

Sulfonamide-induced reactions in desensitized patients with AIDS—The role of covalent protein haptenation by sulfamethoxazole

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Background: Adverse reactions to sulfonamides cause significant morbidity in patients with AIDS. We have demonstrated previously a ≈ 40 kD sulfamethoxazole (SMX)-substituted protein in the serum of some individuals treated with SMX. **Objective:** The purpose of this study was to examine patients with AIDS who had undergone SMX desensitization because of a prior history of SMX allergy for the presence of SMX-haptenated serum proteins and to determine whether these proteins, SMX-specific IgG antibodies, or both predict the development of subsequent clinical reactivity.

Methods: Four patients with no history of allergy and in whom SMX prophylaxis was initiated and eight patients with AIDS who had undergone SMX desensitization because of prior allergy were evaluated. SMX-conjugated serum proteins were identified with an immunoblotting assay, and SMX-specific IgG antibodies were identified by ELISA inhibition.

Results: One of the four patients receiving SMX prophylactic treatment demonstrated SMX-protein haptenation, none had detectable SMX-specific IgG antibodies, and none developed an SMX-associated reaction during the time in which they were followed. Of the eight patients who underwent SMX desensitization, six (75%) demonstrated SMX-protein haptenation, and three of these six (50%) subsequently developed SMX-induced cutaneous reactions. Only one of these six patients had detectable SMX-specific IgG antibodies. The two individuals who did not demonstrate SMX-protein haptenation have not developed a clinical reaction.

Conclusion: These preliminary data suggest that SMX haptenation, but not SMX-specific antibodies, may be important in the development of clinical sensitivity in patients with AIDS who have undergone SMX desensitization. (*J Allergy Clin Immunol* 1998;101:371-8.)

Key words: Sulfamethoxazole, AIDS, prophylaxis, desensitization, haptenation

Although adverse reactions to sulfonamides occur in 1% to 2% of individuals without HIV infection, they take place in 50% to 60% of patients with AIDS, causing

Abbreviations used

BSA:	Bovine serum albumin
PBS:	Phosphate-buffered saline
PCP:	<i>Pneumocystis carinii</i> pneumonia
SDS-PAGE:	Sodium dodecylsulfate–polyacrylamide gel electrophoresis
SMX:	Sulfamethoxazole
TBS:	Tris-buffered saline
TMP:	Trimethoprim

significant morbidity and mortality.¹⁻¹⁴ Reactions to sulfonamides vary clinically, suggesting diverse mechanisms. Although several studies¹⁵⁻¹⁷ indicate that reactions to sulfonamides are toxic in nature, evidence from several laboratories, including our own,¹⁸ supports immunologic mechanisms for at least some reactions. Specific antibodies of all isotypes,¹⁹⁻²⁵ as well as sensitized lymphocytes,²⁶ have been detected in individuals undergoing sulfonamide reactions. Despite the fact that evidence supports an immune mechanism in some reactions, knowledge about the underlying immunopathology is insufficient to predict, to prevent, or to inhibit such reactions.

Sulfonamides are metabolized in the liver by N-acetylation, producing nontoxic metabolites, and by cytochrome P-450-catalyzed N-oxidation, producing reactive intermediates, possibly hydroxylamines (Fig. 1). These reactive metabolites are reduced by glutathione and then excreted. However, when the capacity for glutathione conjugation is exceeded, reactive metabolites may haptenate protein carriers.²⁷⁻³⁰ Not only do these reactive intermediates cause toxic reactions, but their formation is also thought to cause immunologic reactions. We have demonstrated previously that patients with histories of immediate hypersensitivity reactions to sulfamethoxazole (SMX) possess SMX-specific IgE^{19,21} antibodies. Moreover, the major antigenic determinant to which the antibodies were directed was the N⁴-sulfonamidoyl group, which is quite similar to both the free drug and the hydroxylamine intermediate.

