

SULFONAMIDE ALLERGY

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Sulfonamides occupy a unique position in clinical medicine. As a group, these drugs were the first effective agents to be used as antibiotics. The antibiotic properties of the sulfonamides were discovered serendipitously in 1935 by Domagk,⁷ who would win the Nobel prize for medicine in 1938. Following Domagk's discovery, French investigators at the Pasteur Institute reported that in patients who had been treated with prontosil, an azo dye agent containing a sulfonamide group, the azo linkage was split, yielding para-aminobenzene sulfonamide (PABS).²⁷ These investigators and others subsequently demonstrated that PABS was as effective in treating experimental infections as prontosil. By the late 1930s, the worldwide medical community became aware of the tremendous beneficial effects of this newly discovered group of antibiotics.

CHEMISTRY

The sulfanilamide moiety is responsible for the major therapeutic effect of the sulfonamides. The direct link of the sulfur to benzene, as well as to the para-amino group, appears to be the most critical chemical characteristic. Subsequent developments have focused on developing better systemic absorption and high urinary solubility, as well as the development of combination agents, such as trimethoprim sulfa with broader antimicrobial activity. Structural formulas of selected sulfonamides are depicted in Figure 1.

The mechanism of action of the sulfonamides involves competitive inhibition of para-amino benzoic acid.¹¹ Sulfonamides by virtue of this action are capable of inhibiting bacterial growth by preventing incorporation of PABA into folic acid. Several cell cycles are required for this action to occur, suggesting that stored folic acid is being used. Because human cells require preformed folic acids, sulfonamides do not affect their cell turnover. The mechanism of action of the sulfonamides as anti-inflammatory agents used in inflammatory bowel disease and rheumatoid arthritis is unknown at this time.

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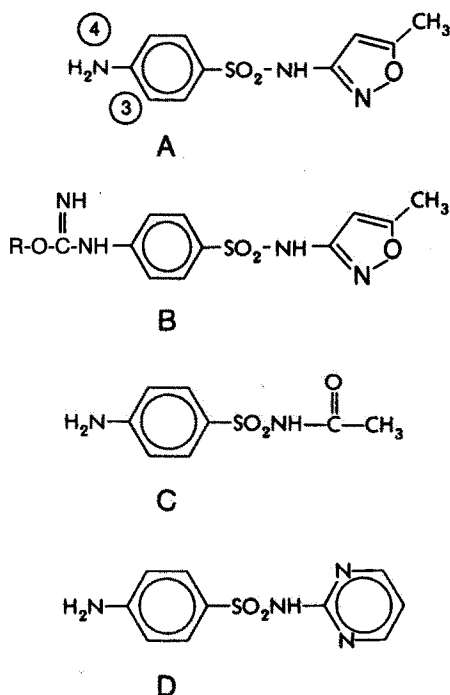


Figure 1. Sulfonamides. A, Sulfamethoxazole. B, N^4 -sulfamethoxazoyl determinant. C, Sulfacetamide. D, Sulfadiazine.

PHARMACOKINETICS

Sulfonamides are rapidly and primarily absorbed in the small intestine. Oral, mucosal, vaginal, or cutaneous absorption is unpredictable; however, these routes may provide adequate access to the immune system for sensitization or toxicity. This group of drugs is variably protein-bound,^{1, 11} with albumin representing the major bound plasma protein. Acetylated sulfonamides have enhanced protein binding. Once absorbed, sulfonamides are distributed throughout the total body water to all tissues. They readily enter serosal spaces, such as pleural and peritoneal fluids, as well as synovial tissue. In addition, this group of drugs passes the blood-brain barrier, as well as the placenta.

Sulfonamides undergo extensive metabolic changes following systemic administration. Acetylation and oxidation occur primarily in the liver. The major metabolic product is the N^4 acetylated sulfonamide. This by-product has no antibacterial property, although it maintains all the potential toxicities and antigenicity.

Sulfonamides are primarily excreted in the urine, and their excretion is dependent on renal function. Tubular reabsorption and secretion may occur with some agents. Small amounts of the drug may be excreted in the feces, bile, breast milk, and other body fluids.

TRIMETHOPRIM SULFAMETHOXAZOLE

The most widely used sulfonamide is the combination of trimethoprim and sulfamethoxazole (TMP-SMX). It was first noted by Bushby and Hitchings² and others in the 1960s when the addition of trimethoprim to sulfonamides resulted in a synergistic therapeutic benefit. TMP is an effective and selective inhibitor of microbial dihydrofolate reductase. This enzyme is required for microbial production of tetrahydrofolate and DNA. This additional mechanism is likely to be responsible for observed synergistic bactericidal effect with many gram-positive, as well as gram-negative, organisms, which is not observed with either agent alone.²¹ Because this combination antibiotic has represented the major sulfonamide responsible for allergic hypersensitivity reactions, this article focuses on the recognition and management of this important clinical topic.

