

Severe Co-trimoxazole Reaction In A Man With AIDS

John Shepherd, MD, Carolyn Shepherd, MD, Chris Tonozzi, MD, and Eric Boysen, MD

With the increasing incidence of acquired immunodeficiency syndrome (AIDS) in the United States, family physicians and other primary care specialists will provide health care for a growing number of immunocompromised persons. Research has documented that primary care physicians individually seeing few cases of human immunodeficiency virus (HIV) infection together treat a large number of HIV-infected men, women, and children.¹ Indeed, health care providers have recognized that AIDS is a chronic disease and that earlier diagnosis of an increasing number of cases necessitates more outpatient care. HIV-infected individuals require more health care than infectious disease consultation alone.^{2,3} Simultaneously, primary care providers have realized their responsibility to care for these patients and their need for more information about this disease. Primary care journals and publications have begun to disseminate these data.⁴⁻⁷ Other educators have initiated clinical training programs to prepare community physicians.⁸

Trimethoprim-sulfamethoxazole (co-trimoxazole) is one of the most frequently prescribed drugs for HIV-positive patients. Commonly utilized for prophylaxis against *Pneumocystis carinii* pneumonia (PCP), the most common AIDS-defining infection, this antibiotic also treats active PCP and *Isopora belli* gastrointestinal infections and probably provides prophylaxis against central nervous system toxoplasmosis.⁹ We report a severe systemic reaction to co-trimoxazole to publicize the potentially serious adverse affects of co-trimoxazole in the HIV-infected population.

Case Report

In October 1993 approximately 10 years after his last reported use of intravenous drugs, a 44-year-old man was found to be HIV positive. He had

not sought medical care prior to this time and admitted to denial of his risk for HIV infection. On 11 November 1993 his family physician prescribed double-strength co-trimoxazole (160 mg trimethoprim, 800 mg sulfamethoxazole) one tablet a day as *Pneumocystis carinii* pneumonia (PCP) prophylaxis after discovering that the patient's CD4 cell count was 80/ μ L. The patient had completed a 10-day course of co-trimoxazole 1 month earlier without any observed adverse effects.

The patient took only one dose of double-strength co-trimoxazole and 25 mg of amitriptyline during the evening of 15 November 1993. He denied the use of any illicit or over-the-counter drugs. His wife returned from work at 8:30 PM and found him poorly responsive and disoriented. In the morning of 16 November 1993 the patient was totally unresponsive and was taken to the hospital by his family.

Table 1 displays the patient's hypotension and fever on admission and the initial laboratory results. A toxicology screening test uncovered only the prescribed medications. Other than his marked change in mental status, his physical examination was notable for a generalized erythema of his skin. He also experienced profuse diarrhea on admission. The patient required intensive fluid replenishment and dopamine to maintain his blood pressure; because sepsis headed the list of potential diagnoses, he was prescribed a combination of three antibiotics (ampicillin, cefotaxime, imipenem-cilastatin). Blood cultures from two separate sites subsequently grew *Staphylococcus epidermitis*. On the second hospital day, he developed bilateral pulmonary infiltrates (right upper lobe and left base), which progressed to generalized edema on 18 November and required 4 days of ventilatory support. By the fifth hospital day, his pancytopenia worsened with his white cell count dropping to 2200/ μ L and his hemoglobin to 8.8 g/dL. His low total protein and albumin levels reflected his poor nutritional state. In addition, he had an elevation in his liver function tests (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) and a prothrombin time 3.5 seconds longer than control.

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From the Department of Family Medicine, University of Colorado, Denver (JS), and Clinica Campesina Community Health Center, Lafayette (CS,CT,EB), Colorado. Address reprint requests to John Shepherd, MD, Department of Family Medicine, University of Colorado, 1180 Clermont, Denver, CO 80202.

Table 1. Hospital Admission Data for 44-Year-Old Man with AIDS and Severe Co-trimoxazole Reaction.

