

A Patient with Acute Liver Injury after Sulfamethoxazole/Trimethoprim Treatment for Pyelonephritis

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How to cite this paper: Green, M., Baroud, S., Sayegh, M. and Zainah, H. (2020) A Patient with Acute Liver Injury after Sulfamethoxazole/Trimethoprim Treatment for Pyelonephritis. *Open Journal of Nephrology*, 10, 367-374.

<https://doi.org/10.4236/ojneph.2020.104036>

Received: October 30, 2020

Accepted: December 14, 2020

Published: December 17, 2020

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Abstract

Background: Sulfamethoxazole/Trimethoprim is a commonly used drug in a variety of clinically indicated scenarios, but it is not without side effect. Case-reports have stated that adverse reactions secondary to Sulfamethoxazole/Trimethoprim can present very early in the course of treatment, especially in patients who have a higher predisposition. Thus, the burden is placed on the clinician to be wary of these side effects and be able to recognize them in the correct clinic scenario. **Objective:** To discuss the risk of developing cholestatic hepatic dysfunction secondary to treatment with sulfamethoxazole/trimethoprim. **Methods:** We present the history, physical findings, laboratory investigations, and clinical course of a 47-year-old African-American female who developed cholestatic hepatic dysfunction after treatment with sulfamethoxazole/trimethoprim for pyelonephritis. **Results:** Drug-induced liver injury is a rare complication of sulfamethoxazole/trimethoprim therapy and only 20% of cases are secondary to cholestatic hepatic dysfunction. Our patient, who had been on sulfamethoxazole/trimethoprim for 7 days for pyelonephritis, presented to our hospital with a clinical picture consistent with hepatic injury; her laboratory investigations were noteworthy for an elevated white blood cell count, platelet count, and elevated transaminases, along with alkaline phosphatase levels greater than 2 times the upper limit of normal. Promptly following the discontinuation of sulfamethoxazole/trimethoprim, our patient improved clinically and her liver enzymes down-trended during the course of her hospital stay. She returned to normal at her 4 month follow up, thus confirming the diagnosis of cholestatic hepatic dysfunction secondary to sulfamethoxazole/trimethoprim. **Conclusion:** Cholestatic hepatic dysfunction is a form of drug-induced liver injury and a rare complication of sulfamethoxazole/trimethoprim treatment. The majority of cases resolve fol-

lowing discontinuation of the offending medication. However, a small percentage of patients may progress to liver failure and ultimately require liver transplantation. Clinicians should be aware of these risks to avoid delaying the discontinuation of sulfamethoxazole/trimethoprim.

Keywords

Sulfamethoxazole/Trimethoprim, Cholestatic Hepatic Dysfunction

1. Introduction

First introduced in 1974 [1], sulfamethoxazole/trimethoprim has become one of the most commonly prescribed antibiotics in the United States [2]. It is FDA-approved for the treatment of acute infective exacerbation of chronic bronchitis, urinary tract infections, and shigellosis in adults [1]. In addition, sulfamethoxazole/trimethoprim has been shown to decrease mortality in HIV-positive patients with a depressed CD4 count when given as a low-dose prophylaxis against opportunistic infections such as *P. jiroveci* and *T. gondii* [3]. Sulfamethoxazole/trimethoprim is commonly prescribed as a combination therapy, making it a strong bactericidal. This is in part due to the synergistic collaboration preventing the breakdown of folic acid into its active form, tetrahydrofolic acid, which is a necessary component for bacterial growth and development [1]. The majority of side effects caused by sulfamethoxazole/trimethoprim are non-life threatening and can be experienced in up to 6 to 8 percent of non-HIV patients. In contrast, patients who are HIV positive have an adverse reaction rate as high as 25 to 50 percent [4]. The majority of these side effects are secondary to the sulfonamide portion of the drug; sulfamethoxazole [5]. The most common side effects include nausea, vomiting, pruritus, and skin rash. A less common side effect is drug-induced liver injury (DILI), which can further be categorized into hepatocellular, mixed, or cholestatic depending on the mechanism of liver injury [6]. DILI can range from mild elevations in liver enzymes to acute fulminant liver failure [7]. In the absence of another identifiable cause, the majority of patients experiencing side effects secondary to sulfamethoxazole/trimethoprim use will improve following its discontinuation [3].

