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Sulfamethoxazole-Trimethoprim

Updated: December 5, 2017.

OVERVIEW

Introduction

Sulfamethoxazole with trimethoprim is a fixed antibiotic combination that is widely used for mild-to-moderate bacterial infections and as prophylaxis against opportunistic infections. Like other sulfonamide-containing medications, this combination has been linked to rare instances of clinically apparent acute liver injury.

Background

Trimethoprim-sulfamethoxazole (TMP-SMZ) is a combination of a sulfonamide antibiotic and a methoprim. This combination is widely used for therapy of infections due to susceptible bacteria as well as prevention of opportunistic infections with Pneumocystis jiroveci (formerly carinii) in immune deficient individuals. The two agents are synergistic in inhibition of folate synthesis – the sulfamethoxazole (sul" fa meth ox' a zole) inhibiting production of dihydrofolate from para-aminobenzoic acid, and the trimethoprim (trye meth' oh prim) inhibiting the next step in the pathway from dihydrofolate to tetrahydrofolate. TMP-SMZ was approved for use as a combination antibiotic in the United States in 1973 and is still in wide use, more than 8 million prescriptions being filled yearly. TMP-SMZ is recommended for use in adults and children for urinary tract infections, bronchitis, sinusitis and otitis media and for prophylaxis against opportunistic infections due to parasites and pneumocystitis jiroveci. TMP-SMZ is available in multiple generic and trade formulations in tablets containing 80 or 160 mg of trimethoprim and 200, 400 or 800 mg of sulfamethoxazole. Trade names include Bactrim, Cotrim, Septra and Sulfatrim.

Trimethoprim is also available separately and is used as an antibiotic for uncomplicated urinary tract infections. Trimethoprim is a synthetic antifolate that acts on a late step in the pathway of folate synthesis. Trimethprim has activity against many aerobic gram-negative organisms such as Escherichia coli, Kiebsiella pneumoniae, Proteus mirabilis and Enterobacter species. Resistance is common. Trimethoprim was approved for use in the United States in 1980, but is used much less frequently that TMP-SMZ. Trimethoprim is available in several generic forms in tablets of 100 mg and the usual oral adult dose is 100 mg twice daily for 10 days. Trimethoprim is generally well tolerated; side effects can include nausea, abdominal upset, rash and pruritus.

Hepatotoxicity

TMP-SMZ causes a characteristic idiosyncratic liver injury that has features of drug-allergy or hypersensitivityand that resembles the injury attributable to the sulfonamides. The typical onset is sudden development of fever and rash followed by jaundice within a few days or weeks of starting the medication. Eosinophilia or atypical lymphocytosis are also common. The pattern of injury is typically cholestatic or mixed and can be complicated and prolonged. As with other sulfonamides, TMP-SMZ has been linked to cases of

hepatocellular injury that can be severe and lead to acute liver failure. In most recent case series, TMP-SMZ has ranked within the top 5 to 10 causes of drug induced, idiosyncratic fulminant hepatic failure. However, most cases resolve rapidly, usually within 2 to 4 weeks unless cholestasis is severe. TMP-SMZ can also cause mild elevations in ALT levels that do not proceed to more severe liver injury or jaundice, and may be accompanied by hepatic granulomas.

Trimethoprim by itself is also capable of causing idiosyncratic, clinically apparent acute liver injury. The injury usually arises after 2 to 12 weeks of therapy and the typical pattern of serum enzyme elevations is mixed or cholestatic. Immunoallergic features are not common, which separates the typical hepatotoxity of trimethoprim from that of sulfamethazole, the sulfonamide component of TMP-SMZ. In several instances, patients who have developed clinically apparent liver injury due to TMP-SMZ, have re-developed symptoms and laboratory abnormalities when treated with trimethoprim alone.

Mechanism of Injury

The clinical pattern of injury with TMP-SMZ suggests a drug-allergy or hypersensitivity mechanism, perhaps through its metabolism to a toxic, reactive or antigenic metabolite. Adverse hypersensitivity-like reactions to TMP-SMZ are particularly common in HIV-infected individuals, toxicity requiring discontinuation developing in up to 75% of patients, with hepatic enzyme abnormalities in 20%.