TMP-SMX is marketed in the United States primarily as Bactrim, Septra, or its generic equivalent. It is available in oral and parenteral forms. It is available as a single-strength tablet, containing 80 mg of TMP and 400 mg of SMX, or as double-strength tablets, containing twice the amount of these agents. Oral suspensions, containing 40 mg of TMP and 200 mg of SMX, are available. Intravenous preparations contain 30 mg/5 cc of TMP and 400 mg/5 cc of SMX. Following oral administration, TMP-SMX is absorbed, distributed, metabolized, and excreted following first-order kinetics. TMP-SMX, the combination, appears to be absorbed as efficiently as either agent alone. Following systemic absorption, both TMP and SMX are extensively protein-bound. It is estimated that TMP is 45% bound and SMX is 66% bound by plasma proteins. Tissue concentrations of TMP represent 30% to 50% of plasma concentrations, and those of SMX represent 20%.⁹ TMP is concentrated in prostatic and seminal fluid, as well as in saliva, breast milk, and bile.²¹ TMP and SMX appear to cross the placenta. Approximately 10% to 30% of TMP is metabolized by N⁴ acetylation or glucuronide conjugation.¹³ Unlike sulfonamide metabolites, these metabolites appear reactive bacteriologically. The half-life of TMP-SMX is approximately 11 hours. Because both drugs are excreted in the urine, dosage adjustments are recommended for those individuals with impaired creatinine clearance.

CURRENT INDICATIONS

Despite the fact that sulfonamides were the first antibiotic to be introduced in clinical medicine, the clinical indications remain substantial. TMP-SMX remains the drug of choice for the treatment of acute, chronic, and recurrent urinary tract infections in many clinical settings. Because of the accumulation of TMP in the prostatic fluid, TMP-SMX is a highly effective agent for acute or chronic prostatitis. TMP-SMX may be used in gonococcal, as well as nongonococcal, urethritis. Because TMP-SMX has substantial activity against *Streptococcus pneumoniae* and *Haemophilus influenzae*, it is a useful agent in upper and lower respiratory tract infections, including otitis media, sinusitis, and bronchitis. Because of increasing bacterial resistance to amoxicillin, TMP-SMX has emerged as an important therapeutic option for the treatment of enteric infections caused by *Shigella*, *Salmonella*, and enteropathic *Escherichia coli*. *Pneumocystis carinii* infection is susceptible to TMP-SMX and certainly is one of the most serious infections that affects individuals with AIDS or individuals with primary and secondary cellular immune deficiencies. Because of the AIDS epidemic, an increasing number of patients are receiving both acute parenteral therapy for *P. carinii* pneumonia (PCP), as well as long-term oral prophylaxis.

ADVERSE REACTIONS

Despite its long duration of availability and extensive use in inpatient and outpatient settings, serious adverse reactions to TMP-SMX before the AIDS epidemic were unusual. In a large, multicenter, international review of 1121 hospitalized patients receiving TMP-SMZ from 1966 to 1980, 8% experienced an adverse reaction.¹⁷ Gastrointestinal upset and skin rash were the most commonly reported reactions. Skin reactions, including erythroderma, urticaria, and pruritus, occurred in 3.3% of all patients receiving TMP-SMZ. There were no cases of Stevens-Johnson syndrome. Upper gastrointestinal reactions, including nausea, vomiting, and anorexia, occurred in 3.2%. Diarrhea occurred in only 0.5%. Other adverse effects, occurring in less than 1%, included fever, vertigo, thrombocytopenia, renal tubular acidosis, and elevated creatinine. One half of the reactions occurred in the first 3 days of treatment. Adverse reactions were observed up to 14 days following institution of therapy. All reactions resolved promptly with drug discontinuation. Adverse reactions occurred twice as commonly in women than in men. These observations clearly indicate that serious toxicity of TMP-SMZ is rare. This report is likely to overestimate the potential toxicity of oral administration of TMP-SMZ because it included hospitalized patients who received oral and parenteral forms.

If certain precautions are followed in non-HIV-infected individuals, adverse reactions are minimal. Because of its metabolic effects, TMP-SMX may potentiate the effects of coumadin, dilantin, tolbutamide, and chlorpropamide. It should be avoided in patients receiving these agents.¹⁹ Furthermore, TMP-SMX should be avoided in pregnancy because of its ability to cross the placenta. Because of the potential antimetabolic effect described above, TMP-SMX should be avoided in patients with G-6PD deficiency or folic acid deficiency.