In this report, we present the case of a 47-year-old female who developed symptoms consistent with cholestatic hepatic dysfunction 7 days after taking SMZ-TMP DS for pyelonephritis.

2. Case Presentation

A 47-year-old African-American Jehovah's witness female presented to the emergency department for syncope following a seven-day history of nausea, vomiting, dizziness, and general malaise. She presented 1 week prior for evaluation of fever, chills, body aches, and headaches, of which at that time her laboratory

and microbiology findings suggested urinary tract infection alongside a hemoglobin level of 6.3 g/dl (reference range: 12.0 to 15.5 g/dL). Liver function studies at the time were normal and a CT scan of the abdomen confirmed pyelonephritis. At the time of discharge, she refused blood transfusion and instead accepted to receive a single infusion of 200 mg of IV Venofer and was sent home on a 7-day course of SMZ-TMP DS therapy (800 mg of sulfamethoxazole and 160 mg of trimethoprim). During the course of her treatment, she reported worsening of her symptoms. On the 5th day of treatment, she reported low-grade fevers, chills, nausea, vomiting, and dark urine. She denied the recent use of acetaminophen or any personal history of liver disease. Her past medical history is remarkable for iron deficiency anemia managed with iron tablets, hypertension, headaches, menopause, uterine fibroids, depression, and anxiety. There is no family history of liver diseases. Her current medications include bupropion, sumatriptan, venlafaxine, iron tablets, losartan, Excedrin, and hydrochlorothiazide, and she denies any recent change in her prior standing medications or the use of any herbal supplements. She drinks alcohol sparingly and denies intravenous drug abuse. She has no recent travel history. Physical examination was only remarkable for scleral icterus and costovertebral tenderness; vital signs were within normal limits and she had no skin rash, abdominal tenderness, or hepatomegaly.

The patient returned to the hospital and preliminary laboratory investigations demonstrated a hemoglobin of 6.7 (reference range: 12.0 to 15.5 g/dL); an increased white blood cell count of count of $22.1 \times 10^3/\text{mm}^3$ (reference range: 3.8 to $12.7 \times 10^3/\text{mm}^3$); an absolute neutrophil count of 12.6 (reference range: 1.5 to $8.0 \times 10^3/\text{mm}^3$); a platelet count of 595 (reference range: 150 to $450 \times 10^9/\text{L}$); an AST level 130 (reference range: 15 to 41 U/L); ALT 169 (reference range: 8 to 40 U/L);, an ALP level 978 (reference range: 24 to 280 U/L); total bilirubin 4.8 mg/dl (reference range: <1.5 mg/dl), an INR of 1.52 (reference range: <1.1), and an albumin of 2.6 g/dl (reference range: 3.3 - 5.2 g/dl). The patient was admitted to the hospital for acute liver injury and anemia.

During the course of her hospital stay, her platelet count continued to increase, and her liver profile continued to worsen, despite the gradual decline in her white blood cell count (**Table 1**). Serologic studies were sent for hepatitis A, hepatitis B, and hepatitis C and returned negative. Serum copper, ANA, and anti-Smooth Antibodies were all negative. Acetaminophen levels were <2.0 ug/ml (reference range: 10 to 25 ug/ml). Repeated blood and urine cultures also returned negative. Ultrasound of the liver showed normal liver size and echogenicity, with no obstruction or dilation of the biliary tree, no gallstones, and no focal liver abnormalities. MRCP further confirmed ultrasound findings by demonstrating no dilation of the biliary duct tree or evidence of choledocholithiasis. Findings on CT of the abdomen/pelvis remained consistent with a resolving pyelonephritis. Based on the timing of hepatic injury in relation to SMZ-TMP DS exposure, and the absence of any other identifiable cause to her clinical manifestations, we surmised her hepatic damage must be secondary to her SMZ-TMP

Table 1. Laboratory results.

