

Article Type: Letter to the Editor

TITLE: Trimethoprim-sulfamethoxazole (cotrimoxazole) desensitization in an HIV-infected 5-year-old girl.

Carmen Gómez-Traseira^{ab}, Teresa Boyano-Martínez^{ab}, Luis Escosa-García^c, María Pedrosa^{ab}, Flor Martín-Muñoz^{ab}, Santiago Quirce^{ab}.

Department of Allergy^a and Department of Pediatrics^c.

^bHospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Key Words: desensitization, drug hypersensitivity, HIV-infection, trimethoprim-sulfamethoxazole.

To the Editor,

Opportunistic infections are a major cause of morbidity and mortality in HIV-infected patients. Trimethoprim-sulfamethoxazole (TMP-SMX) (cotrimoxazole) has been shown to dramatically reduce the risk of opportunistic infections, particularly *Pneumocystis carinii* pneumonia, and has been used extensively in their treatment and prevention (1). Since 2006, WHO has recommended cotrimoxazole preventive therapy for all HIV-exposed infants and children born to mothers living with HIV, and continuing until cessation of risk of HIV transmission (cessation of breastfeeding) and infection can be excluded (2). In HIV-infected patients, cotrimoxazole use causes

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12353

This article is protected by copyright. All rights reserved.

Accepted Article

a higher rate of adverse drug reactions than in the general population (20-100% compared with 5-8% of healthy individuals) (3,4). Hypersensitivity to cotrimoxazole is the most frequent drug reaction among HIV-infected patients, typically manifesting as a maculopapular rash, with or without fever, and usually occurring 1-2 weeks after commencing treatment (5). IgE-mediated hypersensitivity is rare. The pathogenesis of TMP-SMX reactions is complex, multifactorial and not completely understood. One or more metabolic, toxic, immunologic or viral factors are likely to contribute, and the typical explanation is based on the variability in metabolic parameters for N-acetylation and N-oxidation (HIV-infected patients are more likely to have a slow acetylator phenotype which results in greater oxidation and the formation of toxic intermediate SMX-derived metabolites thereby stimulating an immune response). (3,5,6).

There are 3 options for the clinical management of hypersensitivity to cotrimoxazole in these patients: treating through the reaction (continuing therapy despite adverse reaction), rechallenge or desensitization (4). Although a variety of cotrimoxazole desensitization protocols have emerged for HIV-infected patients, there is a lack of desensitization protocols for use in pediatric patients (4).

A 5-year-old Nigerian girl, with no known allergies, who was infected with HIV at birth (MTCT) was referred to the allergy department because a pruritic erythematous maculopapular rash had appeared on her face, chest and limbs after two weeks of treatment with cotrimoxazole, 7 ml/day, 3 times/week (Septrim Pediatric oral suspension®: 8 mg trimethoprim /40 mg sulfamethoxazole /1 ml). The reaction had occurred 15 days before she was first seen in the allergy department.

Accepted Article

She did not present fever or systemic symptoms. Hematological analysis showed a leukocyte count of $6.02 \times 10^3/\mu\text{l}$ with 44.5% ($2.68 \times 10^3/\mu\text{l}$) neutrophils and 43.9% ($2.64 \times 10^3/\mu\text{l}$) lymphocytes. The CD4+ T lymphocyte (CD4+) count was 6% ($158.4 \times 10^3/\mu\text{l}$). As CD4 cell count was $<200 \text{ cells/mm}^3$ ($<200 \text{ cells}/\mu\text{l}$), prophylaxis with cotrimoxazole for at least 6 months was mandatory. After informed consent was obtained, the patient underwent a routine allergy work-up (skin tests) following the protocol of the Drug Allergy Interest Group of European Academy of Allergy and Clinical Immunology (7). Afterwards, an oral desensitization protocol was carried out. The procedure was performed at the hospital, with a physician and nurse in attendance and emergency medications readily available.

