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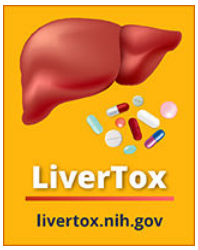


Cephalosporins, Parenteral

Updated: May 9, 2024.

OVERVIEW

Introduction

The parenterally administered cephalosporins are widely used as broad spectrum antibiotics for moderate-to-severe infections with susceptible organisms. Despite their widescale use, cases of drug induced liver disease from the cephalosporins are rare, but more frequent with the parenteral forms.

Background

Parenterally administered cephalosporins include cefazolin (Ancef: 1st generation), cefepime (Maxipime: 4th), cefiderocol (Fetroja: 4th), cefoperazone (Cefobid: 3rd), cefotaxime (Claforan: 3rd), cefoxitin (Mefoxin: 2nd), ceftaroline (Teflaro: 5th), ceftazidime (Ceptaz, Fortaz, Tazicef, Tazidime: 3rd), ceftibuten (3rd), ceftizoxime (Cefizox: 3rd), ceftolozane/tazobactam (Zerbaxa: 5th), ceftriaxone (Rocephin: 3rd), cefuroxime (Zinacef: 2nd), and cephradine (1st); the latter two are also available in oral formulations. Most of these cephalosporins can be given either intravenously or intramuscularly and are indicated for therapy of moderate-to-severe bacterial infections caused by susceptible organisms. Typical dose regimens in adults range from 250 mg, 500 mg, 1 gram or 2 grams every 6 to 12 hours for 7 to 14 days. The parenteral cephalosporins are widely used in medicine for serious infections and can be safely given to patients with advanced liver disease, dose modifications being required mainly for renal insufficiency. Many of these agents are also approved for use in children. The parenteral cephalosporins are generally well tolerated; adverse events can include diarrhea, nausea, abdominal pain, dyspepsia, headache, and rash. Rare but potentially severe adverse events include Clostridium difficile-associated diarrhea, hypersensitivity reactions, angioedema, anaphylaxis and Stevens Johnson syndrome/toxic epidermal necrolysis.

Hepatotoxicity

Parenteral administration of cephalosporins can be associated with minor elevations in serum aminotransferase and alkaline phosphatase values, but these are generally mild, transient and not associated with symptoms or development of more severe liver injury. The frequency of these elevations is reported to be as high as 11%, but varies depending upon the frequency of monitoring, duration of therapy, and nature and severity of the underlying illness. Aminotransferase elevations above 5 times ULN are uncommon and typically occur in <1% of treated subjects.

Clinically apparent liver injury from parenteral cephalosporin administration is uncommon but multiple cases have been reported, although not all of the parenteral formulations have been linked to cases of liver injury. Cefazolin has been most frequently linked to cholestatic jaundice and ranks in the top 10 to 15 causes of jaundice from medications. It is also one of the most frequently used cephalosporins. The clinical pattern of

injury suggests that hepatotoxicity is largely a class effect from the cephalosporins and is likely due to hypersensitivity. The typical latency period is 1 to 4 weeks with an abrupt onset of liver injury. Symptoms and jaundice can arise after the antibiotic has been stopped and typically consist of nausea, abdominal pain, pruritus and jaundice. The pattern of serum enzyme elevations is usually described as cholestatic, but mixed and hepatocellular instances have been reported. Liver injury is often accompanied by fever, rash and eosinophilia or other signs and symptoms of hypersensitivity. A history of penicillin allergy is not common, but the liver injury resembles that associated with penicillin hepatotoxicity. The course is usually self-limiting and the fatality rate is low as is typical of cholestatic hepatitis.

Likelihood score: A (cephalosporins as a class are well known and characterized, although uncommon, causes of clinically apparent liver injury, the association having been made largely with the most frequently used agents, such as cefazolin, cephalexin and ceftriaxone).

Mechanism of Injury

The mechanism of hepatic injury due to cephalosporins is unknown, but believed to be hypersensitivity, similar to that of other penicillins. Cases of cholestatic liver injury attributed to cefazolin have been linked to HLA-A*02:01 which is a fairly common HLA allele, the allele frequency being 0.28 in the general population and 0.48 in patients with cefazolin induced liver injury.

Outcome and Management

In most case reports, recovery has been rapid within 4 to 8 weeks, without residual injury or persistent serum enzyme elevations. Among the few cases reported, none have been fatal, although in some complicated cases the hepatic injury and cholestasis may have contributed to the mortality from the underlying illness. It is unclear whether there is cross sensitivity to hepatic injury or hypersensitivity reactions among the various cephalosporins. In many published cases, patients have been switched to an alternative cephalosporin without recurrence of injury, but it is more judicious to switch to another class of agents. Similarly, patients with a history of penicillin allergy have a higher rate of hypersensitivity reactions to cephalosporins, and they should be avoided or started with careful supervision and monitoring.

References to the safety and potential hepatotoxicity of parenteral cephalosporins are provided in the introductory overview chapter on Cephalosporins.