Laboratory Test	Hospital Day			
	Day 1	Day 3	Day 6	Day 12
Total bilirubin (mg/dl)	4.8	6.6	5.8	4.0
INR	1.52	1.60	1.38	1.38
Albumin (mg/dl)	2.6	2.2	2.0	2.0
Aspartate Aminotransferase (U/L)	130	150	290	148
Alanine Aminotransferase (U/L)	169	124	175	104
Alkaline Phosphatase (U/L)	978	784	989	885
White blood cell count ($\times 10^3/\text{mm}^3$)	22.1	18.4	10.6	10.1

DS therapy and a decision was made by the 3rd day to discontinue all her prior medications and to refrain from prescribing any potentially hepatotoxic medication.

Following the discontinuation of SMZ-TMP DS, our patient began to clinically improve, and by the 7th day, her liver enzymes began to show a downward trend. We continued to monitor her liver enzymes and addressed the concerning decline in her hemoglobin. An extensive workup was carried out to rule out any potential secondary causes to her anemia and laboratory investigations were ordered to rule out hemolytic anemia, celiac disease, thalassemia, sickle cell disease, and G6PD, all of which were negative. An EGD was performed and returned positive only for chronic gastritis. Hematology consulted and diagnosed her with iron deficiency anemia secondary to anemia of chronic disease. The patient was amenable to blood transfusion at that time and she received a total of 1 unit of blood during the course of her hospital stay, but as she continued to improve clinically, further blood transfusions were held off unless she developed symptoms. By her 9th day of admission, the patient's complete blood count had normalized, and she had clinically recovered. It was decided that she could be discharged with close follow up with her primary care physician and Gastroenterologist to monitor her liver enzymes ensuring their return to baseline. The possibility of a liver biopsy prior to her discharge was discussed given that her Fibrosis-4 (FIB-4) score was 1.64 (reference range < 1.45), but with the gradual improvement in her liver enzymes, it was deferred. Our patient was able to follow up 4 months later at which time her AST and ALT had returned to normal limits.

However, given that the patient had no previous history of drug allergies prior to this incident and the prompt improvement in her clinical state once SMZ-TMP DS was discontinued, she was diagnosed with cholestatic hepatic dysfunction secondary to sulfamethoxazole/trimethoprim.

3. Discussion

Sulfamethoxazole/trimethoprim is a combination of trimethoprim and sulfamethoxazole which acts synergistically to inhibit bacterial growth by inhibiting the

synthesis of tetrahydrofolic acid, the physiologically active form of folic acid, and necessary cofactor in the synthesis of bacterial DNA. Sulfamethoxazole forms the sulfonamide portion and it is predominantly metabolized by the liver. It is the component that is most implicated in the adverse effects secondary to sulfamethoxazole/trimethoprim use. The most common adverse effects are skin reactions, which account for 3 to 4 percent of the general population taking sulfamethoxazole/trimethoprim. Furthermore, gastrointestinal symptoms, which commonly include nausea, vomiting, and anorexia, occur in approximately 3 to 8 percent of patients. Severe adverse reactions are less common, except in HIV-positive patients who are receiving sulfamethoxazole/trimethoprim for the prophylaxis and treatment of *Pneumocystis carinii* pneumonia (PCP). They can account for nearly 65 percent of cases. Hypersensitivity reactions are the most common types of adverse reactions and include a rash and fever that develop 8 to 12 days after the initiation of therapy. Other less common adverse reactions include nausea and vomiting, diarrhea, neutropenia, thrombocytopenia, anemia, transaminase elevations, cholestatic jaundice, and azotemia [5]. Oxidative hemolysis is implicated in patients with glucose-6-phosphate dehydrogenase deficiency in patients taking sulfamethoxazole/trimethoprim. Although rare, clinicians should still hold a reasonable degree of clinical suspicion, especially in the setting of unexplained anemia following sulfamethoxazole/trimethoprim therapy. In contrast, side effects secondary to trimethoprim are less common, especially at therapeutic doses. However, trimethoprim can cause dose-related leukopenia and megaloblastosis in patients receiving a high dose of trimethoprim-sulfamethoxazole over an extended period of time and periodic monitoring of the complete blood count may be advisable [3].

