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Cephalosporins, Oral

Updated: January 9, 2017.

OVERVIEW

Introduction

The orally available cephalosporins are widely used as broad spectrum antibiotics for mild-to-moderate infections with susceptible organisms. Despite their widescale use, cases of drug induced liver disease from the cephalosporins are very rare, with only isolated case reports having been published.

Background

The oral cephalosporins are available in both generic and trade formulations and include cefaclor (Ceclor, Raniclor: 2nd), cefadroxil (Duracef: 1st), cefdinir (Omnicef: 3rd), cefditoren (Spectracef: 3rd), cefixime (Suprax: 3rd), cefpodoxime (Vantin: 3rd), cefprozil (Cefzil: 2nd), ceftibuten (Cedax: 3rd), cephalexin (Keftab: Apo-Cephalex, Biocef, Keflex, NovoLexin, Nu-Cephalex: 1st), cefuroxime (Ceftin: 2nd), cephradine (Velosef: 1st), and loracarbef (Lorabid: 2nd). Cefuroxime and cephradine are also available in parenteral forms. The typical dose regimens for oral cephalosporins are 250 to 500 mg two to four times daily for 7 to 14 days. The oral cephalosporins are widely used in medicine for mild-to-moderate infections due to susceptible bacteria.

Hepatotoxicity

Oral 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. Clinically apparent liver injury from oral cephalosporin use is rare, only isolated case reports having been published, and not all of the formulations have been linked to cases of liver injury. The clinical pattern of injury suggests that hepatotoxicity is largely a class effect from the cephalosporins, even though it is idiosyncratic and rare. The typical latency period has been 1 to 4 weeks with an abrupt onset of liver injury. The pattern of serum enzyme elevations is usually 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.

Likelihood score: B (cephalosporins as a class are very likely but rare 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 and similar to that of other penicillins.

Outcome and Management

In most case reports, recovery has been rapid within 4 to 8 weeks with residual injury or persistent serum enzyme elevations. Among the few cases reported, none have been fatal.

References to oral cephalosporin induced liver injury are provided in the introductory Overview section on Cephalosporins.

Drug Class: Antiinfective Agents, Cephalosporins

CASE REPORT

Case 1. Cholestatic hepatitis related to cefuroxime.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 52 year old man was given a 10 day course of oral cefuroxime for recurrent folliculitis, but developed worsening skin rash and itching, and was found to be jaundiced 7 weeks after starting the antibiotic. Laboratory testing showed prominent elevations in serum AST and alkaline phosphatase with a total bilirubin of 8.4 mg/dL (Table). Tests for autoantibodies and for serologic evidence of hepatitis A, B and C were negative. Imaging tests of the liver including ultrasound, MRI and MRCP were unremarkable. The patient had a complex past medical history of diabetes, hypertension, coronary artery disease, chronic back pain and asthma for which he took several medications chronically, none of which had been changed recently. He abused alcohol for many years, but had abstained for 4 years. He had no known allergies. His cholestasis and liver disease were prolonged, and ultimately he underwent liver biopsy which showed changes of chronic inflammation and intrahepatic cholestasis compatible with drug induced liver disease. The diagnosis of cephalosporin induced liver injury had not been fully appreciated and he received two 10 day courses of cephalexin during this period of jaundice. These exposures were not associated with appreciable changes in serum enzyme levels, but were followed by an increase in serum bilirubin levels and skin rash (Table). Because of persistent pruritus, he was treated with ursodiol, cholestyramine and several antihistaminics. Ultimately, his rash and itching resolved; serum bilirubin fell to normal, but there were minor elevations in ALT and alkaline phosphatase that did not fall into the completely normal range for more than a year after the initial presentation.

Key Points

Medication:	Cefuroxime, 500 mg daily for 10 days
Pattern:	Cholestatic (R=1.2)
Severity:	3+ (jaundice and hospitalization)
Latency:	6 weeks
Recovery:	More than 6 months
Other medications:	Fluticasone and salmeterol inhalant and albuterol (for asthma), insulin (diabetes), gabapentin (neuropathy), lisinopril and hydrochlorothiazide (hypertension), cyclobenzaprine and the combination of hydrocodone and acetaminophen (low back pain)

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Ten day course of cefuroxime: weeks 1-2					
8 weeks	6 weeks	268	651	8.4	Jaundice and pruritus
9 weeks	8 weeks	264	595	7.1	
Two courses of cephalexin: weeks 10-14					
15 weeks	14 weeks	284	720	11.8	
Five day course of cefuroxime: week 19					
20 weeks	19 weeks	189	812	4.7	Erythema
21 weeks	20 weeks	191	859	3.6	
22 weeks	21 weeks	176	717	2.1	Pruritus
6 months	6 months	111	428	1.0	
7 months	7 months	69	174	0.7	
8 months	8 months	74	217	1.0	Asymptomatic
15 months	15 months	42	169	0.7	
18 months	18 months	32	131	0.4	
20 months	20 months	35	119	0.4	
Normal Values		**<35**	**<130**	**<1.2**	

Comment

The prolonged course of cholestasis with no obvious cause was most likely due to drug induced liver injury, and cefuroxime (a third generation, orally available cephalosporin) was the most likely cause. The long incubation period is unusual for cephalosporin related liver injury. Furthermore, rechallenge with cephalexin and then with cefuroxime appeared to worsen the course minimally, if at all, but may have been the reason for the delayed recovery. A year after the initial presentation, the patient was without symptoms, but serum enzymes were still mildly abnormal. Ultimately, however, even these mild biochemical abnormalities resolved.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Cefuroxime – Ceftin®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Cefuroxime	55268-75-2	C16-H16-N4-O8-S