Cribb and Spielberg²⁷ and Rieder et al.²⁹ have shown that sulfonamide metabolites associate covalently with murine microsomal proteins. However, regulatory mechanisms in the formation of reactive drug metabolites have not been identified. Subsequently, our labora-

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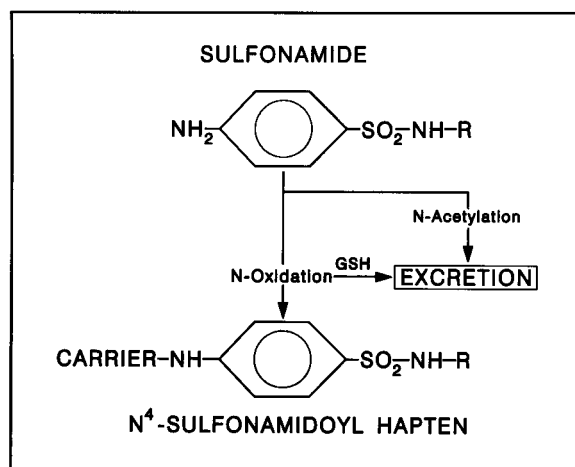


FIG. 1. Sulfonamide metabolism. Sulfonamides are metabolized by N⁴-acetylation or by N⁴-oxidation by the cytochrome P-450 mixed-function oxidase system. Acetylated sulfonamides and glutathionyl (GSH) compounds are excreted. Haptenation of protein carriers occurs if the capacity for glutathione conjugation is exceeded. The N⁴-sulfonamidoyl determinant is the major, and possibly the only, hapten formed during sulfonamide metabolism. GSH, Glutathionyl compounds.

tory demonstrated the presence of sulfonamide-conjugated serum proteins in the peripheral blood of treated human subjects.¹⁸ We propose that, similar to the mechanism responsible for halothane hepatitis,³¹⁻³⁹ sulfonamide metabolism causes the formation of haptenated proteins that contribute to the pathogenesis of sulfonamide hypersensitivity reactions in patients with AIDS. The purpose of this study was to determine if an association exists between SMX-induced clinical reactivity and the presence of SMX-substituted proteins or SMX-specific IgG antibodies in two populations of patients with AIDS: those who are receiving primary SMX prophylactic therapy and those who have undergone SMX desensitization because of a prior history of SMX allergy.

METHODS

Materials

Rabbit immunizations and antibody purification. SMX-bovine serum albumin (BSA) (Sigma Chemical Co., St Louis, Mo.) prepared as described previously¹⁸ was used as the immunizing antigen. Rabbit IgG antibodies were purified by using an Econo-Pak Protein A kit from Bio-Rad (Richmond, Calif.) as previously described.¹⁸

ELISA. Phosphate-buffered saline (PBS-10×); blocking solution (Porcine gelatin, 1.0 gm/L in PBS/Tween); PBS/Tween (Tween 20, 0.5 ml/L in PBS); diluent buffer (5.0 gm bovine gamma globulin/L PBS/Tween, 1.0 gm porcine gelatin/L PBS/Tween); 3,3',5,5'-tetramethylbenzidine (TMB) one component substrate and stop solution (Kierkegaard and Perry Laboratories [KPL], Gaithersburg, Md.); and KPL affinity-purified goat F(ab')₂ anti-human IgG (Horseradish peroxidase-labeled, diluted 1:5000 in diluent buffer) were all used. Control porcine gelatin (CI-0301), SMX-gelatin (14 copies/mol) (CI-0567), and SMX-Dextran (42 moles SMX/mol Dex₁₀) (CI-0694F) were all

provided by Dr. Catherine McCall at Cortech, Inc. (Denver, Colo.). The approximate molecular weight of the SMX-gelatin construct was 100 kd. The approximate molecular weight of the SMX-dextran construct was 36 kd.

Amplified alkaline phosphatase goat anti-rabbit immunoblotting assay. Tris-buffered saline (TBS); TTBS (TBS with 0.05% Tween-20), blocking solution (5% nonfat dry milk in TTBS); washing solution (9.5% nonfat dry milk in TTBS); second antibody solution (biotinylated goat anti-rabbit antibody [KPL] 1:2500 in TTBS); and Streptavidin-biotinylated alkaline phosphatase complex (1:3000 in washing solution) were all obtained from Bio-Rad Laboratories (Richmond, Calif.).

Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Nitrocellulose, 7.5% mini-gels, electrophoresis chemicals, and molecular weight markers were obtained from Bio-Rad Laboratories (Richmond, Calif.).

Methods

Rabbit immunizations and antibody purification. Immunizations were performed as described previously.¹⁸ Briefly, New Zealand white rabbits (Myrtle's Rabbitry, Thompson Station, Tenn.) were injected intramuscularly with 25 µg SMX-BSA (emulsified in Hunter's TiterMax) in each hind flank and boosted 6 weeks later. One month after boosting, the animals were bled, killed, and serum assayed for the presence of SMX-specific IgG antibodies by ELISA inhibition.

