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Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients

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Background: Trimethoprim-sulfamethoxazole (T/S) is an effective and important prophylactic medication for HIV-infected patients that must frequently be discontinued because of allergic reactions.

Objective: Our objective was to assess the safety, the frequency of success, and the duration of desensitization to T/S in HIV-infected patients.

Method: We studied oral desensitization with T/S of patients with a history of allergy to the medication and longitudinal follow-up. Twenty-eight men with a history of T/S-induced skin rashes were studied. Mean age was 35 years (range, 26 to 50 years). Mean CD4 count was 89 cells/mm³ (range, 0/mm³ to 210/mm³). Patients were seen every 4 to 6 weeks. Mean follow-up was 19.07 weeks (range 2 to 81 weeks).

Results: After 32 weeks, 23 of 28 (82%) patients were successfully desensitized (four had rashes develop, and one could not continue for personal reasons). Of the 23 patients who were successfully desensitized, six were known to have subsequently discontinued T/S (four had rashes; two discontinued on the advice of their personal primary physicians). Six patients were lost to follow-up. One patient died of pulmonary Kaposi's sarcoma. Ten patients are taking the medication regularly without any problems.

Conclusion: T/S desensitization is a simple, safe and effective means to provide it for most patients with a history of "allergic" rashes. (J ALLERGY CLIN IMMUNOL 1994;93:1001-5.)

Key words: trimethoprim/sulfamethoxazole, desensitization, AIDS, HIV-1 infection, drug reactions.

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Dr. Absar was partially supported by a UCLA Fogarty International Postdoctoral Fellowship in AIDS. Some of the patients were participating in clinical trials supported by the AIDS Clinical Trials Group Cooperative Agreement NIH NIAID AI27660.

Received for publication Sept. 29, 1993; revised Jan. 13, 1994; accepted for publication Feb. 4, 1994.

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0091-6749/94 \$3.00 + 0 1/1/54938

Abbreviations used

AIDS: Acquired immunodeficiency syndrome
HIV: Human immunodeficiency virus
PCP: *Pneumocystis carinii* pneumonia
T/S: Trimethoprim-sulfamethoxazole

Pneumocystis carinii pneumonia (PCP) is the most common life-threatening opportunistic infection complicating the acquired immunodeficiency syndrome (AIDS). As a result of the AIDS

TABLE I. Patient characteristics

Characteristic	Patient No. (%)
Past reactions with T/S	
Skin rash	19 (68)
Skin rash with fever	4 (14)
Generalized erythema with fever	4 (14)
Generalized erythema, no fever	1 (4)
Indication for desensitization	
PCP prophylaxis	22 (79)
Isosporiasis	6 (21)
Risk factor for HIV infection	
Homosexual/bisexual	27 (96)
IVDU/homosexual	1 (4)
Race	
White	13 (46)
Hispanic	11 (39)
African American	3 (11)
Other	1 (4)
Age	
25-34	13 (46)
35-44	12 (43)
45-54	3 (11)

IVDU, Intravenous drug user.

epidemic, the number of cases of PCP recognized per year in the United States has increased dramatically, from less than 500 from 1967 to 1970 to an estimated 20,000 to 60,000 in the late 1980s and early 1990s.^{1, 2} In the 1980s PCP represented the index disease in approximately 65% and eventually developed in over 80% of patients with AIDS.^{3, 4}

Prophylaxis of PCP has been successful—both as a primary intervention before a diagnosis of AIDS and as a secondary intervention after one episode of PCP.^{5, 6} It is probable that PCP prophylaxis is a major contributor to an improved outlook for patients with human immunodeficiency virus (HIV) infection. Several effective means of prophylaxis of PCP have been reported. These include trimethoprim-sulfamethoxazole (T/S), dapsone, and aerosolized pentamidine. There is much evidence that the simplest and most effective form of both primary and secondary prophylaxis for PCP is the administration of T/S. Hardy et al.⁷ have reported that in a randomized, prospective study T/S was 3.25 times more effective in the prevention of recurrent PCP than was aerosolized pentamidine. Although prospective comparisons of T/S with dapsone have not been published, Martin et al.⁸ reported in a retrospective study that T/S was a more effective agent than aerosolized pentamidine to prevent

the occurrence and recurrence of PCP. Dapsone occupied an intermediate position.

T/S is also an extremely cost-effective therapy, an important consideration in attempting to preserve the integrity of our overburdened health care system.⁹ Dosing regimens varying from one double-strength tablet three times weekly to two double-strength tablets daily appear to be effective.^{2, 5, 7, 10} In addition, there is suggestive information that T/S may be prophylactic against toxoplasmosis and bacterial infections,⁷ as well as *Mycobacterium avium* infection.¹¹

In addition to its role in prophylaxis and treatment of PCP, T/S is the drug of choice for the treatment of isosporiasis—*Isospora belli* infestation—a severe and AIDS-defining diarrheal illness.

