Management of Hypersensitivity to Trimethoprim-Sulfamethoxazole With an Ultrarapid Desensitization Protocol in HIV Infection

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Prophylaxis for opportunistic infections has been a major advance in the treatment of HIV-infected patients, significantly decreasing morbidity and mortality. Nevertheless, these improved treatment options have been accompanied by an increase in reports of hypersensitivity reactions (HSRs) to sulfonamides. The most common cutaneous manifestations of the reactions are as follows: maculopapular rash (36.6%); fixed drug eruption (22%); and type IV HSRs (urticaria) and type I HSRs (angioedema) (12.6%).

Withdrawal of the drug and desensitization are both possible therapeutic approaches following confirmed diagnosis of adverse reactions to cotrimoxazole [1]. Many protocols for desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients are described in the literature. These initially took several days and, more recently, a single day, although few take less than 6 hours [2].

The objective of this study was to report 3 cases of HSR to trimethoprim-sulfamethoxazole in HIV-infected patients and describe their management with a novel ultrarapid 3.25-hour, 13-step oral desensitization protocol. Written informed consent for publication was obtained from the patients.

Three HIV-infected men presented clinical manifestations of drug-induced HSR after receiving treatment with trimethoprim-sulfamethoxazole.

The first patient was a 30-year-old man with a complicated appendectomy and abdominal collections who had recently been diagnosed with HIV infection ($CD4^+$ 140/µL) and syphilis. Trimethoprim-sulfamethoxazole was started owing to fever and intra-abdominal collection. After administration of the third dose, he developed disseminated dermatosis on the head, face, neck, and thorax. He was diagnosed with maculopapular rash secondary to trimethoprim-sulfamethoxazole, and patch testing yielded a positive reaction (+++, vesicles covering 50% of the test site). Premedication with chlorphenamine was given prior to the protocol (3 solutions [A 1:100, B 1:10, C 1:1]), with no adverse events (Table).

The second patient was a 31-year-old man diagnosed with HIV infection ($CD4^+$ 95/µL), tuberculosis, cryptococcosis, syphilis, type 1 herpes virus, encephalitis, and *Pneumocystis jirovecii* pneumonia. Prophylactic trimethoprim-sulfamethoxazole was started, and 4 hours after administration, the patient developed a single violet-colored macula on the right iliac fossa accompanied by desquamation. A second exposure to the drug was followed by the same lesion 2 hours later. The patient was diagnosed with fixed drug eruption, and erythema and papules were seen on >50% of the patch test site. Premedication with chlorphenamine was given prior to the protocol (13 steps, 3 dilutions), which was carried out successfully.

The third case involved a 27-year-old man with HIV infection ($CD4^+$ 25/µL), cytomegalovirus, and tuberculosis who had been diagnosed with non-Hodgkin lymphoma. Prophylaxis was started with trimethoprim-sulfamethoxazole. Two months later, he developed a systemic reaction characterized by urticaria, pruritus, and abdominal pain 20 minutes after administration. A type I HSR was diagnosed, and prick testing with cotrimoxazole (80 mg/1 mL concentration) yielded a positive result. Premedication with chlorphenamine was given prior to the protocol, which was performed successfully.

Antibiotics containing sulfonamide are the second most frequent cause of allergic reactions to medications, after ß-lactams. In a large study, the incidence of reactions to trimethoprim-sulfamethoxazole was 34 per 1000 exposed patients, compared with 51 per 1000 for amoxicillin [3].

Effective regimens for prophylaxis of opportunistic infections were the first major advance in therapy for HIV-infected patients, significantly decreasing mortality. Trimethoprim-sulfamethoxazole is currently indicated as primary and secondary prophylaxis against toxoplasmosis, isosporiasis, and *P jirovecii* infection [4].

Sulfonamide allergies can cause various manifestations, with rash being the most frequently observed. Skin reactions can occur in 1.5% to 3% of immunocompetent patients and in up to 30% of HIV-infected patients [5].

