), flatulence (4%), loose stool, and nausea (6%–7%) [1]. Hepatitis, hepatotoxicity, jaundice or abnormal liver enzymes, acute renal failure, seizures, and thrombocytopenia are among the rarely reported adverse drug reactions during clinical trials with an incidence of <2% [1]. This combination of rare adverse reactions has not been reported previously in the medical literature, but only two cases reported including hepatotoxicity, in adult female, and nephrotic syndrome, in an infant, that could possibly be attributed to cefixime, and both of them were reversible after discontinuation of the antibiotic [2,3]. We report an unusual case that could possibly be associated with cefixime.

We present a case that highlights the need to suspect medication-induced liver or kidney injury in cases of no other obvious diagnosis and if resolution occurred rapidly after drug withdrawal.

Case Presentation

A 7-month-old female infant, not known to have any medical illness, was admitted to emergency department with 2 days history of fever, vomiting, and diarrhea. Treated and discharged home as a case of urinary tract infection on oral cefixime and oral rehydration solution. After receiving two doses of cefixime, she came back to emergency department severely dehydrated requiring bolus intravenous normal saline and was drowsy. The parent denied any herbs ingestion. After that she developed generalized tonic convulsions with up rolling of eyes, inspiratory stridor, tachypneic, irritable on handling and this was aborted with intravenous Lorazepam and Phenobarbital bolus. She was then admitted to PICU.

On admission to PICU, she was drowsy, glasgow coma scale (GCS) = 7/15, pupils equal & reacted to light (size 2–3 mm), tachypneic with inspiratory stridor, desaturating, and requiring face mask oxygen, febrile with a temperature of 38.5°C, a blood pressure of 93/50 mm Hg, a heart rate of 130 bpm, with warm extremities and capillary refill time of <2 seconds. Her physical examination was normal. Her laboratory investigations thoroughly explored different system functions (Tables 1–4).

Table 1. Complete blood count at admission.

PERIOD/VALUE	WBC	HGB	PLATELETS
During ER admission	11.1 × 10.e9/L	11 g/dl	163 × 10.e9/L
During PICU admission	9.1 × 10.e9/L	8.3 g/dl	93 × 10.e9/L

ER, emergency room; WBC, white blood cell.

Table 2. Venous blood gases on admission.

PERIOD/VALUE	pH	PCO_2	PO_2	HCO_3	CHLORIDE	BASE EXCESS
During ER admission	7.38	28.8 mm Hg	69.3 mm Hg	17 mmol/l	107 mmol/l	–7.2

ER, emergency room.

Procalcitonin level on day 4 of admission was 17.44 ng/ml (normal < 0.05 ng/ml), which declined to 2.19 ng/ml on day 7.

Lactate: 4.4 mmol/l (normal 0.5–2.2 mmol/l) and ammonia = 261 µmol/l on admission.

Table 3. Liver function tests, coagulation profile, blood urea, and serum creatinine values during the patient's clinical course.

VALUE TESTED	NORMAL RANGE	ADMISSION	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	DAY 10
ALT	0–40 IU/l	7,346	4,848	3,676	2,595	-	-	-	708
AST	0–46 IU/l	>10,000	QNS	1,288	410	-	-	-	66
GGT	0–55 IU/l	84	63	61	66	-	-	-	99
Total bilirubin	3–17 µmol/l	25	22	39	35	-	-	-	10
Direct bilirubin	0–5 µmol/l	17	15	24	23	-	-	-	5
Albumin	30–50 g/l	27	27	29	26	28	29	27	32
PT	11.5–16.5 seconds	66.8	26.9	27.3	20.6	17.1	-	15.4	-
APTT	26–39 seconds	64.9	45.8	41.3	42.9	46.5	-	46.5	-
INR	0.8–1.3	8.31	2.48	2.53	1.74	1.36	-	1.18	-
BUN	1.4–6.8 mmol/l	15.6	16.3	16.7	12.7	9.9	10	8.1	2.9
Serum creatinine	18–35 µmol/l	105	108	110	115	96	69	64	42

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; INR, international normalized ratio; PT, prothrombin time; QNS, quantity not sufficient.

Table 4. Serum ammonia level during the patient's clinical course.

VALUE TESTED	NORMAL RANGE	ADMISSION	DAY2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Ammonia	20–50 µmol/l	261	141	55	63	52	-	60

Viral markers for hepatitis A, B, and C were negative. Acetaminophen level was done to rule out overdose and the level came below toxic (126 µmol/l). Cerebrospinal fluid (CSF) analysis was normal. Viral NPA, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) were negative, polymerase chain reaction (PCR) herpes and enterovirus, as well as stool culture for shigella, salmonella, campylobacter, Yersinia, C. difficile, and viruses, came negative. H1N1 was negative. Electroencephalogram (EEG) results were normal. Ultrasound revealed mildly enlarged liver and acute renal parenchymal disease.

At that time, she was electively intubated and underwent urgent computed tomography brain scans that came normal with no acute brain insult. There were no recurrent seizures with maintenance phenobarbital and midazolam infusion while on ventilator support. She required a short course of epinephrine infusion (0.5 mcg/kg/minute). Supportive management was commenced with fresh frozen plasma transfusion and vitamin K. She was empirically covered with antibiotics, including vancomycin, meropenem, and acyclovir. Pending culture results all came negative later on, and she was febrile at that time. Therefore, vancomycin and acyclovir discontinued afterward. Neurology team advised for magnetic resonance imaging if normal EEG to rule out ischemic changes. After 1 week of admission, her general condition was stable, extubated on room air, on enteral feeding with good tolerance and fully conscious with GCS of 15/15.