Drug Class: Antiinfective Agents, Cephalosporins

CASE REPORT

Case 1. Cholestatic hepatitis after single intravenous infusion of cefazolin.(1)

A 60 year old man received a single iv infusion of cefazolin during outpatient surgery and developed symptoms of liver disease 3 days later. He was healthy without major medical illnesses when he injured his shoulder while playing hockey. Approximately 2 months later, he underwent outpatient surgical repair of a torn right supraspinatus muscle under general anesthesia using inhaled nitrous oxide with intravenous propofol, fentanyl and midazolam. He also received a single intravenous infusion of 2 grams of cefazolin (a first generation parenteral cephalosporin) for prophylaxis against infection. Other perioperative medications included dimenhydrinate (Dramamine) and hydromorphone. The surgery lasted 5 hours and he recovered without incident, being sent home the same day with a prescription for a combination of acetaminophen (500 mg) and codeine (5 mg) 2 or 3 times daily for pain control, which he took as directed. Three days after surgery, he developed nausea and pruritus and 2 days later noted dark urine and jaundice. On testing, he had moderate

elevations in serum aminotransferase and alkaline phosphatase levels and hyperbilirubinemia (Table). He was admitted for evaluation. His past medical history was remarkable for several previous orthopedic procedures. He had a history of asbestos exposure and mild chronic bronchitis for which he used albuterol by inhaler irregularly. He took occasional ibuprofen for muscle aches. He denied alcohol use or exposure to viral hepatitis. On admission to the hospital, he had mild eosinophilia (~640 cells/μl), but no rash or fever. Tests for hepatitis A, B and C were negative as well as autoantibodies. Ultrasound of the abdomen was normal. Importantly, review of two previous surgeries showed that he had received cefazolin at the time of both, and had jaundice following the second surgery that had been attributed to "halothane." Careful review of anesthesia records showed no exposure to halogenated anesthetics during this third surgery; the names of the inhalational agent used during previous surgeries were not available.

Key Points

Medication:	Cefazolin, 2 g iv at time of surgery
Pattern:	Mixed → cholestatic (R=2.2→0.9)
Severity:	3+ (jaundice and hospitalization)
Latency:	Three days
Recovery:	Complete 8 weeks
Other medications:	Chronically, salbutamol and ibuprofen, perioperatively nitrous oxide, fentanyl, propofol, midazolam, dramamine, acetaminophen with codeine

Laboratory Values

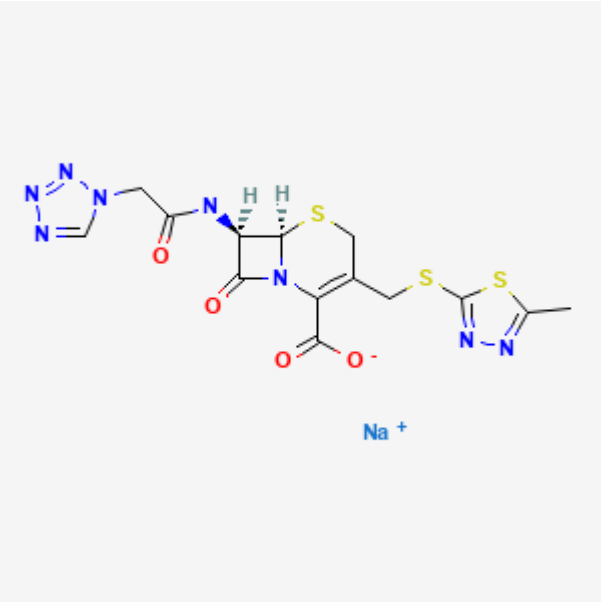
Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	24	65	0.4	Presurgery evaluation
Orthopedic surgery under nitrous oxide and propofol, and iv cefazolin (2 g)					
7 days	6 days	194	309	5.7	10% eosinophils
8 days	7 days	192	240	5.3	
11 days	10 days	193	358	4.4	
2 weeks	13 days	116	385	4.3	
3 weeks	20 days	92	373	2.9	
4 weeks	27 days	92	293	1.4	
2 months	2 months	62	97	0.8	No symptoms
8 months	8 months	20	60	0.6	
Normal Values		**<40**	**<140**	**<1.2**	

Comment

Postoperative jaundice can be caused by sepsis, hypotension, viral hepatitis, benign postoperative cholestasis or anesthetic induced hepatotoxicity. Less well defined is postoperative liver disease due to other medications given at or around the time of surgery. In this instance, multiple medications were given in addition to inhaled nitrous oxide, but no halogenated anesthetics such as halothane, isoflurane, enflurane, desflurane or sevoflurane. In addition, the pattern of liver injury was typical of cephalosporins with short latency period, eosinophilia, cholestatic pattern of enzyme elevations and mild, self-limited course. Halothane hepatitis typically causes fever and is associated with a hepatocellular pattern of injury. Acetaminophen generally causes liver injury only when given in doses above 4 grams daily and causes marked aminotransferase elevations with minimal changes in

alkaline phosphatase levels. Nitrous oxide and propofol have not been convincingly linked to drug induced liver injury. A single, intravenous administration of a cephalosporin at the time of outpatient surgery may be a more common cause of jaundice and liver injury than is currently thought.

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Cefazolin Sodium	27164-46-1	C14-H13-N8-Na-O4-S3 C14-H13-N8-O4-S3.Na C14-H14-N8-O4-S3.Na	

CITED REFERENCES

1. Alqahtani SA, Kleiner DE, Ghabril M, Gu J, Hoofnagle JH, Rockey DC; Drug-Induced Liver Injury Network (DILIN) Study Investigators. Identification and characterization of cefazolin-induced liver injury. Clin Gastroenterol Hepatol 2015; 13: 1328-36.e2. PubMed PMID: 25528012.

NOTE

References to both the oral and parenteral cephalosporins as well as review articles on the relative frequency of cephalosporin-related liver injury are given in the overview chapter on Cephalosporins.