Trimethoprim-Sulfamethoxazole-Induced Sepsis-like Syndrome in a Patient with AIDS

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As a result of acquired immunodeficiency syndrome (AIDS) becoming increasingly common, primary care providers are seeing more diseases that are predominantly found in immunodeficient hosts, such as *Pneumocystis carinii* pneumonia (PCP). PCP, which is among the most common opportunistic infections, has a 2-year incidence of approximately 40 percent in AIDS patients[1] and accounted for 14 percent of HIV deaths in 1992.[2] Currently trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for prophylaxis and treatment of PCP. It is frequently used and believed to be relatively safe. It is with this background that we report an unusual reaction to this drug in a patient with AIDS.

Case Report

A 46-year-old man with AIDS, with a CD4 (T-helper) cell count of 96/μL, was brought to the emergency department by ambulance with acute onset of dizziness, fever, chills, and mild shortness of breath. Several months earlier, when the patient had used TMP-SMX for PCP prophylaxis, he developed a severe maculopapular rash involving the skin but not the mucous membranes. He had no systemic symptoms, and his prophylaxis was changed to dapsone, 50 mg twice a day. His other medications included nortriptyline, zidovudine (AZT), and didanosine (DDI).

Two weeks before admission he visited his primary care physician complaining of a nonproductive cough and fever. Findings on a chest radiograph were consistent with PCP, though he was unable to produce a deep sputum sample. No further diagnostic testing was done. His prescription for dapsone was changed to oral atovaquone, 750 mg three times a day for 10 days, and his respiratory symptoms improved considerably. He did experience nausea and stopped taking the atovaquone and the didanosine 3 days before admission. On the afternoon before admission, he looked well and was without any respiratory symptoms or pulmonary findings on clinical examination. It was decided at that time to prescribe TMP-SMX for PCP prophylaxis. He took one dose of TMP-SMX the evening before admission at approximately 9 PM.

At 2 AM on the morning of admission, the patient experienced fever and rigors and was unable to stand. When he was brought to the emergency department, he complained of severe dizziness, mild shortness of breath, and an intense headache. He denied nausea, vomiting, diarrhea, neck pain or stiffness, chest pain, or swelling of the tongue or mouth.

On examination his temperature was 39.8°C, respirations 24/min, pulse 140 beats per minute, and blood pressure 90/50 mmHg. In general, he was an alert, anxious man in moderate to severe distress. He had very dry mucous membranes, injected sclera, and no palpable lymphadenopathy. His skin was hot and dry without rashes. His lungs had fine, bibasilar crackles, and his heart was tachycardic, but regular without murmurs, rubs, or gallops. His abdomen had active bowel sounds and was soft, nontender, and without hepatosplenomegaly or masses. Extremities showed no clubbing, cyanosis, or edema. The neurological examination was nonfocal. Arterial blood gases on 100 percent nonrebreather showed a pH of 7.46, a PO_2 of 93 mmHg, a PCO_2 of 30 mmHg, a bicarbonate of 21 mEq/L, and an arterial oxygen saturation of 99 percent. A chest radiograph showed diffuse, interstitial infiltrates with nodular foci in the right upper, right lower, and left lower lobes.

The patient was admitted with a presumed diagnosis of PCP, and after sputum, blood, and

Submitted, revised, 31 July 1996.

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urine samples were obtained for culture, he was prescribed inhaled pentamidine and atovaquone. Given his earlier rash while taking TMP-SMX, we were reluctant to challenge him with the high doses that are required for treatment. He was also prescribed gentamicin and ampicillin-sulbactam to cover bacterial sources. Later that morning repeated arterial blood gas measurements on room air were a pH of 7.56, a PO_2 of 82 mmHg, a PCO_2 of 24 mmHg, a bicarbonate of 21 mEq/L, and an oxygen saturation of 97 percent.

By evening his blood pressure had dropped to 83/50 mmHg despite 6 L of normal saline, and he was transferred to the Intensive Care Unit. His therapy for PCP was changed to intravenous pentamidine with steroids, and low-dose dopamine was added to support his blood pressure. Laboratory tests showed a white cell count of 4000/μL, bicarbonate 20 mEq/L, hematocrit 23 percent, and lactate dehydrogenase 274 U/L. Arterial blood gases on room air were a pH of 7.42, a PCO_2 of 33 mmHg, a PO_2 of 131 mmHg, a bicarbonate of 20 mEq/L, and an oxygen saturation of 99 percent. Sputum Gram stain showed white blood cells (3+) and gram-negative rods that were coliform in appearance. He received two units of packed red blood cells. Ampicillin-sulbactam was changed to ceftriaxone.

After 24 hours he was hemodynamically stable. A computed tomogram of his head showed bilateral maxillary, ethmoid, and sphenoid sinusitis, but findings were otherwise normal. A lumbar puncture was considered but deferred because the patient's headache resolved, and his neurological examination remained nonfocal. Bronchoscopy with bronchoalveolar lavage produced a Gram stain with white blood cells (3+), epithelial cells (2+), and gram-negative rods (1+). It was negative for PCP, acid-fast bacilli, fungi, *Legionella*, Rous sarcoma virus, adenovirus, influenza A and B viruses, and parainfluenza virus. Bacterial culture grew mixed flora, as did the sputum culture from admission. PCP treatment was continued because bronchoalveolar lavage is only about 85 percent sensitive,[3,4] and the clinical picture suggested PCP despite the unusual course.

