Sulfadiazine-induced Crystalluria and Renal Failure in a Patient With AIDS

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Cerebral toxoplasmosis is one of the most treatable opportunistic infections of the central nervous system in patients with the acquired immunodeficiency syndrome (AIDS).[1,2] A combination of sulfadiazine and pyrimethamine is the therapy of choice, producing a favorable clinical response in 68 to 95 percent of patients receiving this regimen.[3,4] Reports of sulfadiazine-induced crystalluria and renal failure were common during the 1940s and 1950s, before more soluble sulfonamides, such as trimethoprim-sulfamethoxazole (TMP/SMX), became available. Recently, case reports of sulfadiazine nephrotoxicity have reappeared as widespread use of this regimen for human immunodeficiency virus (HIV)-related cerebral toxoplasmosis increased.[5-17] We report a patient with AIDS and central nervous system toxoplasmosis who developed nonoliguric renal failure caused by sulfadiazine-induced crystalluria.

Case Report

A 42-year-old man with AIDS was admitted to the hospital in November 1996 with an 1-day history of urinary incontinence and confusion. At admission he reported poor appetite and a mild headache not associated with fever, neck pain, or photophobia.
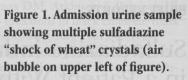
Three weeks earlier he had complained of 2 to 3 weeks of watery diarrhea, mild abdominal pain, some lightheadedness, and a low-grade fever (temperature of 99°F), which responded to antimotility agents and discontinuation of saquinavir monotherapy. He denied chills, dysuria, nausea, vomiting, or anorexia. At that time his serum creatinine

was elevated to 3.7 mg/dL compared with his baseline of 1.0 mg/dL. The patient was instructed to begin oral rehydration, but follow-up did not occur until admission. Stool cultures for ova and parasites were negative. His hemoglobin was 7.3 g/dL, hematocrit 24.0 percent, and white blood cell count 3400/µL. His CD4+ lymphocyte count was 3/L and his HIV-1 RNA by branched DNA assay was 365,600 copies/mL.
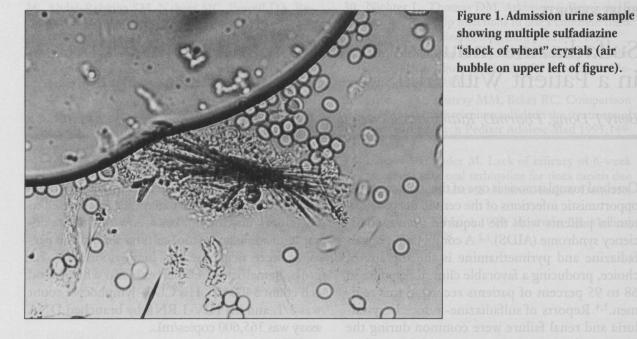
HIV disease had been diagnosed in 1993 when his CD4+ lymphocyte count was 289/L. The patient felt well, had no opportunistic infections or HIV-related sequelae, and repeatedly declined to take or adhere to prescribed medications. One double-strength TMP/SMX tablet daily was prescribed for *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis (positive toxoplasmosis antibody titer) prophylaxis when his CD4+ lymphocyte count was 165/L, but adherence was poor. In February 1996 cerebral toxoplasmosis was diagnosed by a computed tomographic (CT) scan, and he began treatment with pyrimethamine and sulfadiazine. His adherence was inconsistent, however, and 2 months later he was readmitted for an exacerbation of cerebral toxoplasmosis and edema. Renal function at that time was normal (serum creatinine 1.0 mg/dL). Subsequently, adherence was improved by home visits and a medication-dispensing device. Antiretroviral therapy was started in August 1996 when he agreed to start taking only saquinavir (Invirase) monotherapy 600 mg three times a day.

He had no previous history of diabetes, hypertension, or renal disease. His medical history was also notable for treated neurosyphilis and untreated *Mycobacterium avium* complex (MAC) disease. Blood cultures, obtained 3 weeks earlier, became positive for MAC just before hospital admission, so treatment had not yet begun. On admission his medications included one double-strength TMP/SMX tablet three times weekly for

PCP prophylaxis, pyrimethamine 100 mg daily, sulfadiazine 1.5 g every 6 hours, and folinic acid 25 mg daily for treatment of cerebral toxoplasmosis. The toxoplasmosis medications had not been reduced to maintenance doses because the primary care provider did not perceive that medication adherence was adequate. The patient denied use of other medications, including nonsteroidal anti-inflammatory agents.

When examined, the patient was alert but cachectic and confused. Neurologically he was oriented to name only, he had an intact gag reflex, and there was no asterixis or clonus. His motor strength was normal with symmetric reflexes (2+) in the upper and lower extremities. Findings from examinations of the cranial nerve, senses, and coordination were normal. Plantar reflexes were down-going. His temperature and blood pressure were normal, but his pulse was 124 beats per minute and respirations were 18/min. Findings from a chest, heart, and abdominal examination were within normal limits. There was no costovertebral tenderness, and his extremities were without cyanosis, clubbing, or edema.