Physical Examination and Laboratory Data	Hospitalization 1	Hospitalization 2
Temperature (°F)	104	103.9
Blood pressure (mmHg)	70/40	80/50
Laboratory results		
Complete blood count		
White cell count/mm ³	6.8	7.7
Hemoglobin (g/dL)	10	10.7
Hematocrit (%)	29	30.6
Platelets ($\times 10^3$ /mm ³)	65	154
Chemical analysis-blood		
CO ₂ (mEq/L)	14	16
Urea nitrogen (mg/dL)	44	26
Creatine (mg/dL)	4.6	2.4
Albumin (g/dL)	2.7	2.6
Creatine kinase (IU/L)	2664	—
Calcium (mg/dL)	7.2	8.3
Glucose (mg/dL)	102	96
Cerebral spinal fluid		
Protein (mg/dL)	74	143
White cell count (% polymorphonuclear)	42 (94%)	46 (100%)
Glucose (mg/dL)	77	40
Gram stain	Negative	Negative
India ink	Negative	
Acid-fast bacilli, stain and culture	Negative	
Fungal culture	Negative	
<i>Cryptococcus neoformans</i> antigen	Negative	
Radiology		
Chest radiograph	Normal	Normal
Computed tomogram: head	Negative	
Echocardiogram	Normal	
Culture and smears		
Blood: <i>Staphylococcus epidermidis</i>	Positive	Negative
Urine	Negative	Negative
Cerebral spinal fluid	Negative	Negative
Sputum: <i>Candida albicans</i>	Positive	Negative
Stool		
Ova and parasites	Negative	
<i>Cryptosporidium</i>	Negative	
<i>Campylobacter</i>	Negative	
<i>Candida albicans</i>	Positive	
Cytology		
<i>Pneumocystis carinii</i> , sputum	Negative	
Serology		
IgG toxoplasmosis	Negative	
VDRL	Negative	
Other		
Streptococcal antigen, throat	Negative	
<i>Legionella pneumophila</i> , sputum	Negative	

Interestingly, his alkaline phosphatase level was low. During this hospitalization, multiple subspecialists provided consulting care, but the diagnosis of drug reaction was not entertained.

The patient gradually improved and his laboratory values returned to normal, although a repeat lumbar puncture was not performed. He was discharged home with a prescription for oral cephalexin after physical, occupational, and nutritional therapy. At discharge he had episodes of minimal confusion and deficits in fine motor coordination.

His family physician saw him on 1 December 1993, 1 week after hospital discharge, when he had recovered enough to continue his usual activities. He was again prescribed prophylactic doses of co-trimoxazole. The patient took one double-strength tablet that evening, complained of crampy abdominal pain approximately 30 minutes later, and took a second tablet. In the morning of 2 December 1993 his wife again found him confused, febrile, flushed, and incontinent of stool and brought him to the emergency department. His temperature, blood pressure, and laboratory data on this hospitalization also are shown in Table 1. Examination of his skin again revealed a generalized erythema. Compared with his first hospitalization, findings on his chest radiograph remained normal, and he did not require ventilatory support. The other laboratory data looked similar to the November 1993 admission. He needed vigorous fluid administration, and on this admission he received diphenhydramine, cimetidine, and prednisone. To protect him from the possibility of sepsis, he was prescribed imipenem-cilastatin followed by ceftriaxone. All of his cultures showed no growth, and his temperature and blood pressure rate returned more rapidly to normal. Unfortunately, his mental status remained abnormal, and he was placed in full-time hospice care. The patient died in February 1994 of an undiagnosed febrile illness.