The results of skin prick test (SPT) with trimethoprim (10mg/ml; Almofarma SL, Barcelona, Spain), and SPT (10mg/ml) and intradermal test (IDT) with sulfamethoxazole (10mg/ml; Almofarma SL, Barcelona, Spain) were negative. As the reaction related to cotrimoxazole use was very likely a hypersensitivity drug reaction, an oral challenge test was not performed. Instead, an oral desensitization protocol was carried out (Table 1). On the first day, gradually increasing doses of cotrimoxazole (Septrim Pediatric oral suspension®) at 15-min intervals (1 and 5 ml of dilution 1/200 and 1 and 2 ml of dilution 1/20) were tolerated. On the second day the patient received 3 and 4 ml of 1/20 dilution at 15-min intervals with good tolerance, and on the third day, 2 undiluted doses of 0.5 and 1 ml at 45-min intervals were tolerated. On the fourth day, 30 minutes after the undiluted dose of 4 ml was administered (cumulative dose 6 ml), she developed a generalized pruritic erythematous maculopapular rash. The reaction immediately subsided after oral administration of dexchlorpheniramine and prednisolone. As the following 2 days

Accepted Article

were not working days, she was advised to take single undiluted doses of 0.5 ml each day. The protocol continued the next 3 days with two increased doses of 0.5 ml at 60-minute intervals each day. Sixty minutes after the dose of 3 ml, an erythematous maculopapular rash developed on the patient's back and chest, and mild angioedema appeared on her ears. She also presented generalized pruritus, and palmar erythema. Treatment with oral dexchlorpheniramine and prednisolone was successful at stopping the reaction. At this point, a newly-designed protocol to gradually increase doses by 0.5 ml every 72 hours was used and after 28 days the patient tolerated a daily dose of 5 ml. Six months later, the patient continued to tolerate this daily dose without any side effects.

Adverse reactions to cotrimoxazole in HIV-infected patients are rarely IgE-mediated. While skin tests (SPT and IDT) may be somewhat useful for a diagnosis of IgE-mediated reactions, allergy to cotrimoxazole is diagnosed based mainly on medical history. Once an adverse reaction to cotrimoxazole has occurred, A desensitization protocol is the management strategy of choice as it has proven to be more beneficial and less risky than rechallenge for prophylaxis or opportunistic infections (4). As in most cases of cotrimoxazole allergy, symptoms are usually very clear and repetitive, and an oral challenge is not always necessary for diagnosis (5). This fact led us to perform skin tests on our patient followed by oral desensitization.

A variety of desensitization protocols to cotrimoxazole in HIV-infected patients have been published, especially in the 90's, Studies were of variable duration (lasting just a few hours to several days) and few are useful for comparative analysis. In 1994 Absar et al (6) carried out 23 desensitizations in 28 adult patients

with a 10-day protocol (3 patients dropped out because of maculopapular rashes, 1 had general erythema with fever and one subject abandoned for personal reasons). All 23 patients tolerated cotrimoxazole over the following 32 weeks. In 1998, Moreno-Ancillo et al (5) published a 6-day protocol in adult patients increasing from a dose of 0.2 mg to 4 mg on the first day (with 45 minutes between doses), followed by two daily doses with a 1-hour interval on the second to fourth days and ending with a daily single dose on days five and six. This protocol was successful in 31 out of 32 subjects, only 1 patient dropped out due to a severe reaction, and 10 patients had mild rashes that improved with the use of antihistamines. All of the skin tests performed on patients before starting the desensitization protocol yielded inconclusive results. An oral challenge test with cotrimoxazole was performed before desensitization in 2 of the 32 patients included in the protocol. In 1991, Kletzel et al (8) successfully desensitized 6 of 7 HIV-infected hemophilic patients (aged 7 to 33 years) in 48 hours. After 5.7 months follow-up all patients still tolerated cotrimoxazole. In 1996, Palusci et al (9) reported a very fast (4 hours; a total of 12 doses given at 15 minute intervals) desensitization protocol for five HIV-infected patients (7.5 months-11.8 years old) who had developed urticaria, angioedema or maculopapular rashes when taking cotrimoxazole. All of the patients had a negative TMP-SMX skin test. The protocol was completed in 4 out of 5 patients (80%). The patient who could not finish the protocol had two reactions (after doses 5 and 6) consisting in localized pruritus and laryngospasm. Treatment with diphenhydramine, methylprednisolone, and epinephrine was necessary and the protocol was stopped. Of the 4 patients who completed the protocol, one had a cytotoxic reaction (shaking chills and fever) 2 hours after desensitization. A maintenance dose was administered

to the remaining patients and tolerated well over follow-up period lasting between 4 and 30 months.