Direct ELISA. Ninety-six well Immulon II microtiter plates (Dynatech Laboratories, Chantilly, Va.) were coated with 100 µl of either control gelatin (CI-0301) or SMX-gelatin (CI-0567) at 1 µg/ml and incubated overnight at 4° C. The next day, solutions in the wells were aspirated, and plates were coated with 200 µl blocking solution and incubated for 1 hour. After incubation, the plates were washed 5 times with PBS/Tween, and 100 µl of each human serum sample dilution (1:50, 1:150, and 1:450) was added in triplicate to a plate coated with CI-0301 and another coated with CI-0567. Plates were incubated 2 hours and washed 5 times with PBS/Tween. One hundred microliters of secondary antibody solution was added and incubated for 90 minutes. Plates were then washed 5 times with PBS/Tween and 2 times with PBS only. One hundred microliters of (3,3',5,5'-tetramethylbenzidine) TMB reagent (warmed to 37° C) was added to each well and incubated for 10 minutes. The reaction was stopped with 100 µl of stop solution, and absorbance was measured at 450 nm. Unless specified otherwise, all incubations were performed at 37° C in a humidified atmosphere.

ELISA inhibition. The ELISA inhibition assay was performed according to the method described by Macy et al.⁴⁰ with minor modifications. Two hundred microliters of diluted human serum (1:25) was incubated with 200 µl of competitor (serial threefold dilutions of SMX-dextran [CI-0694F] beginning with 0.1 mg/ml) in polystyrene tubes overnight at 4° C. Ninety-six well microtiter plates were coated with 100 µl SMX-gelatin (CI-0567) (1 µg/ml in PBS) and incubated overnight. The following day, the plate was aspirated and blocked as above, and 100 µl of serum/competitor mixture was added to each well. Triplicates were performed. The remainder of the assay was performed according to the direct ELISA protocol described above.

Amplified alkaline phosphatase goat anti-rabbit immunoblotting assay. Human serum samples taken from individuals before and during a course of trimethoprim (TMP)-SMX were immunochemically analyzed for SMX-conjugated proteins with partially purified rabbit anti-SMX antibodies. Proteins were

TABLE I. Characteristics of patients with AIDS

Patient no.	Prophylaxis/desensitization	Date SMX prophylaxis begun (mo/yr)	CD4 cells/ μ l	Previous OI	Previous SMX RXN
1	Prophylaxis	9/95	144	None	NA
2	Prophylaxis	11/95	172	None	NA
3	Prophylaxis	5/96	157	None	NA
4	Prophylaxis	12/96	199	PCP	NA
5	Desensitization	9/95	33	None	Rash
6	Desensitization	8/95	2	MAI, PCP, KS, CMV	Rash
7	Desensitization	10/95	199	None	Pruritis
8	Desensitization	12/96	203	PCP	Probable rash
9	Desensitization	9/96	31	KS	Probable rash
10	Desensitization	6/96	18	PCP	Probable rash
11	Desensitization	9/96	4	PCP	Pruritis
12	Desensitization	5/96	11	None	Rash

OI, Opportunistic infection; NA, not applicable; MAI, mycobacterium avium-intracellulare; KS, Kaposi's sarcoma; CMV, cytomegalovirus.

separated by molecular weight (25 μ g/lane) according to the procedure of Laemmli⁴¹ on a discontinuous 7.5% SDS-polyacrylamide mini-gel electrophoresis system with a 4% stacking gel layer. Electrophoretically separated proteins were electroblotted onto nitrocellulose membranes, and SMX-conjugated proteins were detected with the amplified alkaline phosphatase goat anti-rabbit immunoblotting assay described previously.¹⁸

