

Management of adverse reactions to prophylactic trimethoprim-sulfamethoxazole in patients with human immunodeficiency virus infection

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Background: In hospitals attended by patients with human immunodeficiency virus infection, adverse reactions are often observed to trimethoprim-sulfamethoxazole, particularly cutaneous reactions. Given the importance of this drug for prophylaxis we have attempted to establish a desensitization or tolerance protocol so that patients can continue the drug without repeated adverse reactions.

Methods: We studied 34 HIV patients with adverse cutaneous reactions to trimethoprim-sulfamethoxazole, slight to moderate in nature but not life-threatening. Skin tests (prick and intradermal) were done in an attempt to rule out a mechanism of hypersensitivity. Subsequently, trimethoprim-sulfamethoxazole was administered orally in increasing doses beginning with trimethoprim, 0.2 mg, and sulfamethoxazole, 1 mg. The same dose was repeated after 12 hours and then doubled every 24 hours until the therapeutic dose was achieved. If adverse reactions appeared we maintained the last dose administered and administered antihistamines until the reactions cleared or improved.

Results: None of the patients had positive skin tests (immediate or delayed). Twenty-seven patients were satisfactorily desensitized. After a follow-up of 3 months, 25 patients were still incident-free on trimethoprim-sulfamethoxazole prophylaxis, and 19 returning for check-ups at 6 months could still tolerate the drug well.

Conclusions: Our data indicate that patients with adverse reactions to trimethoprim-sulfamethoxazole can continue prophylactic treatment after oral desensitization.

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INTRODUCTION

The prophylaxis of *Pneumocystis carinii* pneumonia is probably what has most contributed to improving the life quality of patients with human immunodeficiency virus (HIV) infection. Various prophylactic treatments have been reported for *Pneumocystis carinii* pneumonia, including trimethoprim-sulfamethoxazole, dapsone, and aerosolized pentamidine although the simplest and most efficient includes

trimethoprim-sulfamethoxazole administration.² We usually administer a double-strength tablet every 24 hours (three times each week), and in our experience this is efficient. There is sufficient information to show that including trimethoprim-sulfamethoxazole is prophylactic (preventive) against toxoplasmosis, isosporiasis, bacterial infections, and *Mycobacterium avium-intracellulare* infection.

Despite the advantages offered by this therapy there is a high incidence of adverse reactions, particularly in patients with HIV infection.³ These adverse reactions include rash and cutaneous eruptions, fever, leukopenia, hepatitis, and nephritis.⁴ The incidence of cutaneous reactions to trimethoprim-sulfamethoxazole is 3.3% in hospitalized patients and 40% to 60% in patients with acquired immu-

nodeficiency syndrome (AIDS).⁵ Many patients have developed adverse reactions to this drug, usually maculopapular rashes, that limit its use.

Before beginning this study we observed that patients on trimethoprim-sulfamethoxazole prophylaxis who presented with rashes could tolerate administration of this drug if we simultaneously administered high doses of antihistamines. In a number of cases, the rashes disappeared without the need to stop trimethoprim-sulfamethoxazole treatment. These and other observations found in the medical literature were the reason for us to attempt to establish a tolerance protocol. We also found various articles that report on the ability to tolerate increasing doses of trimethoprim-sulfamethoxazole.⁶⁻¹⁰

There are data to suggest that these adverse reactions are caused by immunologic mechanisms that could be allergic, infectious, or toxic. The mechanism by which these adverse reactions are caused and the mechanism by which tolerance or desensitization is induced are as yet unknown.

The present report describes the clinical management of the problems usually attributed to drug allergy in 34 patients with HIV on trimethoprim-sulfamethoxazole prophylaxis. We believe tolerability of these procedures is important because the number of patients is unfortunately increasing and preventive therapeutic regimens offer better life quality at lower cost.

METHODS

Patients

Thirty-four patients participated in the study. They were all informed and consented to the desensitization protocol. The criteria for inclusion were ev-

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idence of HIV infection or AIDS and a history of adverse cutaneous reactions attributable to trimethoprim-sulfamethoxazole. The patients included had not had any other type of trimethoprim-sulfamethoxazole related adverse reaction. All the patients were on prophylaxis at a dose of one double-strength tablet three times weekly. The symptoms disappeared in all the patients when the drug was discontinued without discontinuation of other treatments such as tuberculostatics, zidovudine, didanosine, or pyrimethamine and returned when trimethoprim-sulfamethoxazole was readministered. All the patients were treated with zidovudine, except one who was receiving didanosine. Furthermore, one patient was receiving treatment with pyrimethamine and five with isoniazid, rifampicin, and pyrazinamide.