Despite these advantages, a major concern in usage of T/S is the great frequency of allergic reactions, particularly in persons with HIV infection. While the incidence of cutaneous reactions to trimethoprim-sulfamethoxazole (T/S) has been reported to be 3.3% in hospitalized patients,¹² the incidence of these reactions in AIDS is far greater, with reports of reaction rates from 44% to 69%.^{13, 14}

Thus T/S is needed for many reasons in patients with HIV-infection, but many have had previous untoward reactions, usually rashes, limiting its availability.

Numerous anecdotal reports have appeared documenting patients' ability to tolerate T/S after incremental increases in doses were administered.¹⁵⁻¹⁹ Neither the mechanism of T/S rashes, or "allergy", nor the effect of this "desensitization" is understood. (We will refer to the procedure as desensitization with no intent to imply that an immunologic change has been accomplished by the incremental T/S administration.) Because some investigators have documented severe adverse reactions and have cautioned against the procedure,²⁰ and because the duration of the desensitization induced was not known, we elected to carefully administer increasing amounts of T/S to "allergic" patients and follow them up prospectively to document the results of the procedure.

METHODS

Patients

Twenty-eight patients entered the study. Inclusion criteria included evidence of HIV seropositivity, CD4 count ≤ 200 cells/mm³ or diagnosis of AIDS, and a history of an allergic reaction to T/S. The types of

TABLE II. Procedure for trimethoprim/sulfamethoxazole desensitization

Day	Dose	T/S
1	1 ml of 1:20 pediatric suspension of T/S	(0.4mg/2mg)
2	2 ml of 1:20 pediatric suspension of T/S	(0.8mg/4mg)
3	4 ml of 1:20 pediatric suspension of T/S	(1.6mg/8mg)
4	8 ml of 1:20 pediatric suspension of T/S	(3.2mg/16mg)
5	1 ml of pediatric suspension of T/S	(8mg/40mg)
6	2 ml of pediatric suspension of T/S	(16mg/80mg)
7	4 ml of pediatric suspension of T/S	(32mg/160mg)
8	8 ml of pediatric suspension of T/S	(64mg/320mg)
9	1 tablet of T/S	(80mg/400mg)
10	1 tablet of double-strength (DS) T/S	(160mg/800mg)

Thereafter 1 tablet of DS T/S on Monday, Wednesday, and Friday for PCP prophylaxis or two tablets a day for the treatment of isosporiasis.

reactions and other characteristics of the patients are documented in Table I. All patients gave written informed consent to the protocol, which was approved by the Human Subjects Committee of Harbor-UCLA Medical Center.

Patients who met other criteria but who had total white cell counts ≤ 1500 cells/mm³, Hct $\leq 22\%$, platelet count $\leq 50,000$ cells/mm³, liver enzymes ≥ 3 times upper limits of normal, creatinine ≥ 2.5 mg/dl, or were pregnant or had a history of life-threatening reactions to sulfa drugs, such as Stevens-Johnson syndrome or severe hepatitis, were excluded. Twenty-eight men participated (Table I).

All but two patients were desensitized as outpatients; in the remaining two desensitization was attempted during hospitalization for profuse diarrhea caused by *Isospora belli*.

Procedure

The study was performed between October 1991 and May 1993. After history and physical examination, patients had hematologic and blood chemistry evaluations. The desensitization procedure is delineated in Table II.

The patients were seen four times during the 10-day desensitization period to repeat the clinical and laboratory examinations.

Antihistamines were used in four patients for treatment of pruritus. Systemic adrenal corticosteroids were not used. After the desensitization the patients were seen every 4 to 6 weeks. Total follow up has been from 2 to 81 weeks (median, 15; mean, 19 weeks).

RESULTS

With the 10-day desensitization, 23 patients tolerated the procedure with no problems and continued taking T/S. The desensitization failed for four patients, one on day 6, and three others 5 to 10 days after completion of the 10 days of incremental dosing. Severe maculopapular rashes

developed in three of these men, and one other man had generalized erythema with fever. These symptoms did not improve with antihistamine treatment. A fifth patient did not finish desensitization for personal reasons (Table III). Subsequently, medication was discontinued by six patients. Four patients had skin rashes develop 12 to 33 weeks after desensitization. One of these patients had significant eosinophilia 2 weeks before the rash appeared. Another of these men had a rash develop when he was treated with high-dose sulfadiazine for treatment of a suspected central nervous system toxoplasmosis. Two patients with only mild pruritus discontinued T/S on the advice of their primary physicians at 4 and 12 weeks of follow-up. No fever, rashes, or eosinophilia were documented (Table IV).