Experimental subjects. Characteristics of the patients evaluated are presented in Table I. Four patients with AIDS who were beginning TMP-SMX prophylactic therapy for *Pneumocystis carinii* pneumonia (PCP) and eight patients with AIDS who had had previous adverse SMX reactions and had undergone TMP-SMX desensitization according to a 10-day protocol⁴² were evaluated prospectively. CD4 counts were available for the patients receiving prophylactic treatment, and all of them had values below 200×10^6 cells/ μ l. One of them had had a previous opportunistic infection. None of these individuals had a history of SMX allergy, and the majority were receiving one double-strength TMP-SMX tablet 3 times per week. The eight patients who had undergone SMX desensitization had CD4 counts at or below 200×10^6 cells/ μ l, and five of these individuals had had previous opportunistic infections. The prior SMX-induced adverse reactions consisted of either a maculopapular rash or severe pruritus to SMX. Three individuals had a probable rash, but their histories were not clear. After desensitization, each of these patients received one double-strength TMP-SMX tablet 3 times per week as PCP prophylaxis. None of the patients had markedly elevated liver-function tests. Six of 12 patients had a slightly elevated aspartate amino transaminase level only; patient 6 had elevated aspartate amino transaminase and alkaline phosphatase levels, and patient 11 had elevated aspartate amino transaminase, alkaline phosphatase, and total bilirubin levels. These experiments were approved by the University of Texas Southwestern Institutional Review Board. Informed consent was obtained from each of the patients before phlebotomy and drug administration.

Statistical analysis. The strength of the association between the presence of the SMX-haptenated protein in the peripheral blood and the development of a rash was evaluated with Fisher's exact test. Risk ratios and confidence intervals on the

risk were accomplished with the logit estimates. Probability (*p*) values less than 0.05 were considered statistically significant.

RESULTS

Detection of SMX-substituted proteins in patients with AIDS receiving SMX prophylactic therapy

Polyclonal SMX-specific antibodies were generated in rabbits, partially purified, characterized, and used in amplified alkaline phosphatase immunoblotting experiments to detect SMX substitution of serum proteins as described previously.¹⁸ Four patients with AIDS receiving prophylactic TMP-SMX therapy were evaluated. None had a history of SMX allergy, and only one had had an opportunistic infection. All had CD4 counts below 200×10^6 cells/ μ l. Western blot analysis was performed on serum samples taken before and at one or more times after the initiation of SMX prophylaxis.

Fig. 2 demonstrates results from two of the four patients evaluated. Immunoblotting was performed with rabbit anti-SMX-BSA antibodies that had been absorbed with BSA as the detecting antibodies. As shown, a ≈ 40 kD SMX-substituted protein is well demonstrated in both of the serum samples obtained from patient 1 after the initiation of SMX prophylaxis, but it was not demonstrable in the serum sample from patient 2 obtained approximately 4 months after the initiation of SMX prophylaxis. As expected, the SMX-substituted protein was not detectable in either serum sample obtained before the initiation of SMX prophylaxis. Patient 1 continues to receive SMX and has never had a reaction. Patient 2 did not have a reaction during the 7-month time period in which he was followed. He since has been lost to follow-up. Sera taken from patient 3 before and 1 month after initiation of SMX prophylaxis and from patient 4 before and 1 week after initiation of SMX prophylaxis also were analyzed. SMX-

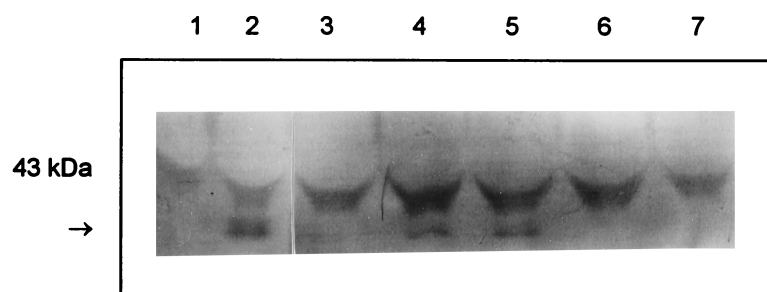


FIG. 2. Western blot analysis of SMX-substituted human serum proteins. Human serum samples were taken from patients with AIDS during SMX prophylactic therapy and were immunochemically analyzed for SMX-conjugated proteins by SDS-PAGE and immunoblotting. *Lane 1:* serum from an individual without HIV not receiving SMX; *lane 2:* serum taken from the same individual 10 days into SMX therapy after the development of a drug reaction; *lanes 3 to 5:* sera from patient 1 before the initiation of SMX prophylaxis, 1 week into therapy, and 7 weeks into therapy; *lanes 6 and 7:* sera from patient 2 before and 4 months after the initiation of SMX prophylaxis.

protein haptenation was not detectable in any of these samples (data not shown), and both of these individuals continue to receive SMX.