He continued to improve, and on day 4 was prescribed oral clindamycin, 450 mg four times a day, and oral primaquine 52.6 mg each day; and pentamidine was discontinued. On day 6, he went home with prescriptions for a prednisone taper, clindamycin, and primaquine for an additional 17 days. At time of discharge all blood cultures, including those drawn before he started taking antibiotics, were negative. The bronchoalveolar lavage samples grew cytomegalovirus, but this pathogen was not believed to be clinically important, and no additional treatment was added.

Discussion

TMP-SMX is the most commonly used drug for treating PCP in patients with AIDS. Studies in the 1970s showed TMP-SMX to be as efficacious as, but less toxic than, pentamidine in treating cases of PCP. There was a 15 percent rate of mild adverse effects using TMP-SMX compared with a 50 percent rate using pentamidine.[5]

When treating AIDS-associated PCP, however, TMP-SMX has been reported to have a more serious side effect profile than previously found.[6,7] Gordin and colleagues[8] reviewed the charts of 38 patients with AIDS and biopsy-proven PCP who were treated in San Francisco from October 1981 to April 1983. Of the 37 prescribed TMP-SMX, 2 (5 percent) died within 7 days, 29 (78 percent) developed some toxicity, 19 (51 percent) stopped taking it because of adverse effects, and 11 (30 percent) had their prescriptions changed to another medication. Only 5 (14 percent) completed treatment. Toxicity included rash, fever, neutropenia, thrombocytopenia, and transaminase elevation. Of the 30 patients who received pentamidine, 7 (23 percent) died and toxicity occurred in 13 (43 percent), but only 4 (13 percent) required a change in medication. Adverse reactions to pentamidine included fever, rash, neutropenia, transaminase elevation, azotemia, and hypoglycemia. Severe toxicity occurred in 62 percent of patients prescribed TMP-SMX compared with 20 percent prescribed pentamidine ($P < 0.005$).[8]

Despite the relatively high rate of side effects, TMP-SMX remains the drug of choice for AIDS patients with PCP largely because of its proven efficacy.[9] As a result, it is common to give another trial of TMP-SMX even when adverse reactions have been documented in the past. Carr and colleagues,[10] showed that rechallenging without desensitizing can be successful if done in patients without life-threatening adverse reactions to TMP-SMX. With rechallenging, however, there is a subset of patients who respond with sepsis-like reactions, including pulmonary infiltrates,

hypoxemia, fever, rash, and hypotension.[11]

A literature review by Johnson and colleagues[12] described six cases in which similar reactions were observed. Previous TMP-SMX exposure occurred in four and was unknown in two, all patients had one or two doses before the reaction, and all had symptoms within 12 hours of the first dose. All had fever in excess of 39°C and rash, and 5 had systolic blood pressure of less than 70 mmHg (one was "low"). Five had new infiltrates on chest radiographs (one was "unknown"). All patients improved within 72 hours of discontinuation of TMP-SMX and 5 improved within 48 hours.

More recently, Shepard et al[13] reported a sepsis-like condition experienced by a patient with AIDS after taking TMP-SMX. He had taken TMP-SMX without problem for 10 days a month before his first admission, which was characterized by fever, hypotension, and pulmonary infiltrates. He recovered, but no source was found, and he was again prescribed prophylactic doses of TMP-SMX. Again his symptoms returned, and again no source was found. The authors felt that an adverse reaction to TMP-SMX caused this reaction.

These cases highlight a serious side effect of a commonly prescribed drug in the AIDS patient population. One of the most difficult aspects of this reaction is the diagnostic dilemma it presents. Our patient seems to fit the pattern of TMP-SMX induced sepsis-like reaction. He had acute onset of fever, rigors, hypotension, and pulmonary infiltrates very shortly after rechallenge with this drug. When examined in the clinic approximately 12 hours earlier, his condition was stable and he was in no distress. His symptoms resolved within 48 hours of his single dose of TMP-SMX and within 24 hours of initiating antimicrobial therapy. Bacterial septic shock would not be expected to resolve so rapidly. He also did not have cardiomegaly or peripheral edema and recovered without diuresis, making acute pulmonary edema unlikely. The case is also unusual for PCP, as he had multiple negative sputum samples, minimal shortness of breath, and very rapid onset and recovery.

Many patients with a mild reaction to TMP-SMX are able to tolerate desensitization or rechallenge. As TMP-SMX is clearly the best treatment for AIDS-associated PCP, the ability to prescribe this drug safely is critically important. Cases such as this one, however, show that a serious adverse effect can occur upon re-exposure to TMP-SMX in patients who have a history of relatively mild side effects. These cases illustrate that caution must be exercised when prescribing TMP-SMX for patients with HIV infection.

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