Procedure

The study was carried out between June, 1992 and March, 1994. All the patients underwent the desensitization protocol as outpatients, except three who received it during hospitalization: two for pulmonary tuberculosis and one for cerebral toxoplasmosis.

We first performed skin tests on all the patients (prick and intradermal, taking readings at 15 minutes, 8 and 48 hours) with trimethoprim (10 and 0.1 mg/mL) and sulfamethoxazole (10 and 0.1 mg/mL) to attempt to rule out an immediate or delayed allergy mechanism.

The desensitization or tolerance procedure is described in Table 1. We administered the same dose orally every 12 hours, and if no adverse reactions appeared we doubled the dose every 24 hours until the therapeutic dose was achieved. If adverse cutaneous reactions appeared, we administered hydroxyzine, 25 mg every four to six hours and maintained the last dose of trimethoprim-sulfamethoxazole administered until the cutaneous lesions improved or cleared.

RESULTS

Of the 34 patients referred to the allergy department after meeting the cri-

teria for being included in the desensitization protocol, one did not consent to the study. The characteristics of the rest are shown in Table 2. All the patients had negative skin tests for trimethoprim-sulfamethoxazole (prick and intradermal at 15 minutes, 8 hours, and 48 hours). The study was discontinued in two patients because of 40°C fever lasting eight to twelve hours, with doses at 6/30 and 24/120 mg, respectively. A week later the same doses were readministered and the patients again developed fever of several hours' duration, which could not be attributed to any other cause. The prophylaxis was interrupted in another patient once the therapeutic dose was achieved due to the appearance of cutaneous lesions on the legs, reported by the dermatology department as being medicamentose lichenoid toxicoderma. Another patient stopped treatment because of the progressive appearance of erythematodesquamative lesions and ulceration on both legs (exfoliative dermatitis), which improved rapidly after oral administration of steroids. Two patients on the initial doses developed intense pruritus and a generalized morbilliform rash, which could not be controlled with hydroxyzine, 25 mg/4 h, and the study was interrupted. The remaining 27 patients (81%) were desensitized satisfactorily. Eleven presented with cutaneous rashes and 6 with mild pruritus between the 6/30 and 48/240 mg doses. They all recovered fully with antihistamines and were able to reach and continue the prophylactic doses.

Three months later, one of the patients did not return for checkup; we do not know his tolerance to trimethoprim-sulfamethoxazole. One patient had died from pulmonary tuberculosis and 25 (75%) still showed a good tolerance to the preventive treatment at three months. Six months later, 19 (57%) patients were still on the treatment without repeated adverse reactions, two patients had died (of causes unknown to us), and four patients did not return for checkup (we do not know their tolerance). Nine months later, we were able to re-con-

tact 21 (63%) patients, who showed good tolerance to the prophylaxis. The immediate and long-term results of the desensitization protocol are summarized in Tables 3 and 4.

DISCUSSION

Trimethoprim-sulfamethoxazole is currently the drug of choice for the prophylaxis of *Pneumocystis carinii* infection because of its efficacy and safety; however, there is a high incidence of adverse reactions in patients with HIV infection.³ Most of these reactions affect the skin, are generally mild and in few cases have been life-threatening. There are rare reports of hematologic, renal, and hepatic toxicity.

In recent years, studies have been carried out in patients with adverse reactions to the drug who were able to tolerate it after oral desensitization, however, these studies include a small number of patients. Absar et al published a study of 28 patients, in whom they achieved good tolerance in 47%.⁹ We achieved good tolerance in 63% of our patients after 9 months of treatment following the desensitization protocol. In contrast to what other authors report, we had no adverse reactions for 9 months after desensitization.

The mechanism by which these adverse reactions occur is unknown; nor do we know why most of the

Table 1. Trimethoprim-Sulfamethoxazole Desensitization Schedule

Day	Morning Dose	Evening Dose
1	0.2 mg / 1 mg	0.2 mg / 1 mg
2	0.4 mg / 2 mg	0.4 mg / 2 mg
3	0.8 mg / 4 mg	0.8 mg / 4 mg
4	1.6 mg / 8 mg	1.6 mg / 8 mg
5	3.2 mg / 16mg	3.2 mg / 16 mg
6	6 mg / 30 mg	6 mg / 30 mg
7	12 mg / 60 mg	12 mg / 60 mg
8	24 mg / 120 mg	24 mg / 120 mg
9	48 mg / 240 mg	48 mg / 240 mg
10	80 mg / 400 mg	80 mg / 400 mg
11	160 mg / 800 mg	none

Thereafter one tablet of double strength trimethoprim-sulfamethoxazole three days each week for *Pneumocystis carinii* prophylaxis.