Drug allergy is very frequent in patients with HIV infection/AIDS (up to 25%), and more than 10% of HIV-infected patients are allergic to sulfonamide antibiotics [3].

Maculopapular rash can present 1 to 2 weeks after the introduction of trimethoprim-sulfamethoxazole and often dissipates within a similar time period, ie, 1-2 weeks after withdrawal. Risk factors associated with HSR to trimethoprim-sulfamethoxazole include a history of syphilis, high total plasma protein concentration, and low CD4 count, although the most significant risk factor for a sulfonamide allergy is HIV infection [6,7].

The clinical history plays a key role in the evaluation of a patient with an adverse reaction to a drug, and the timing of the reaction in relation to administration is of the utmost importance. Skin prick testing with a concentration of 80 mg/mL and an intradermal test concentration of 0.8 mg/mL (based on the sulfamethoxazole component) of trimethoprim-sulfamethoxazole seems a favorable approach; however, the predictive utility of an IgE-mediated reaction based on skin tests is limited, and type I HSR to sulfonamide antimicrobials is less common than type IV HSR, in which patch testing would be the more suitable diagnostic approach [2].

Drug desensitization is a procedure designed to induce tolerance to a drug after an adverse drug reaction. It has been described in patients with IgE-mediated hypersensitivity and mild type IV hypersensitivity, when there is no alternative drug, and when the drug is more effective or has fewer adverse effects than alternatives or has a unique mechanism of action. In HIV infection, cotrimoxazole is essential both as prophylaxis and as therapy [8]. Although the mechanism of most HSRs to trimethoprim-sulfamethoxazole is unlikely to

Table. Ultrarapid 13-Step Desensitization Protocol for Trimethoprim-Sulfamethoxazole

Step	Solution	Time, min	Concentration per solution	Volume administered, mL	Dose administered, mg	Cumulative dose
1	A	15	80/400 µg/mL	1.25	0.1/0.5 mg	0.1 /0.5 mg
2	A	15	80/400 µg/mL	2.5	0.2/1 mg	0.3/1.5 mg
3	A	15	80/400 µg/mL	5	0.4/2 mg	0.7/3.5 mg
4	A	15	80/400 µg/mL	10	0.8/4 mg	1.5/7.5 mg
5	B	15	0.8/4 mg/mL	1.25	1/5 mg	2.5/12.5 mg
6	B	15	0.8/4 mg/mL	2.5	2/10 mg	4.5/22.5 mg
7	B	15	0.8/4 mg/mL	5	4/20 mg	8.5/42.5 mg
8	B	15	0.8/4 mg/mL	10	8/40 mg	16.5/82.5 mg
9	C	15	8/40 mg/mL	1.25	10/50 mg	26.5/132.5 mg
10	C	15	8/40 mg/mL	2.5	20/100 mg	46.5/232.5 mg
11	C	15	8/40 mg/mL	5	40/200 mg	86.5/432.5 mg
12	C	15	8/40 mg/mL	10	80/400 mg	166.5/832.5 mg
13	C	15	8/40 mg/mL	20	160/800 mg	326.5/1632.5 mg
					Total dose: 326.5/1632.5 mg	Total time: 3.25 h

be mediated by IgE, the term desensitization has been used to describe the various protocols for inducing tolerance after an adverse reaction. Successful desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients using protocols lasting ≥1 day has been widely reported in the literature, although few cases of protocols lasting under 6 hours have been reported [9].

In vitro models have shown that 10- to 15-minute intervals of drug desensitization inhibit the release of B-hexosaminidase from mast cells, thus preventing the release of preformed mediators and the clinical manifestations of HSR [10].

In conclusion, management with trimethoprim-sulfamethoxazole is essential for the management of HIV infection. Our ultrarapid 3.25-hour desensitization protocol is safe and effective for treatment of patients with type I and type IV HSRs, such as fixed drug eruption and maculopapular rash.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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