A year earlier, in 1995, Nagarajan et al (10) had successfully performed a 7- hour desensitization protocol in 4 / 5 (80%) of HIV-infected children. After a 10-month follow-up, all patients continued to tolerate cotrimoxazole.

The desensitization protocol we present here is based on the one developed by Moreno-Ancillo (5). On the first day, the doses (amount in ml and time interval) were identical. Subsequently the amount of the dose (ml) was adjusted based on the child's age, while maintaining the same time interval. When the first reaction occurred, the time between doses was lengthened. Under this 28-day protocol the patient reached the daily maintenance dose of 5 ml prescribed by her pediatrician and has experienced no allergic reactions during the 6 months follow-up period.

In conclusion, although a variety of cotrimoxazole desensitization protocols have been performed in HIV-patients, there is a lack of such protocols in the pediatric population. Even though our patient experienced two allergic reactions, neither was serious and both responded well to conventional medication. WHO recommends that all HIV-exposed infants and children receive cotrimoxazole preventive therapy and the desensitization protocol we describe can provide children who have adverse reactions to cotrimoxazole the benefits of treatment with this chemoprophylaxis.

Acknowledgements

We would like to thank Dr. Courteney Hightower for proofreading the English version of the manuscript.

Carmen Gómez-Traseira, MD ^{a*}

Teresa Boyano-Martínez, MD^{a*}

Luis Escosa-García, MD^b

María Pedrosa, MD ^{a*}

Flor Martín-Muñoz, PhD ^{a*}

Santiago Quirce, PhD ^{a*}

Department of Allergy^a and Department of Pediatrics^c.

^bHospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

REFERENCES

1. Modi S, Chiu A, Ng'eno B, Kellerman SE, Sugandhi N, Muhe L. Understanding the contribution of common childhood illnesses and opportunistic infections to morbidity and mortality in children living with HIV in resource-limited settings. *AIDS* 2013;27:S159-67.
2. WHO. Guidelines on co-trimoxazole prophylaxis for HIVrelated infections among children adolescents and adults: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2006.
3. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol.* 2011;71:659-71.
4. Lin D, Li WK, Rieder MJ. Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of

hypersensitivity to cotrimoxazole. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD005646.

5. Moreno-Ancillo A, López-Serrano MC. Hypersensitivity reactions to drugs in HIV-infected patients. Allergic evaluation and desensitization. Clin Exp Allergy 1998;28:57-60.
6. Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. J Allergy Clin Immunol 1994;93:1001-5.
7. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002;57:45-51.
8. Kletzel M, Beck S, Elser J, Shock N, Burks W. Trimethoprim-sulfamethoxazole oral desensitization in hemophiliacs infected with human immunodeficiency virus with a history of hypersensitivity reactions. Am J Dis Child 1991;145:1428-9.
9. Palusci VJ, Kaul A, Lawrence RM, Haines KA, Kwittken PL. Rapid oral desensitization to trimethoprim-sulfamethoxazole in infants and children. Pediatr Infect Dis J 1996;15:456-60.
10. Nagarajan R, Nelson RP, Day NK, Good RA. Trimethoprim-sulfamethoxazole sensitivity and desensitization in HIV-infected children. J Allergy Clin Immunol 1995;95:287.

Table 1: Cotrimoxazole desensitization protocol.

DAY	DOSAGE		TIME
	ml	dilution	INTERVAL
1	1	1/200	15 minutes
	5		
	1	1/20	15 minutes
	2		
2	3	1/20	15 minutes
	4		
3	0.5	1/1	45 minutes
	1		
4	2	1/1	45 minutes
	4*		
5	0.5	1/1	24 hours
6	0.5	1/1	24 hours
7	1	1/1	60 minutes
	1.5		
8	2	1/1	60 minutes
	2.5		
9	3*	1/1	24 hours
10#	2.5	1/1	

*dose elicited a reaction.

after day 10, the protocol continued with 0.5ml increments every 72 hours. The doses were administered at hospital. Over the weekend, the patient continued with the last tolerated dose.