Six patients have been lost to follow-up, so the ultimate duration of their ability to tolerate T/S is not known. One patient died as a result of pulmonary Kaposi's sarcoma still taking T/S without incident (Table IV).

There were no life-threatening reactions to T/S and no evidences of disturbances of laboratory values.

The remaining patients are followed up regularly and are taking T/S without any problems. An interstitial pneumonia developed in one of these patients, and it was treated empirically with intravenous T/S and prednisone for a presumption of PCP soon after completing desensitization. He tolerated T/S without incident.

DISCUSSION

PCP causes considerable morbidity, mortality, and expense. Prophylaxis against PCP is warranted in any group of patients with an incidence

TABLE III. Early desensitization failures

Subject	Day	Comment
SA	4	Stopped for personal reasons
KO	6	Generalized rash
LE	14	Generalized rash
BE	15	Generalized erythema with fever
HO	19	Generalized rash

T/S was discontinued in five of the 28 subjects in the first 3 weeks.

of the infection that is unacceptably high when weighed against the efficacy, toxicity, cost, and convenience of available prophylactic regimens. In patients with HIV infection, lifelong prophylaxis is warranted for all patients with CD4 cell counts below 200 cells/mm³ (0.2×10^9); for patients with unexplained persistent fever ($>37.8^\circ\text{C}$ [100°F]) for 2 weeks or oropharyngeal candidiasis (unrelated to antibiotic or corticosteroid therapy), regardless of CD4 cell count; and for patients who have recovered from an episode of PCP.²

The underlying cause of the hypersensitivity reaction to T/S is unclear. Positive prick and intradermal skin tests to a dilute T/S solution were reported by White et al.²¹ suggesting the involvement of IgE. Gruchalla and Sullivan²² have recently developed a skin testing reagent that detects IgE antibodies to a sulfonamide determinant. However, the common symptoms of T/S sensitivity: erythematous or maculopapular rash, leukopenia and fever are more suggestive of cell, IgG-, or IgM-mediated reactions. T/S reactions are believed to be dose related because they are more commonly observed when high doses of T/S are administered for the treatment of PCP rather than at lower prophylaxis doses.

As an alternative to immunologic explanations of adverse reactions to T/S or sulfonamides, evidence has been put forward that such adverse reactions are caused by hydroxylamine metabolites of sulfonamides.²³ Susceptibility to adverse reactions to sulfonamides could be duplicated in vitro by using the patient's cells. Thus susceptibility to adverse reactions may be due to a metabolic, rather than to immunologic, abnormality.^{24, 25}

The reasons for apparent successful desensitization are not known. It does not seem likely that incremental dosing can alter a patient's pattern of drug metabolism. There is precedent, in other situations, for the belief that incremental dosing may result in a state of antigen excess so that antibody or immunocompetent cells cannot be

TABLE IV. Late discontinuation of T/S

Subject	Week	Comment
PA	4	Lost to follow-up
FL	4	Pruritus; no rash, fever, or eosinophilia
FI	9	Lost to follow-up
KE	12	Pruritus; no rash, fever, or eosinophilia
GA	12	Rash, later diagnosed to be secondary syphilis
NE	12	Rash
VA	18	Lost to follow-up
PI	29	Generalized rash preceded by eosinophilia
LI	33	Lost to follow-up
TI	33	Generalized rash and fever when patient received high doses of sulfadiazine for toxoplasmosis
CA	36	Lost to follow-up
MO	44	Lost to follow-up

cross-linked by antigen. Such cross-linking is often a requirement for hypersensitivity reactions. The clinical suspicion that T/S reactions are dose related makes it likely that the incremental dosing is only a safe means to find those patients who will not react to the relatively small doses of T/S used for prophylaxis.

Successful oral desensitization of sulfonamides has been reported in the past in smaller series of patients. We studied a larger group of patients and followed them up for several months. The procedure was well tolerated, and none of our patients had life-threatening reactions. It is important to note, however, that patients with previous life-threatening reactions to T/S or sulfonamides were excluded from our study. Severe reactions have been reported by others, and appropriate caution is necessary.

Allergic reactions to T/S appear at varying intervals and are not predictable. In this series 4/28 (14%) of the patients had a cutaneous eruption develop in the first 3 weeks, and 4/28 (14%) between 9 and 33 weeks after desensitization. Six of the 28 (17%) patients were lost to follow-up, and two (7%) discontinued the medication on the advice of another physician. The remaining 12 (43%) continued to tolerate T/S without incident. Thus we conclude that T/S desensitization is safe, simple, and effective and allows continued administration of T/S to patients needing the agent.

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