

## **Management of Hypersensitivity to Trimethoprim-Sulfamethoxazole with Ultra-Rapid Desensitization Protocol in HIV Infection**

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Prophylaxis for opportunistic infections has been a major advance in therapy for HIV-infected patients, significantly decreasing morbidity and mortality. Nevertheless, with better treatment options, there has also been an increase in reports to hypersensitivity reactions (HSR) to sulfonamides, being the most common cutaneous manifestations: maculopapular rash (36.6%), fixed drug eruption (22%) both type IV HSR, and urticaria and angioedema (12.6%) a type I HSR.

Two possible therapeutic approaches following confirmed diagnosis of adverse reactions to cotrimoxazole are withdrawal of the drug or desensitization [1]. Many protocols for desensitization to trimethoprim-sulfamethoxazole in HIV patients are described in the literature, initially for several days and more recently for a single day, but few with a duration of less than 6 hours. [2].

The objective of this study is to describe and report three cases of HSR to trimethoprim-sulfamethoxazole (TMP/SMX) in HIV patients and the management with a novel ultra-rapid 3.25-hour oral desensitization protocol.

### **Case description**

Three male patients with HIV infection present clinical manifestations of drug HSR after receiving treatment with trimethoprim-sulfamethoxazole.

#### **Case 1**

A 30-year-old male patient with a complicated appendectomy and abdominal collections, with recent diagnosis of HIV (CD4+ 140) and syphilis. Trimethoprim-sulfamethoxazole was started due to fever and intra-abdominal collection and after the administration of the third dose, he started with disseminated dermatosis on the head, face, neck and thorax.

Maculopapular rash secondary to trimethoprim-sulfamethoxazole was diagnosed and patch test was performed, obtaining a positive reaction +++ (vesicles covering 50% of patch test site). Premedication with chlorphenamine was given prior to the ultra-rapid oral desensitization 13 steps– 3 solutions (A 1: 100, B 1: 10, C 1:1) protocol, without any adverse events (Table 1).

### Case 2

A 31-year-old male patient with HIV(CD4+ 95) diagnosis as well as tuberculosis, cryptococcosis, syphilis, type 1 herpes virus, encephalitis and *Pneumocystis jiroveci* pneumonia. Prophylactic trimethoprim-sulfamethoxazole was started and after a 4-hour administration, he developed a single violet-colored macula in the right iliac fossa accompanied by desquamation. Subsequently, he presented a second exposure to the drug and presented the same lesion 2 hours later. Fixed drug eruption secondary to the drug is diagnosed and erythema and papules >50% of patch tests site. Premedication with chlorphenamine was given prior to a rapid oral desensitization protocol of 3.25 hours, 13 steps- 3 dilutions was carried out successfully.

### Case 3

A 27-year-old male patient with a HIV (CD4+ 25), cytomegalovirus and tuberculosis infection, is diagnosed with non-Hodgkin lymphoma. Prophylaxis is started with trimethoprim-sulfamethoxazole and 2 months later he presents 20 minutes after its administration, a systemic reaction characterized by urticaria, pruritus and abdominal pain. A HSR type I is diagnosed so a prick test was performed with cotrimoxazole (80 mg/1mL concentration), resulting in a positive test. Premedication with chlorphenamine was given prior to an ultra-rapid oral desensitization protocol in 3 hours and 15 minutes, which was performed successfully.

Antibiotics containing sulfonamide are the second most frequent cause of allergic reactions to medications, after beta-lactams. In a large study, the incidence of reactions to trimethoprim-sulfamethoxazole was 34 per 1,000 exposed patients, compared to 51 per 1,000 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 *Pneumocystis jirovecii*. [4].

Sulfonamide allergies can cause various manifestations, being rash the most frequently observed one. Skin reactions can occur in 1.5 to 3% of patients who are immunocompetent and up to 30% in patients with human immunodeficiency virus [5].

HIV/AIDS patients have a high frequency of reported drug allergy (up to 25%) and more than 10% of HIV patients have an allergy to sulfonamide antibiotics [3].

Maculopapular rash may present 1 to 2 weeks after the introduction of trimethoprim-sulfamethoxazole therapy and often dissipating within a similar time course, between 1 to 2 weeks of antimicrobial withdrawal. Risk factors that have been identified to develop HSR to trimethoprim-sulfamethoxazole include a history of syphilis, high total plasma protein concentration, low CD4 count but the most significant risk factor for a sulfonamide allergy is HIV infection [6,7].