The mechanism underlying sulfonamide hypersensitivity still remains poorly understood and is one of the underlying reasons behind how the under-reporting of this syndrome [8]. One theory postulates that the by-products released following the metabolism of sulfamethoxazole/trimethoprim in the liver inadvertently cause indirect and/or direct damage to lymphocytes and other immune cells. Another theory, entitled the “danger hypothesis”, suggests that certain immune system activators, such as an infection, may result in a misdirected immune response towards a drug that would otherwise be well tolerated [9]. This theory may provide an explanation for our patient who was still in the process of recovering from her pyelonephritis when she developed the adverse reaction to sulfamethoxazole/trimethoprim.

Drug-induced Liver Injury (DILI) is one of the well-known yet less common adverse reactions to sulfamethoxazole/trimethoprim treatment. It accounts for approximately 10% of all cases of acute hepatitis and it alone is the most common cause of acute liver failure in the United States [10]. DILI can be further categorized into 3 sub-types: 40% hepatocellular, 40% mixed, and 20% cholestatic [6]. In the setting of DILI, cholestasis can be defined as an increase in alkaline phosphatase (ALP) greater than 2 times the upper limit of normal (ULN)

and/or an alanine aminotransferase (ALT)/ALP ratio of less than 2. However, there is still no specific diagnostic markers for drug induced liver injury [11] nor are there standard guidelines dictating when to perform a liver biopsy, although this is to be considered in a patient with progressively worsening liver enzymes and an otherwise unremarkable evaluation [11].

Drug-induced cholestasis can present as bland cholestasis, cholestatic hepatitis, secondary sclerosing cholangitis, or vanishing bile duct syndrome, but more commonly it causes asymptomatic cholestasis with mild elevations in liver enzymes [11]. The prevalence of drug induced cholestasis in the United States was reported to be 20% in the elderly population [12]. The most common risk factors for drug-induced cholestasis include old age, genetic determinants, and properties of certain medications, particularly trimethoprim/sulfamethoxazole, amoxicillin/clavulanate, isoniazid, and nitrofurantoin. The mechanism underlying this phenomenon is unclear, but there is increasing evidence that medications primarily excreted by the liver into the bile hold the greatest disposition for producing cholestatic liver disease in the susceptible patients. In the majority of cases, liver test abnormalities reverse with the cessation of the offending drug. However, there has been a reported 10% of case subjects with cholestatic jaundice secondary to trimethoprim/sulfamethoxazole who either died or underwent liver transplantation [10].

Our patient had been taking sulfamethoxazole/trimethoprim for 7 days before she presented to our hospital with hepatic injury. Studies have reported adverse reactions secondary to sulfamethoxazole/trimethoprim presenting as early as the second day of treatment, especially in patients who have a higher susceptibility. For example, those with a pre-existing liver disease, patients who present concomitantly with another unrelated illness, or patients with a documented sulfa allergy following a prior exposure [8]. Although patients who had no previous exposure to sulfamethoxazole/trimethoprim could typically begin experiencing symptoms as early as four or five days into therapy, or after several in some cases [3]. With our patient's laboratory workup returning negative for any secondary cause of hepatic injury and the immediate improvement in her liver panel following the discontinuation of sulfamethoxazole/trimethoprim, we concluded that the likely cause of her illness is secondary to the effects of sulfamethoxazole/trimethoprim.

The majority of cases completely resolve within 6 months of discontinuing sulfamethoxazole/trimethoprim [6]. We believe this is of utmost importance, because returning our patient to her clinical baseline as a result of discontinuing her sulfamethoxazole/trimethoprim, decreased her risk of developing acute liver failure and subsequent liver transplantation.

4. Conclusion

Cholestatic hepatic dysfunction is an uncommon complication secondary to sulfamethoxazole/trimethoprim treatment that can be reversed in the majority

of cases following discontinuation of the medication. In rare circumstances, it can lead to acute liver failure if left untreated. With the rise in sulfamethoxazole/trimethoprim use amongst the general population, it is critical for clinicians to be aware of these adverse effects and to be able to intervene early to prevent them.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

SMZ-TMP DS: Sulfamethoxazole/Trimethoprim;

AST: Aspartate Aminotransferase;

INR: International Normalized Ratio;

EGD: Esophagogastroduodenoscopy;

FDA: Food and Drug Administration;

ALT: Alanine Aminotransferase;

ALP: Alkaline Phosphatase.