In contrast to the relatively low incidence of serious adverse effects of TMP-SMX in non-HIV-infected individuals, the frequency of adverse reactions in patients with AIDS is striking and problematic. In some series, the incidence of adverse reactions has been as high as 70%.¹⁶ The incidence of skin rash and fever, which required cessation of the drug in patients receiving TMP-SMX as prophylaxis for PCP, has been estimated to range from 9% to 34%.¹⁸ In patients receiving active therapy for PCP, discontinuation is required because of adverse reactions in 18% to 57%.¹⁵ Because alternative therapy is not as effective and is much more expensive in preventing PCP as TMP-SMX, attempts to minimize adverse reactions have been important. Although the precise mechanism of the increased frequency of adverse reactions in HIV-infected individuals is unknown, attempts to modify the immune response to TMP-SMX have been documented for over a decade.^{8, 12} Although immunologic mechanisms have been presumed to occur, it is not clear whether direct toxicity is involved as well.^{12, 26}

Carr and colleagues⁴ have reported the administration of TMP-SMZ to 143 patients with AIDS and PCP. In their series, 39 of 143 (27%) patients experienced hypersensitivity reactions compared with 3% of the control group who received pentamidine. Regression analysis of clinical and laboratory parameters of these patients revealed a CD4:CD8 ratio greater than 10 and treatment for less than 14 days as independent predictors of hypersensitivity reactions. All the affected patients developed a morbilliform skin rash that promptly resolved with discontinuation of the drug. No patient developed urticaria, angioedema, vasculitis, or Stevens-Johnson syndrome. Concomitant use of corticosteroids was associated with a decreased incidence of reactions (7% versus 30%). These authors showed that although many risk factors—including atopy, glutathione deficiency, slow

acetylator phenotype, rate of HIV replication, and coexisting viral disease—have been suspected in the induction of TMP-SMZ hypersensitivity in AIDS, T lymphocytes may be the important effector cell. They further hypothesize that as AIDS progresses, a fall in total lymphocytes, CD4+ lymphocytes, and CD4:CD8 ratios may be associated with a decline in TMP-SMZ hypersensitivity responses.

The immunologic response to TMP-SMX is well documented. Patients who have a history of immediate hypersensitivity reactions to SMX demonstrate SMX-specific IgE antibodies.¹⁴ In laboratory rats, SMX-NO appears to be much more immunogenic than the parent drug,¹⁰ whereas in humans, it has been shown that SMX alone can be presented to T cells in a major histocompatibility complex (MHC)–restricted fashion independent of processing, suggesting a direct covalent binding of SMX to MHC peptide complex.²⁴ Further support for T-cell activation has been presented with evidence of increased T-cell activation markers in the peripheral blood of SMX-sensitive individuals.⁶ In addition, SMX stimulated peripheral blood mononuclear cells (PBMC) in these individuals to produce higher levels of interleukin-5 (IL-5).²² Antibody responses to SMX in HIV-infected individuals have been analyzed.⁶ Although HIV-positive patients without clinical sensitivity have a high incidence of SMX-specific IgG and IgM (45 and 85% respectively), the titers of these antibodies were much higher in 100% of HIV-positive individuals with a history of hypersensitivity. The antibodies appeared to be exclusively of the IgG₁ and IgG₃ subclasses. HIV-negative controls without clinical sensitivity do not appear to have any specific IgG or IgM. Antibodies appear to recognize N-acetyl sulfonamide, N-sulfanilamide, N-sulfadiazine, and N-sulfisoxazole but not sulfanilamide or 3-amino-5-methoxazole.

The role of reactive SMX metabolites in patients with AIDS has been further elucidated. Increased toxicity or immunogenicity may be caused by decreased levels of glutathione in cells that metabolize SMX in HIV-infected individuals.²⁵ Toxicity and antigenicity of SMX is believed to be a consequence of activation of the hydroxylamine metabolite of SMX and subsequent oxidation to the nitroso-SMX (SMX-NO). When glutathione reduction normally occurs, the reactive SMX metabolites can be harmlessly excreted. When the capacity for glutathione reduction is exceeded, however, these reactive metabolites of SMX may covalently haptenate proteins. Gruchalla and colleagues,¹⁴ who had previously described a 40 kD SMX-substituted protein in the serum of patients treated with SMX, examined patients with AIDS who were receiving SMX for PCP prophylaxis or who had undergone SMX desensitization. Six of the 8 (75%) patients who underwent SMX desensitization demonstrated SMX protein haptenization. One half of these patients subsequently developed adverse skin reactions. The two patients who did not demonstrate haptenization did not experience skin rash. Only one of the four patients receiving SMX prophylaxis demonstrated SMX haptenization. None of these patients developed SMX-specific IgG antibodies or demonstrated adverse skin reactions. These authors concluded that SMX haptenization may be an important determinant of clinical sensitivity to SMX.