Table 2. Characteristics of 34 Subjects Undergoing Trimethoprim-Sulfamethoxazole Desensitization

	Number of Patients
Age, (yr)	26 ± 8
Sex:	
Male	31
Female	3
HIV infection risk factors	
Homosexual male contact	2
Intravenous drug abuse	31
Heterosexual contact	3
CD4 Lymphocyte count (cells/ μ L)	153 ± 38
Therapy at time of desensitization:	
Zidovudine	33
Tuberculostatics	5
Pyrazinamide	1
Didanosine	1

Table 3. Outcome of Trimethoprim-Sulfamethoxazole desensitization (no. of patients)

	During Desensitization	Desensitization Interrupted
Fever	2	2
Exfoliative dermatitis	1	1
Morbilliform rash		
not controlled with hydroxyzine	2	2
Morbilliform rash		
controlled with hydroxyzine	11	0
Pruritus	6	0
No adverse reactions	11	0

Table 4. Long-Term use of Trimethoprim-Sulfamethoxazole (no. of patients)

	3 Months Later	6 Months Later	9 Months Later
Followup lost	1	4	—
Followup recovered	—	—	2
Death	1	2	—
No adverse reaction	25	19	21

patients tolerate the drug if it is administered in steadily increasing small doses. Various mechanisms have been suggested, but none can provide a satisfactory explanation. The clinical manifestations and latency period of these adverse reactions suggest an allergic-type immunologic mechanism, but this has so far not been demonstrated.¹² It has been reported that lymphocytes sensitized to trimethoprim-sulfamethoxazole might be determinants in the pathogenesis of these adverse reactions, although it has not been confirmed in all the patients studied.¹³ All the patients in our study had negative skin

tests, both immediate at 15 minutes and delayed at 8 and 48 hours; this is not consistent with the possibility that sensitized lymphocytes induce adverse cutaneous reactions, especially considering that these patients have a greater or lesser degree of immunodepression.

The appearance of cutaneous reactions has also been related to the hydroxymetabolite levels of trimethoprim-sulfamethoxazole; however, the incidence does not seem greater in patients receiving therapeutic treatment with doses greater than preventive doses. Nor do we or others believe that the association of

other drugs influences the frequency and intensity of these adverse reactions.

It seems probable that increasing doses of this drug can alter a regulating mechanism of the immune system. Faced with this uncertainty we believe we can use the terms desensitization or tolerance interchangeably.

Some authors believe that trimethoprim-sulfamethoxazole should be readministered to certain patients only when essential and after assessing the relationship between risk and benefit.⁸ None of the patients in our study presented with life-threatening reactions, although we did not include patients who had had severe reactions. If severe reactions occurred during the study, the drug was discontinued.

Various articles, like ours, report that most patients with trimethoprim-sulfamethoxazole-related cutaneous reactions tolerate the drug after oral desensitization.^{14,15} We believe, therefore, that since other therapeutic alternatives are less efficient, this procedure is safe, simple, efficient, and permits continued prophylaxis and even therapy if necessary.

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LATEX HYPERSENSITIVITY IN CHILDREN

To understand various clinical aspects of latex hypersensitivity in children better the authors performed a retrospective analysis of the first 35 cases evaluated over a 2-year period.

Although patients with spina bifida and urinary tract abnormalities have been recognized as high risk, in this population 40% were not in these groups and 60% of the reactions occurred outside an immediate perioperative period. Forty percent of reactions were classified as grade 3 or 4 (moderate or severe systemic reactions). Latex-containing intravenous devices were a particularly potent cause for serious reactions. Seventy-seven percent of patients were atopic by history and multiple surgical procedures at an early age had been performed in most subjects.

Latex specific IgE antibodies were found in 92.3% of sera tested by ELISA and 93.8% using RAST.

Those children with preceding histories of latex allergy who required surgery or other procedures using general anesthesia were managed by limitation of recognized sources of latex in the environment and premedication with steroids and H₁ and H₂ blocking agents. Fourteen of 17 had no allergic reactions, one had transient urticaria and two had severe reactions attributable to medications. Four additional patients had anaphylaxis on the ward secondary to intravenous therapy.

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