All her labs returned to normal or near normal. She was discharged from PICU to the ward for regular follow up with a final diagnosis of drug induced hepatorenal toxicity. Since cefixime induced adverse drug reactions were among the differential diagnosis, Naranjo causality scale for an adverse drug reaction, which is a validated scale that can be used to estimate the probability that a drug caused an adverse clinical event rather than using a sole clinical judgment [4]. Applying this scale on our case, it indicated a possible relationship between cefixime administration and hepatorenal toxicity (score = 3). Use of the Roussel Uclaf Causality Assessment Method (RUCAM), developed specifically for causality assessment for hepatocellular reactions, indicated a possible relationship between cefixime administration and elevated hepatic transaminases [5,6]. Thus, our patient's hepatorenal toxicities were attributed to cefixime administration, as they resolved after discontinuation.

Discussion

Our patient's alanine aminotransferase (ALT) level was 180 times the upper limit of normal (ULN), and aspartate aminotransferase (AST) level was 250 times the ULN. While this is considered clinically significant, it is unknown how often cefixime induces such substantial increase in hepatic transaminase levels. Other possibilities that might have caused this reaction include sepsis, viral infections, meningitis, or encephalitis. But all investigations that have been done ruled out those causes. Sepsis was not likely because the patient was hemodynamically stable although she required bolus fluid, but this was because she was severely dehydrated secondary to the vomiting history and even epinephrine was used but she required very small doses and she became hemodynamically stable immediately afterward and also all cultures came negative later on. Viral infections were out because nasopharyngeal aspirate (NPA) and viral markers for hepatitis A, B, C, and CMV, EBV as well as stool culture came negative. Meningitis and viral encephalitis excluded when CSF analysis came, herpes simplex virus PCR was negative and EEG was normal.

Overview of hepatotoxicity among cephalosporins

There have been several cases of hepatotoxicity related to other cephalosporins. Eggleston et al. [7] documented two cases of jaundice in patients who were taking cefamandole and cephalothin, with resolution of the symptoms when the antibiotics were discontinued. Cholestatic jaundice was also associated with cephalexin and cefazolin. A newer third-generation cephalosporin, cefproxil, similar to cefdinir in its pharmacokinetics, and adverse effect profile has been associated with hepatitis [8]. Ceftriaxone sodium, a parenteral cephalosporin, causes hepatotoxicity infrequently, with AST, ALT, and alkaline phosphate elevations reported in 3.1%, 3.3%, and <1% of patients, respectively [9]. Oakes et al. [10] found an overall 5% incidence of hepatic abnormalities with ceftriaxone therapy, with abnormal AST and ALT levels in 3.1% and 3.3% of study participants. Multiple case reports and prospective studies in the medical literature describe the relationship between ceftriaxone and the development of biliary pseudolithiasis or gallbladder sludge in adults and children [11]. Cephalosporins are not typically known to be hepatotoxic; therefore, the mechanism continues to be poorly understood, although hypersensitivity has been postulated [12].

Incidence of acute renal failure induced by cephalosporins

Interstitial nephritis and increases in BUN and creatinine have been reported in less than 1% of patients receiving cefotaxime sodium [12]. Eron et al. [13] reported two cases of azotemia with ceftazidime. Two studies indicated a small but significant decrease in glomerular filtration rate during ceftazidime therapy [14,15]. Urine casts were reported in less than 1% of patients receiving ceftriaxone in clinical trials [9]. Many studies reported nephrolithiasis and nephrotoxicity in association with ceftriaxone [9,16].

Conclusion

Although the course of illness of our patient seems complicated to be drug-induced and we cannot exclude the possibility of other reasons, but given the nature of rapid resolution of all organ-related insults and no other confirmed diagnosis had been made and with the support of Naranjo and RUCAM scales, we can say that this case may be the first reported one that is possibly secondary to cefixime antibiotic. Even though cefixime is generally known to be a well-tolerated and safe antibiotic, health care professionals should be aware of the risk of those serious adverse drug reactions associated with cefixime use.

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List of abbreviations

ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
EBV	Epstein–Barr virus
EEG	Electroencephalogram
ER	Emergency room
GCS	Glasgow Coma Scale
GGT	Gamma-glutamyl transferase
HSV	Herpes simplex virus
INR	International normalized ratio
PCR	Polymerase chain reaction
PT	Prothrombin time
RUCAM	Roussel Uclaf Causality Assessment method
ULN	Upper limit of normal

Consent for publication

Consent was sought and obtained from the parents of the patient prior to the publication of this report.

Ethical approval

Permission to publish this report was granted by the Institutional Review Board at King Khalid University Hospital.

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Summary of the case

Patient (gender, age)	1	Female, 7 months
Final diagnosis	2	Cefixime-induced hepatotoxicity and acute renal failure
Symptoms	3	Drowsiness and severe dehydration
Medications	4	Bolus intravenous normal saline, lorazepam, phenobarbital bolus, phenobarbital and midazolam infusions, FFP, vitamin K, and epinephrine infusion at 0.5 mcg/kg/minute
Clinical procedure	5	Assessment, rehydration, admission to pediatric intensive care, laboratory investigations and treatment administration
Specialty	6	Pediatrics