Discussion

The unique predisposition of HIV-positive patients to drug hypersensitivity reactions has received thorough review in a number of publications.¹⁰ The incidence of these reactions appears remarkably higher than reported in the general population, particularly for co-trimoxazole. While 2 to 8 percent of the general population have adverse reactions to this drug, 29 to 83 percent

of AIDS patients experience some form of reaction to co-trimoxazole.¹¹⁻¹⁵ Only 3 to 12 percent of other immunocompromised patients, however, react to either intravenous or oral forms of trimethoprim-sulfamethoxazole.¹⁵ Cutaneous eruptions and fever represent the most frequent allergic manifestations.¹⁰ Fortunately the severe hypersensitivity response that our patient suffered occurs rarely. Allergic responses reported in 10 previously published cases have included hyperthermia, rash, hypotension, and new pulmonary infiltrates mimicking sepsis.¹⁶⁻²¹ Other serious signs not consistently described in these case presentations include cytopenia, abnormal liver function, and severe dermatologic reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. These reactions have also been reported in HIV-positive persons after thalidomide, ciprofloxacin, rifampin, or flucytosine ingestion.^{10,21}

The diagnosis of a co-trimoxazole hypersensitivity arises from the similarity of this case to other reported severe reactions, the temporal association with the administration of the drug, the resolution of symptoms more rapidly with the use of steroids and antihistamines, and the absence of a recurrent episode when this patient did not receive the drug. We doubt that an infection caused the problem because only the initial blood cultures grew a possible skin contaminant. In addition, this case is unique because of the apparent concurrent aseptic meningitis possibly secondary to the drug sensitivity. This side-effect is noted in the *Physicians Desk Reference* and in other non-HIV-related case reports but is not mentioned in the previously published AIDS-related co-trimoxazole reactions.^{22,23} The work-up of the previous 10 reported cases did not include a lumbar puncture, perhaps because these patients did not have any change in mental status, as did this patient. Although the changes in cerebral spinal fluid could have arisen from a viral infection or HIV-induced encephalitis, the rapid clearing of his altered mental status with fluids and other supportive care after cessation of drug therapy certainly implicates a drug-induced cause.

While the exact mechanism of co-trimoxazole reactions remains ill-defined, various researchers have speculated on possible methods. The reaction resembles type I immunoglobulin E-mediated

(IgE) hypersensitivity with the Fc portion of IgE attaching to basophils and mast cells, thereby releasing mediators of immediate hypersensitivity.²⁴ Investigators have found an inverse relation between CD4 lymphocyte counts and mean serum IgE levels.²⁵ Perhaps the increase in interleukin-4 and the decrease in interferon- γ seen in AIDS patients also could explain the IgE-like symptoms.²⁶ The absence of upper airway edema, bronchospasm, and angioedema, however, suggests another pathway.^{12,16} Other researchers have noted that HIV-positive individuals have a systemic glutathione deficiency and therefore a reduced capacity to scavenge hydroxylamine derivatives of sulfamethoxazole, which seem to cause an adverse reaction to co-trimoxazole.²⁷ Tumor necrosis factor alpha, also produced more abundantly in HIV-infected patients, can cause many of the signs and symptoms of sepsis and could cause this syndrome, too.²¹

Summary

Although other drugs can be used in the prophylaxis and treatment of HIV-infected persons, family physicians will prescribe co-trimoxazole frequently.⁴ These providers need to recognize the overall increased frequency of adverse reactions to this drug in this population and the potential for severe hypersensitivity effects requiring intensive hospital care. While the exact importance re-exposure has in causing this reaction remains unclear, certainly providers must pay particular attention to patients who have had any earlier sensitivity to the drug before treatment is resumed. Desensitization therapy has been used successfully in some HIV-positive individuals, even after severe reactions; however, this case again teaches the need for prudence in the use of all pharmacological agents.¹⁰

References

1. Wenrich MD, Ramsey PG. Patterns of primary care of patients infected with human immunodeficiency virus. *West J Med* 1991; 155:380-3.
2. Northfelt DW, Hayward RA, Shapiro MF. The acquired immunodeficiency syndrome is a primary care disease. *Ann Intern Med* 1988; 109:773-5.
3. Karan LD. Primary care for AIDS and chemical dependence. *West J Med* 1990; 152:538-42.
4. Goldschmidt RH, Dong BJ. Current report-HIV. Treatment of AIDS and HIV-related conditions — 1994. *J Am Board Fam Pract* 1994; 7:155-78.