The ≈ 40 kD band was not detectable in 24 serum samples analyzed from patients with AIDS not receiving TMP-SMX prophylactic therapy (data not shown) nor was it detectable when preimmune rabbit serum was used as the primary antibody.

SMX haptenation was detectable in the sera of one of the four patients with AIDS receiving TMP-SMX prophylactic therapy. Haptenation was highly selective because only a single ≈ 40 kD protein was substituted. Thus the data suggest that a minority of patients with AIDS tolerating prophylactic TMP-SMX therapy produce a SMX-haptenated protein detectable in peripheral blood. However, we realize that a larger sample size will be required to prove this association.

Absence of SMX-specific antibodies in patients with AIDS receiving SMX prophylactic therapy

SMX-specific IgG antibodies were determined in patients with AIDS receiving TMP-SMX prophylactic therapy by using an ELISA inhibition assay and well-defined SMX antigens (provided by Dr. Catherine McCall at Cortech, Inc). Serum samples evaluated were the same as those used for the immunoblotting studies. SMX-specific antibodies were considered present if an optical density of greater than 0.15 was obtained and specific inhibition (with an SMX-dextran competitor) of at least 25% was demonstrated. By these criteria, none of the four patients had SMX-specific IgG antibodies as summarized in Table II.

Detection of substituted proteins in patients with AIDS who have undergone SMX desensitization

By using the immunoblotting procedure described above, a second group of eight patients with AIDS was evaluated, those who had undergone SMX desensitization. Each of these individuals had had a previous adverse cutaneous reaction to SMX. Desensitization

consisted of administering gradually increasing doses of TMP-SMX over a 10-day period until a therapeutic prophylactic dose was reached.⁴² After desensitization, patients received one double-strength tablet 3 times per week for PCP prophylaxis.

Fig. 3 presents results from three patients. As shown, a ≈ 40 kD SMX-substituted protein is well-demonstrated in each of the postdesensitization and none of the predesensitization serum samples. SMX was discontinued in patient 5 due to the development of a pruritic, erythematous skin rash that occurred approximately 2 months after desensitization. Patient 6 continued to receive SMX without development of an adverse reaction until his death from AIDS-related causes. SMX was discontinued in patient 7 because of the development of a pruritic rash that occurred approximately 1½ months after desensitization. Sera from five additional patients (patients 8 through 12) who underwent desensitization also were analyzed before and at the following time-points after SMX desensitization: patient 8, 1 week; patient 9, 3 weeks; patient 10, 2 months; patient 11, 1 week; and patient 12, 1 month. A 40 kD SMX-substituted serum protein was detectable in the postdesensitization samples from patients 9, 10, and 12 (data not shown).

Detection of SMX-specific antibodies in patients with AIDS who have undergone SMX desensitization

All eight desensitized individuals were evaluated for the presence of SMX-specific IgG antibodies by using an ELISA inhibition assay. The same serum samples that were analyzed in the immunoblotting studies were used for the antibody studies. A representative positive ELISA experiment is shown in Fig. 4. The SMX-haptenation and ELISA data are summarized in Table II. As shown, six of the eight (75%) desensitized patients demonstrated SMX-protein haptenation, and three of these six developed SMX-induced skin reactions. Only one of these three possessed SMX-specific IgG antibodies. There is no significant association between SMX