Notable laboratory findings included a normal serum sodium of 145 mEq/L, a low bicarbonate (8 mEq/L), and elevations in potassium (5.1 mEq/L), chloride (110 mEq/L), blood urea nitrogen (74 mg/dL), serum creatinine (12.2 mg/dL), and serum phosphate (12.1 mg/dL), with an anion gap of 32 mEq/L. The white blood cell count was 700/μL with 72.4 percent neutrophils and an absolute neutrophil count of 500/μL. The hemoglobin and hematocrit were 7.5 g/dL and 24.5 percent, respectively, with a mean corpuscular volume of 76 μm³. Values for the alkaline phosphate (578 U/L), aspartate aminotransferase (106 U/L), amylase (419 U/L), and creatinine kinase (544 U/L) were all elevated. Albumin was slightly low at 3.2 g/dL.

Serologic studies for hepatitis were negative for hepatitis A and C antibodies and hepatitis B surface antigen but positive for antibodies to hepatitis B. Glucose, calcium, magnesium, bilirubin, thyroid function, cryptococcal antigen, and syphilis test results were within normal limits. Urinalysis findings were notable for a pH of 6.0, positive esterase, protein (3+), glucose (2+), blood (3+), red blood cells too numerous to count, 20 to 50 white blood cells, granular casts, and multiple sulfadiazine "shock of wheat" crystals (Figure 1). Urine and blood cultures were negative at 48 hours after admission. A chest radiograph showed normal cardiac and mediastinal silhouettes and no infiltrates. A renal sonogram showed right hydronephrosis and multiple echogenic foci in the kidney (Figure 2). A head CT scan without contrast showed communicating hydrocephalus and no recurrence of toxoplasmosis.

The diagnosis of nonoliguric renal failure caused by obstructive sulfadiazine crystals was suspected. The cause of the altered mental status was

Figure 2. Sonogram of kidney showing multiple echogenic foci (sulfadiazine stones) with shadowing.

believed to be multifactorial and included such contributory factors as uremia, dehydration, possible urinary tract infection, central nervous system toxoplasmosis with hydrocephalus, and AIDS dementia. The neutropenia was ascribed to drug toxicity or MAC infection, and the elevations in liver function tests were presumed secondary to MAC disease or HIV-related cholecystopathy and biliary disease.

Hospital Course
Sulfadiazine was stopped and antitoxoplasmosis treatment was changed to clindamycin 600 mg every 6 hours intravenously, pyrimethamine 50 mg every other day by mouth, and folinic acid 25 mg daily by mouth. Ceftriaxone was given empirically for 7 days to treat a possible urinary tract infection, but urine and blood cultures remained negative. Initially, vigorous intravenous hydration with 5 percent dextrose in normal saline was administered. Satisfactory urine output was maintained but the acidosis and renal function did not improve. On day 2, three ampules of sodium bicarbonate (50 mEq per ampule) in 1 L of dextrose 5 percent water (D5W) was infused at 150 mL/h to treat the acidosis and to increase the urine pH to 7.

During the next 3 to 4 days, hydration and alkalization were gradually reduced to one ampule of sodium bicarbonate in D5W at 100 mL/h to maintain the appropriate urine pH and serum bicarbonate values. Sodium bicarbonate therapy was dis-

continued after 2 days (days 4 and 5 of bicarbonate therapy) because of metabolic alkalosis (serum bicarbonate of 36 mmol/L and urine pH 9.0). Resolution of the renal failure and improvement in mental status occurred after 3 to 4 days of aggressive hydration and bicarbonate therapy.

At discharge on hospital day 15, the patient's serum creatinine was 1.2 mg/dL, blood urea nitrogen was 9 mg/dL, and all electrolytes were normal except for elevated chloride (111 mEq/L) and slightly low bicarbonate (18 mEq/L) levels. A urinalysis on discharge was normal with a pH of 6.0, and no sulfadiazine crystals were seen. A second sonogram was not ordered because his renal function had returned to baseline. Transaminase values normalized, but alkaline phosphatase remained elevated. Blood counts increased toward normal but remained suppressed. Discharge medications included clarithromycin and ethambutol for treatment of MAC disease, dapsone for PCP prophylaxis, and clindamycin and pyrimethamine for maintenance of cerebral toxoplasmosis.

Discussion
Renal toxicity, crystalluria, and nephrolithiasis are serious complications of sulfadiazine therapy in HIV-infected persons.[5-17] Other agents that can produce a similar clinical picture include indinavir and intravenous acyclovir, but not oral acyclovir (Table 1).[18-21]

Predisposing factors for sulfadiazine renal toxi-

Table 1. Principal Drugs Causing Crystalluria, Renal Stones, and Renal Failure in Persons Infected With the Human Immunodeficiency Virus.