5. El Sadr W, Loeske JM, Agins BD, Bauman KA, Brosgart CL, Brown GM, et al. Evaluation and management of early HIV infection. Clinical practice guideline No. 7. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, January 1994. AHCPR publication no. 94-0572.
6. Henry WK. Essential HIV/AIDS facts. What you need to know in 1992. *Postgrad Med* 1992; 91:84-6, 89-92, 95.
7. Nadler JP. Primary care management of human immunodeficiency virus infection. *South Med J* 1993; 86:796-802.
8. Katsufakis PJ, Radecki SE. Clinical training in human immunodeficiency virus disease for community physicians. The Los Angeles experience. *West J Med* 1992; 156:619-23.
9. Lifson AR, Olson R, Roberts SG, Poscher ME, Drew WL, Conant MA. Severe opportunistic infections in AIDS patients with late-stage disease. *J Am Board Fam Pract* 1994; 7:288-91.
10. Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992; 5:1237-57.
11. Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982; 4:426-8.
12. Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim-sulfamethoxazole in patients in *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis* 1993; 167:180-5.
13. Mitsuyasu R, Groopman J, Volberding P. Cutaneous reaction to trimethoprim-sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; 308:1535-6.
14. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1984; 100:495-9.
15. Kovacs JA, Heimenz JW, Macher AM, Stover D, Murray HW, Shelhamer J, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984; 100:663-71.
16. Johnson MP, Goodwin SD, Shands JW Jr. Trimethoprim-sulfamethoxazole anaphylactoid reactions in patients with AIDS: case reports and literature review. *Pharmacotherapy* 1990; 10:413-6.
17. Cohn DL, Penley KA, Judson FN, Kirkpatrick CH, Horsburgh CR Jr, Davis KC. The acquired immunodeficiency syndrome and trimethoprim-sulfamethoxazole adverse reaction. *Ann Intern Med* 1984; 100:311.
18. Silvestri RC, Jensen WA, Zibrak JD, Alexander RC, Rose RM. Pulmonary infiltrates and hypoxemia in patients with the acquired immunodeficiency syndrome re-exposed to trimethoprim-sulfamethoxazole. *Am Rev Respir Dis* 1987; 136:1003-4.
19. Arnold PA, Guglielmo BJ, Hollander H. Severe hypersensitivity reaction upon rechallenge with trimethoprim-sulfamethoxazole in a patient with AIDS. *Drug Intell Clin Pharm* 1988; 22:43-5.
20. Ulstad DR, Ampel NM, Shon BY, Galgiani JN, Cutcher AB. Reaction after re-exposure to trimethoprim-sulfamethoxazole. *Chest* 1989; 95:937-8.
21. Kelly JW, Dooley DP, Lattuada CP, Smith CE. A severe, unusual reaction to trimethoprim-sulfamethoxazole in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1992; 14:1034-9.
22. Joffe AM, Farley JD, Linden D, Golsand G. Trimethoprim-sulfamethoxazole-associate aseptic meningitis: case reports and review of the literature. *Am J Med* 1989; 87:332-8.
23. Escalante A, Stimmler MM. Trimethoprim-sulfamethoxazole induced meningitis in systemic lupus erythematosus. *J Rheumatol* 1992; 19:800-2.
24. Serafin WE, Austen KF. Mediators of immediate hypersensitivity reactions. *N Engl J Med* 1987; 317:30-4.
25. Wright DN, Nelson RP, Ledford DK, Fernandez-Caldas E, Trudeau WL, Lockey RF. Serum IgE and human immunodeficiency virus (HIV) infection. *J Allergy Clin Immunol* 1990; 85:445-52.
26. Romagnani S, Del Prete G, Maggi E, Parronchi P, Tiri A Macchia D, et al. Role of interleukins in induction and regulation of human IgE synthesis. *Clin Immunol Immunopathol* 1989; 50:S13-23.
27. van der Ven AJ, Koopmans PP, Vree TB, van der Meer JW. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; 338:431-3.