Outcome and Management

TMP-SMZ induced liver injury varies greatly in severity, from mild, anicteric and self-limited liver enzyme elevations, to acute symptomatic hepatitis, to a prolonged cholestatic syndrome, and to acute liver failure. Most cases are self-limited and resolve rapidly with discontinuation of drug, with full recovery within 2 to 8 weeks. Severe cholestatic injury may be prolonged and rare cases of chronic liver injury with vanishing bile duct syndrome have been reported. The hepatic injury may be part of a systemic hypersensitivity reaction and categorized as DRESS syndrome (drug rash with eosinophilia and systemic symptoms). Rechallenge should not be done, and patients should be told that they are allergic to sulfonamides ("sulfa-drugs") and not receive other drugs in this class. Trimethoprim by itself can also cause acute liver injury and some patients have re-developed injury when switched from TMP-SMZ to trimethoprim alone. However, in most instances, the sulfonamide component of TMP-SMZ is the culprit. Prednisone has been used with variable success, but may be particularly helpful in patients with prominent allergic features with systemic features and fever, severe rash, arthralgias, lymphoadenopathy, eosinophilia, and atypical lymphocytosis.

References to the safety and potential hepatotoxicity of trimethoprim and TMP-SMZ are given in the Overview on Sulfonamides.

Drug Class: Antiinfective Agents, Sulfonamides

CASE REPORTS

Case 1. Hypersensitivity reaction and ALT elevations due to TMP-SMZ.

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

A 33 year old woman was treated with a 21 day course of sulfamethoxazole-trimethoprim (TMP-SMZ) (80 mg/400 mg) for sinusitis. One day after stopping therapy she developed a macular rash, fever, right upper quadrant abdominal pain and nausea. Three days later she was seen in an emergency room, found to have fever, rash and systemic symptoms, and was hospitalized (Table). She had elevations in ALT and alkaline phosphatase, but serum bilirubin levels remained in the normal range. She had no history of liver disease, high risk behaviors, or exposures to viral hepatitis. She drank little alcohol (1 to 2 drinks per week) and took no other medications

except for multivitamins and an occasional ibuprofen. Blood counts were normal except for mild eosinophilia (7%). Tests for hepatitis A, B and C were negative as were autoantibodies. Ultrasound of the liver was normal without gallstones. Her fever and rash resolved and she was discharged with a diagnosis of sulfonamide hypersensitivity reaction. Liver tests fell into the normal range within 4 weeks on onset of symptoms.

Key Points

Medication:	Trimethoprim (80 mg)-sulfamethoxazole (400 mg) (TMP-SMZ)
Pattern:	Hepatocellular (R=14)
Severity:	1+ (anicteric)
Latency:	Three weeks
Recovery:	Four weeks
Other medications:	Multivitamins, ibuprofen

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
25 days	4 days	981	195	0.5	Hospitalization
26 days	5 days	805	213	0.8	Normal ultrasound
27 days	6 days	623	316	1.1	Discharged
5 weeks	12 days	156	386	0.6	Asymptomatic
6 weeks	3 weeks	49	168	0.4	
9 weeks	5 weeks	34	77	0.4	
Normal Values		**<45**	**<130**	**<1.2**	

Comment

This patient had a typical, but mild immunoallergic hepatitis with fever, rash, constitutional symptoms, eosinophilia and ALT elevations, appearing within 3 weeks of starting TMP-SMZ and resolving rapidly once it was stopped. Despite the height to the ALT elevations, the liver injury was mild, minimally symptomatic and not associated with jaundice or hepatic synthetic dysfunction. Some degree of ALT or alkaline phosphatase elevations is common in patients who have hypersensitivity reactions to sulfonamides and might be missed if blood testing is not done. The patient should be warned against future exposure to sulfonamides; with second exposures, the liver injury can become more acute and more severe.

Case 2. Cholestatic hepatitis due to TMP/SMZ.

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

A 47 year old woman was treated with antihistamines and a 7 day course “double strength” trimethoprim/sulfamethoxazole (160 mg/800 mg: TMP/SMZ) for an upper respiratory tract infection. During the final days of treatment she began to feel unwell and, despite stopping the medication, developed worsening fatigue, nausea and pruritus followed by dark urine, jaundice and right upper quadrant pain. Blood tests showed liver test abnormalities (Table) and she was hospitalized. She had severe itching but no rash or fever. Her liver was tender to palpation and she was jaundiced. She had no history of liver disease, did not drink alcohol and had no risk factors for viral hepatitis. Her only medications were calcium and multivitamins. She had taken TMP/SMZ at least once in the past and was allergic to penicillin (rash). Tests for hepatitis A, B and C and for autoantibodies were negative. An abdominal ultrasound was normal. Blood counts showed mild eosinophilia. Her jaundice and symptoms rapidly improved and itching and liver test abnormalities resolved within a few weeks.