Although immunologic reactivity has clearly been demonstrated *in vitro* to TMP-SMX, direct toxicologic effects also may be important. The cytotoxicity of SMX, as well as the SMX-hydroxy ambien metabolite (SMX-HA), has been measured in PBMCs.^{3, 4} Forty-five HIV-positive patients with and without a history of clinical sensitivity were compared with HIV-negative controls. Cytotoxicity to SMX-HA was significantly elevated in HIV-positive clinically sensitive individuals compared with HIV-positive individuals without clinical sensitivity or HIV-negative controls. Cytotoxicity could be reduced by pre-incubation with glutathione in the hypersensitive group only. These authors suggested that *in vitro* sensitivity assays may be useful clinical markers for SMX sensitivity.

Table 1. SURVEY OF TMP-SMX PROPHYLAXIS FOR PCP

	TMP (mg)	SMX (mg) PO
Day 1		
9 AM	0.8	4
11 AM	1.6	8
1 PM	4	20
5 PM	8	40
Day 2		
9 AM	16	80
3 PM	32	160
9 PM	40	200
Day 3		
AM	80	400

Regardless of the precise mechanisms involved, it appears that desensitization protocols for TMP-SMX are relatively safe and effective. Before 1995, clinical reports were largely anecdotal and retrospective in nature. Subsequently, prospective surveys have outlined effective regimens. In a prospective survey of 48 HIV-infected, previously hypersensitive individuals who required TMP-SMX prophylaxis for PCP, patients were followed for a mean of 16 months following a 2-day desensitization protocol.⁵ A full dose of 400 mg of SMX and 80 mg of TMP was reached by day 3 using Table 1. Seventy-seven percent of individuals undergoing this regimen tolerated the course of therapy without adverse effects. Desensitization failed in 11 cases. In 8 of 11 cases, failure occurred in the first 2 days. Hypotension and acute nonfatal myocardial infarction developed in one individual. Factors predictive of failure included higher CD4 and higher CD4:CD8 ratios. A similar prospective analysis of 22 HIV-positive clinically sensitive patients with a history of fever or nonexfoliative skin rash was reported.²³ The authors used an 8-day incremental dose regimen, beginning at smaller doses than those previously described (Table 2). Nineteen of 22 patients successfully completed the desensitization protocol. Significant reactions occurred in eight patients undergoing the regimen; however, discontinuation of the regimen was necessary because of drug hypersensitivity in only 3 patients.

Table 2. ORAL AMBULATORY INCREMENTAL REGIMEN FOR PATIENTS SENSITIVE TO TMP-SMX (3 doses/d)

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One half of the patients who underwent the regimen had negative tests for antibody specific to the N⁴ determinant of SMX. In the fourth week, 8 of 11 of the remaining patients developed IgG to the SMX-N⁴ determinant. Skin tests were performed with 2 mg/mL TMP-SMX intravenous preparation for scratch testing and with 0.2 mg/mL for intradermal testing if scratch testing was negative. Skin tests to sulfamethoxazole were negative in all patients at the first visit. In all cases, the adverse reaction consisted of mild to moderate skin rash or fever. No hypotension or other signs of systemic anaphylaxis were observed. Rash and fever resolved following administration of systemic corticosteroids. Following discontinuation of corticosteroids at day 12, all affected patients were able to continue on the treatment protocol.

Desensitization to sulfadiazine required to treat cerebral toxoplasmosis in patients with AIDS has also been reported as being successful.²⁰ Moreno and colleagues²⁰ described a rapid oral desensitization protocol in 11 patients with AIDS and cerebral toxoplasmosis. Desensitization was attempted by starting with 1 mg of sulfadiazine, with increasing doses administered every 15 minutes until a total of 1 g was reached after 2.5 hours. Seven of the 11 patients were successfully treated with the rapid protocol. Only two of the patients desensitized had not received premedication with antihistamines and corticosteroids. The authors concluded that rapid desensitization to sulfadiazine should be reserved for acute, life-threatening indications and that slower protocols with premedication may be necessary in those patients that fail the rapid protocol.

CONCLUSIONS

Sulfonamide allergy is an important clinical condition with multiple manifestations and therapeutic implications. Although hypersensitivity reactions are uncommon in the non-AIDS population, the occurrence of these reactions in the AIDS population is striking and troublesome. The pathogenesis of clinical hypersensitivity to sulfonamides is likely to be multifactorial. IgE-mediated mechanisms are important, but the generation of toxic metabolites may result in additional nonimmunologic cytotoxic mechanisms, as well as confer an increase in immunogenic haptenized proteins. In AIDS, the T lymphocyte is an important effector cell. Desensitization protocols have been described that are safe and effective, and have become the standard of care in many clinical settings.

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