In the evaluation of a patient with an adverse reaction to a drug, the clinical history is essential and the timing of the reaction in relation to the administration of medications is of utmost importance. Skin prick test with a concentration of 80 mg/ml and intradermal test concentration 0.8 mg/ml (based on sulfamethoxazole component) of TMP/SMX may seem like a favorable approach; however, the predictive utility of an IgE-mediated reaction using skin tests is limited and HSR type I to sulfonamide antimicrobials is less common than type IV HSR in which patch test 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, there is no alternative drug, the drug is more effective or has fewer adverse effects or has a unique mechanism of action. In HIV infection, cotrimoxazole as a prophylactic and therapeutic regimen is essential.[8]. Although the mechanism of most HSR to trimethoprim-sulfamethoxazole is unlikely to be mediated by IgE, the term desensitization has been used to describe the various protocols for inducing

tolerance after an adverse reaction. Successful desensitization of trimethoprim-sulfamethoxazole in HIV patients using one or several day protocols has been widely reported in the literature, however few cases are reported in less than 6 hours [9].

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

In conclusion, management with trimethoprim-sulfamethoxazole in a patient with HIV is essential, so this ultra-rapid 3.25-hour desensitization is a safe and effective protocol for treatment in patients with hypersensitivity reactions type I and type IV such as fixed drug eruption and maculopapular rash.

### **Consent for publication**

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written and informed consent for publication was obtained from the patient. The patients were informed that de-identified data would be used in the scientific research and publications.

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### **Competing interest**

The authors declare that they have no competing interests.

## References

1. Rial Prado MJ, Rico Díaz MA, Cosgaya Ceballos A, Cuesta Herranz J. A New Rush Schedule for Cotrimoxazole Desensitization: A Report of 2 cases. *J Investig Allergol Clin Immunol*. 2018;28(4):267-9.
2. Khan DA, Knowles SR, Shear NH. Sulfonamide Hypersensitivity: Fact and Fiction. *J Allergy Clin Immunol Pract*. 2019;7(7):2116-23.
3. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393(10167):183-98.
4. Bourke CD, Evans C. Cotrimoxazole Prophylaxis Selects for Antimicrobial Resistance in Human Immunodeficiency Virus-Exposed, Uninfected Infants. *Clin Infect Dis*. 2020;71(11):2869-71.
5. Giles A, Foushee J, Lantz E, Gumina G: Sulfonamide Allergies. *Pharmacy (Basel)*. 2019;7(3):132.
6. Trubiano JA, Stone CA, Grayson ML, Urbancic K, Slavin MA, Thursky KA, et al. The 3 Cs of Antibiotic Allergy-Classification, Cross-Reactivity, and Collaboration. *J Allergy Clin Immunol Pract*. 2017;5(6):1532-42.
7. Chantachaeng W, Chularojanamontri L, Kulthanan K, Jongjarearnprasert K, Dhana N. Cutaneous adverse reactions to sulfonamide antibiotics. *Asian Pac J Allergy Immunol*. 2011;29(3):284-9.
8. Dorn JM, Alpern M, McNulty C, Volcheck GW. Sulfonamide Drug Allergy. *Curr Allergy Asthma Rep*. 2018;18(7):38.
9. Pyle RC, Butterfield JH, Volcheck GW, Podjasek JC, Rank MA, Li JT, et al. Successful outpatient graded administration of trimethoprim-sulfamethoxazole in patients without HIV and with a history of sulfonamide adverse drug reaction. *J Allergy Clin Immunol Pract*. 2014;2(1):52-8.

10. de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. *Int J Mol Sci.* 2017;18(6):1316.

### Table legend

**Table 1.** Ultra-rapid desensitization 13-step protocol for trimethoprim-sulfamethoxazole.

Step	Solution	Time (min)	Concentration per solution	Volume administered (mL)	Dose administered (mg)	Dose Cumulative
1	A	15	80/400 mcg/mL	1.25	0.1 / 0.5 mg	0.1 / 0.5 mg
2	A	15	80/400 mcg/mL	2.5	0.2 / 1 mg	0.3 / 1.5 mg
3	A	15	80/400 mcg/mL	5	0.4 / 2 mg	0.7 / 3.5 mg
4	A	15	80/400 mcg/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
<b>Total dose: 326.5 / 1632.5 mg</b>						<b>Total time: 3.25 h</b>