Key Points

Medication:	Trimethoprim (160 mg)-sulfamethoxazole (800 mg)
Pattern:	Cholestatic (R=0.6)
Severity:	3+ (jaundiced, hospitalization)
Latency:	One week
Recovery:	Two weeks
Other medications:	Multivitamins, calcium

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
6 days	0	77	338	7.2	TMP/SMZ Stopped
9 days	2 days	54	301		
10 days	3 days	54	281	10.2	Hospitalized
11 days	4 days	47	261	3.4	Ultrasound normal
12 days	5 days	46	252	2.3	
18 days	11 days	34	151	2.4	Asymptomatic
6 months	6 months	14	84	0.6	
Normal Values		**<45**	**<130**	**<1.2**	

Comment

This patient developed a cholestatic hepatitis with minimal ALT elevations within a week of starting TMP/SMZ. She had a history of taking this medication in the past, but without apparent problems or hypersensitivity reactions. The liver injury was moderately severe, but resolved rapidly beginning within 4 days of stopping the medication. Signs of hypersensitivity were mild or absent, but the precipitous onset and rapid recovery fit the pattern of typical immunoallergic hepatitis due to sulfonamides.

Case 3. Acute liver failure due to TMP/SMZ.

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

A 49 year old man developed jaundice within days of stopping a one week course of oral trimethoprim-sulfamethoxazole (TMP/SMZ: 160/800 mg twice daily) which was given for a superficial cellulitis. He subsequently developed worsening anorexia, fatigue, dyspepsia, and pruritus with a generalized body rash, but no fever or chills. He had a history of cocaine use, but denied injection drug use or other risk factors for viral hepatitis. He drank alcohol sparingly and had no history of liver disease or drug allergies. His other medications included ranitidine which he had taken for years for gastroesophageal reflux and ibuprofen which he took intermittently for headaches and body pain. Physical examination showed deep jaundice and a macular papular rash over the trunk. Laboratory tests showed marked elevations in serum bilirubin (29.5 mg/dL) and aminotransferase levels (ALT 2229 U/L, AST 2684 U/L), with minimal increase in alkaline phosphatase (188 U/L). Serum albumin was low (2.3 g/dL) and prothrombin time was mildly elevated (INR 1.2). Tests for acute hepatitis A, B and C (including HCV RNA) were negative. Smooth muscle antibody was present in low titer (1:80), but antinuclear antibody was undetectable. Abdominal ultrasound revealed a contracted gallbadder, but no evidence of biliary obstruction. Abdominal CT scan showed a small gallstone but no dilatation of the extra- or intra-hepatic bile ducts. Liver biopsy demonstrated submassive necrosis and collapse with prominent inflammation and eosinophils, suggestive of severe drug induced liver injury. He was treated with

corticosteroids, but without improvement in his liver tests. Because of deepening jaundice and progressive hepatic failure, he was referred for liver transplantation, but was not accepted as a candidate because of recent drug use. He subsequently developed complications of liver failure and died three months after initial presentation.

Key Points

Medication:	Trimethoprim (160 mg)-sulfamethoxazole (800 mg)(TMP/SMZ)
Pattern:	Hepatocellular (R=~34)
Severity:	5+ (acute liver failure and death)
Latency:	3-4 weeks
Recovery:	Incomplete
Other medications:	Ranitidine, ibuprofen chronically

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
5 weeks	3 weeks	2229	188	29.5	Admission
6 weeks	4 weeks	2240	166	28.7	Imaging tests
7 weeks	5 weeks	1164	211	22.1	Liver biopsy
8 weeks	6 weeks	855	297	27.9	INR 1.4
4 months	3 months	Died of hepatic failure			
Normal Values		**<45**	**<130**	**<1.2**	

Comment

Sulfonamides can cause acute liver failure and are usually listed in the top 10 cases of fatal drug induced liver injury in large case serious. Cases of sulfonamide hepatotoxicity presenting with acute liver failure typically have a hepatocellular pattern of serum enzyme elevations with marked increases in serum aminotransferase levels. Corticosteroids are often used, particularly if immunoallergic features (rash, fever, eosinophilia) are present, but it is not clear whether they are beneficial and alter the course and outcome of the liver injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sulfamethoxazole-Trimethoprim – Generic, Bactrim®, Septra®

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
Sulfamethoxazole-Trimethoprim	8064-90-2	C14-H18-N4-O3. C10-H11-N3-O3-S