Drug	Crystalluria	Renal Stones*	Renal Failure	Hydration Indicated	Alkalization Indicated
Sulfadiazine	Yes	Yes	Yes	Yes	Yes
Intravenous acyclovir[†]	Yes	No	Yes	Yes	Unknown
Indinavir	Yes	Yes	Yes	Yes	No

From Kopp et al,[18] Daudon et al,[19] Berns et al,[20] and Don et al.[21]
*Diagnosis by renal sonography or computed tomographic scan.
†Does not apply to oral acyclovir.

city in this patient were diarrhea and the inability to adhere to instructions for rehydration. Nonadherence also postponed reduction of antitoxoplasmosis treatment doses to the lower maintenance doses, which might have decreased the potential for renal toxicity. Nonadherence was especially detrimental in other aspects of his HIV care, such as the lack of standard prophylaxis against MAC disease, PCP, and toxoplasmosis, and his inability to take potent antiretroviral drug combinations that have clearly been shown to reduce morbidity and prolong survival.[22-24] Adherence might have been improved by the elimination of TMP/SMX therapy, because the combination of sulfadiazine and pyrimethamine appears equally effective for PCP and toxoplasmosis prophylaxis.[25] Strategies to improve adherence have been described.[26]

This patient's clinical condition, urinary sediment findings, nonoliguric renal failure, sonography findings, and hospital course are consistent with other reported cases of sulfadiazine-induced renal failure.[5-17] The incidence of sulfadiazine-related crystalluria is reported as 8 to 29 percent, whereas renal dysfunction is observed in 2.0 to 7.5 percent of HIV-positive cases, twice the incidence in HIV-negative persons.[7,10,12] Typically the patient complains of flank, lumbar, or abdominal pain (80 percent of patients), oliguria or anuria, and hematuria. Symptoms are usually delayed, developing in most patients 1 to 4 weeks after beginning therapy, but they can occur at any time. The diagnosis of sulfadiazine-induced renal failure is confirmed by a urine pH of less than 6 and classic "shock of wheat" (acetyl) sulfadiazine crystalluria, hematuria, and pyuria. Renal sonographic findings can show unilateral or bilateral hydronephrosis or echogenic densities caused by sulfadiazine stones, or they can be normal.[7,8]

Acute renal failure secondary to sulfadiazine

crystallization is a predictable toxicity that should be anticipated in patients who develop concomitant dehydration and acidosis from diarrhea, poor fluid intake, or other causes of fluid losses. A retrospective review of 35 patients with sulfadiazine-induced crystalluria and renal dysfunction found that most had normal renal function and no history of renal damage before starting sulfadiazine.[7] Risk factors included a history of volume depletion from poor fluid intake, diarrhea, fever, or administration of radiocontrast dye. Hypoalbuminemia can also predispose to renal toxicity by increasing the serum levels of the free drug.[7]

Factors that decrease sulfadiazine solubility should be avoided. Sulfadiazine is acetylated in the liver to form insoluble metabolites that can precipitate in the renal tubules during volume depletion or low urinary pH. The critical urine pH value that maintains crystal solubility is reported to be 7.15.[27,28] The concurrent use of drugs, such as ascorbic acid, that can acidify the urine pH might also predispose to renal toxicity by decreasing drug solubility. Likewise, the concurrent administration of sulfadiazine with indinavir might create problems, as indinavir crystallization can occur in an alkaline urine pH.[18-20]

Acute treatment requires aggressive intravenous hydration to maintain a daily urinary output of at least 1.5 L and bicarbonate alkalization to achieve a urine pH of greater than 7.5. If renal function does not improve immediately, hemodialysis is indicated to relieve symptoms of pericarditis and tamponade, asterixis, severe acidosis, hyperkalemia, or severe uremic symptoms unresponsive to aggressive medical interventions. If there is complete obstruction, urethral catheterization or nephrostomy tube placement, followed by warm 5 percent sodium bicarbonate lavage, can be successful[14,15] Complete reversal of renal failure generally

occurs unless there is coexisting renal diseases (eg, HIV nephropathy). It is not essential to avoid further sulfadiazine therapy if adequate hydration can be maintained and dehydration avoided. Complete resolution of the crystalluria and nephrolithiasis has been reported even when sulfadiazine was continued, but this approach is not recommended because treatment with clindamycin-primaquine appears equally effective.[16,17]

Sulfadiazine-induced renal toxicity and nephrolithiasis are preventable if patients maintain a fluid intake of 2 L/d, an adequate urine output of at least 2 L/d, and a urine pH greater than 7. Oral sodium bicarbonate 6 to 12 g/d might be required to achieve an alkaline urine pH. Increasing the urine pH is especially important in those patients who have a history of sulfadiazine nephrotoxicity and who require continued sulfadiazine therapy. Patients should be instructed to report immediately any symptoms of fluid losses, flank, lumbar, or abdominal pain, urinary symptoms, or blood in the urine. Renal function, urinary pH, and fluid status should be closely monitored on a regular basis, weekly if there is an increase in diarrhea or other volume losses.

Primary care providers should be aware that sulfadiazine can cause renal toxicity and should be knowledgeable about available strategies to minimize toxicity, including careful adherence to hydration. Patients who are unable or unwilling to maintain adequate fluid intake or who are prone to volume depletion from gastrointestinal losses should be considered poor candidates for sulfadiazine therapy.

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