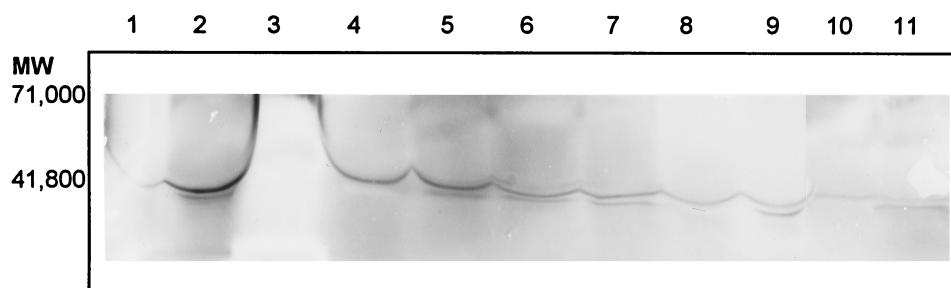


FIG. 3. Western blot analysis of SMX-substituted serum proteins in desensitized patients with AIDS. Human serum samples were taken from patients with AIDS before and during (and/or after the completion of) SMX desensitization and immunochemically analyzed for SMX-conjugated proteins by SDS-PAGE and immunoblotting. *Lanes 1 through 3:* negative control, positive control, and molecular weight standard (see Fig. 2); *lanes 4 through 7:* sera from a desensitized patient taken (patient 5) before and 1 week, 1 month, and 2½ months after SMX desensitization; *lanes 8 and 9:* sera from patient 6 before and 1 week after SMX desensitization; *lanes 10 and 11:* sera from patient 7 taken before and 1 week after SMX desensitization. As shown, only a portion of the 71 kd molecular weight standard is visible. However, the 41.8 kd molecular weight marker is not visible because it had markedly faded when the photograph was taken. A background band at approximately 43 kd is present in both the positive and negative control samples, and its identity is unknown.

TABLE II. Association of SMX-specific antibodies, haptenation, and clinical SMX reactivity in AIDS patients receiving SMX prophylactic therapy or who have undergone SMX desensitization

Patient no.	Prophylaxis/desensitization	SMX-protein haptenation	SMX-specific antibodies	Developed rash
1	Prophylaxis	Yes	No	No
2	Prophylaxis	No	No	No
3	Prophylaxis	No	No	No
4	Prophylaxis	No	No	No
5	Desensitization	Yes	No	Yes
6	Desensitization	Yes	No	No
7	Desensitization	Yes	No	Yes
8	Desensitization	No	No	No
9	Desensitization	Yes	Yes	Yes
10	Desensitization	Yes	No	No
11	Desensitization	No	No	No
12	Desensitization	Yes	No	No

Six of eight (75%) of the desensitized patients demonstrated SMX-protein haptenation and three of these six individuals (50%) developed SMX-associated skin eruptions.

haptenation and the development of an SMX-induced reaction ($p = 0.464$, Fisher's exact test). However, the logit estimate of relative risk (95% confidence interval) of the development of an SMX-induced reaction in the SMX haptenation-positive group compared with that of the SMX haptenation-negative group is 3.0 (0.215, 41.9). Thus while these data do not prove that SMX-protein haptenation is required for the development of clinical SMX reactivity in desensitized patients with AIDS, it is strongly suggestive. Two individuals (patients 8 and 11) did not demonstrate SMX-protein haptenation, did not possess SMX-specific IgG antibodies, and have not had a clinical reaction.

DISCUSSION

In this study three of six SMX-desensitized patients with AIDS who demonstrated SMX-protein haptenation

subsequently developed SMX-induced clinical reactions. Moreover, patients who did not demonstrate SMX-protein haptenation did not have subsequent SMX-associated reactions. These data suggest that the formation of SMX-protein conjugates may be required for the development of SMX clinical reactivity.

The pathogenic mechanisms involved in the reactions to SMX in patients with AIDS are most likely multifactorial. While these reactions are often described as allergic in nature, it is unlikely that a single mechanism alone is operative. In fact, data exist that support the involvement of both toxic and immunologic mechanisms. In addition, other factors that may influence the development of SMX hypersensitivity in patients with AIDS include slow acetylator phenotype, high-dose SMX therapy, severe immunodeficiency, and glutathione deficiency.⁴³⁻⁴⁹

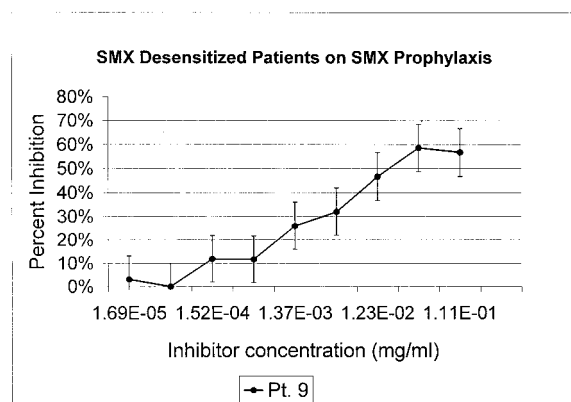


FIG. 4. Analysis of SMX-specific IgG antibodies by ELISA inhibition. Diluted serum-samples from patients who had undergone SMX-desensitization were preincubated with varying concentrations of the competitor, SMX-dextran (14 copies SMX/molecule dextran), and then used in ELISA inhibition experiments. Microtiter plates were coated with SMX-gelatin as described in the Methods section. These data are presented as the mean ($\pm$ SEM) of triplicate determinations. A representative positive experiment (patient 9) is shown.

Evidence supporting a toxic role for reactive SMX metabolites is accumulating rapidly,^{16,29} and concentrations of these metabolites may be greater in patients with AIDS than in individuals without AIDS. Increased metabolite production may occur because of altered SMX metabolism,⁴⁴⁻⁴⁶ whereas a glutathione-deficient state may be responsible for a reduced capacity to scavenge such metabolites.⁴⁷

Rieder et al.²⁹ showed that hydroxylamine metabolites of SMX are responsible for concentration-dependent toxicity in HIV-infected cells. These cells were found to have significantly lower glutathione concentrations than noninfected cells, and toxicity could be reduced by coinubation with glutathione or N-acetylcysteine. However, Lee et al.⁵⁰ subsequently found that the percentage of SMX hydroxylamine metabolites excreted was similar between the patients who discontinued SMX therapy because of toxicity and the patients who did not. These results, taken together, suggest that an increased cytotoxic sensitivity to hydroxylamine metabolites may be more important than the metabolite concentration itself.

In addition to being directly cytotoxic, SMX metabolites have been shown to covalently bind to proteins, possibly leading to the production of immunogenic peptides. Previously, Shear and Spielberg³⁰ demonstrated covalent binding of a sulfadiazine metabolite to murine hepatic microsomes and, subsequently, we demonstrated the covalent substitution of serum proteins in a human system.¹⁸ In light of our findings, we proposed that covalent binding of sulfonamide metabolites to cell macromolecules may lead to SMX-associated reactions, presumably antibody-mediated hypersensitivity reactions.

Data do exist supporting the role of specific antibodies in some of the SMX-induced reactions demonstrated in

patients with AIDS. Daftarian et al.²³ found that 100% of patients with skin reactions to cotrimoxazole had SMX-specific IgG, IgM, or both types of antibodies. In addition, however, the majority of HIV-positive patients who had been exposed to SMX but who had not experienced an adverse reaction also had specific antibodies, albeit at lower concentrations. Despite their presence, a pathogenic role for these antibodies was not determined.

Previously, we attempted to demonstrate the presence of SMX-specific antibodies in HIV-infected individuals, but the results were inconclusive.²⁰ Although data from ELISA inhibition studies suggested that specific antibodies were present, the inhibitors used for the inhibition studies subsequently were found to inhibit in a nonspecific fashion.

In this study we found that all patients with AIDS receiving SMX prophylactic therapy and all but one of those who underwent desensitization did not possess SMX-specific IgG antibodies. Despite their absence, however, two patients who had been desensitized developed an adverse SMX reaction. These data suggest that SMX-specific IgG antibodies may not play a role in the SMX-associated reactions that recur in patients with AIDS who undergo a 10-day desensitization procedure. However, as Coeshott et al.⁵¹ have shown, SMX-specific IgG antibodies may be involved in SMX-associated reactions that occur in individuals who have been desensitized according to other protocols.

In light of the absence of SMX-specific antibodies in two of the three individuals who developed SMX reactions, other explanations must be sought to account for the mechanism involved. There is some evidence to suggest that SMX reactions in patients with AIDS may be T-cell mediated. SMX-reactive lymphocytes have been demonstrated in non-HIV-infected individuals who have had SMX-induced reactions.^{52, 53} In addition, an immunohistological examination of the cutaneous inflammatory infiltrate of SMX and other drug reactions in patients with AIDS revealed that there is a perivascular CD8+ lymphocytic infiltrate of the superficial dermis with involvement of the epidermis.⁵⁴ Although we do not yet have evidence, it is possible that SMX-protein haptenation yields multivalent conjugates that promote T-cell sensitization.

In conclusion, we have found that in patients with AIDS who have undergone SMX desensitization because of a prior history of SMX allergy, SMX-protein haptenation may be a predictor of subsequent SMX clinical reactivity. Studies of other factors are in progress, including the role played by specific T lymphocytes, to assess the mechanism by which these SMX protein conjugates may be responsible for the reactions demonstrated.

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