

Sulfonamide hypersensitivity

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Adverse drug reactions are frequent and potentially life-threatening occurrences. A recent meta-analysis of these reactions in hospitalized patients estimated an incidence of 6.7% and a fatality rate of 0.32% [1]. Hypersensitivity reactions to medications are reported to account for 6% to 10% of inpatient adverse drug reactions, and, of these events, fatalities occur in 1 of 10,000 [2]. Despite this high frequency, for the vast majority of drugs, the pathophysiology of the hypersensitivity reactions is not well understood.

Sulfamethoxazole (SMX) is the best studied and most widely used sulfonamide, and its cost is low relative to more recently introduced antimicrobial agents. Use of sulfonamide antibiotics has declined in recent years [3] owing to the combination of a rise in drug-resistant organisms, concerns about adverse reactions, and aggressive marketing of newer antibiotic classes. Nevertheless, sulfonamides remain a cost-effective medication in many settings. They were the first class of antibiotics introduced, and they still have a broad range of indications, including infections of the urinary, respiratory, and gastrointestinal tracts. Among hospitalized patients, adverse reactions to trimethoprim-sulfamethoxazole (TMP-SMX) occur 8% of the time, most commonly involving the skin and gastrointestinal tract [4]. Only approximately 3% of adverse reactions to TMP-SMX are thought to represent sulfonamide hypersensitivity reactions [5,6], and severe systemic reactions to TMP-SMX are even less frequent. Paradoxically, sulfonamides cause a disproportionate share of life-threatening adverse drug reactions. For example, sulfonamides account for the largest percentage of the 10 cases per million persons per year of antibiotic-induced toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome [7].

For most patients who report an adverse reaction to a sulfonamide, it is appropriate to substitute a different antibiotic for a given infection; however, simply avoiding these agents introduces a variety of potential consequences that must be considered. For example, in the past decade, the preferential use of

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broader-spectrum antibiotics has resulted in a large increase in the overall costs of antibiotics [8]. These more expensive agents, in turn, result in selection pressure favoring resistant organisms, a phenomenon that may limit choices of effective agents in the future. For HIV-infected patients, the risks of simply substituting a different antibiotic class for SMX are more directly apparent. TMP-SMX is the antibiotic of choice for *Pneumocystis carinii* pneumonia (PCP) infection, PCP prophylaxis, and toxoplasmosis prophylaxis; unfortunately, approximately 60% of HIV-infected patients experience TMP-SMX hypersensitivity reactions during their therapy [4,5,9,10].

The following sections explore several aspects of sulfonamide hypersensitivity reactions in more detail—pathophysiology, physical manifestations, diagnosis, sulfonamide desensitization, and cross-reactivity between sulfonamide antibiotics and sulfa-containing nonantibiotics.

Pathophysiology

Among the antibiotics, hypersensitivity reactions involving the penicillins and sulfonamides have been studied most intensively. For penicillin, this research has resulted in the availability of diagnostic skin-testing reagents with excellent sensitivity for detecting penicillin-specific IgE. In contrast, sulfonamide hypersensitivity is still incompletely understood [11]. Although IgE-mediated hypersensitivity reactions to sulfonamides are known to occur, other mechanisms are more often responsible for sulfonamide reactions, and recent advances indicate that the pathophysiology of these reactions is more complicated than originally postulated.

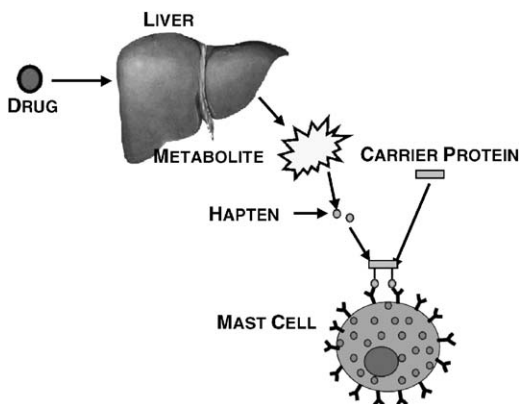


Fig. 1. Metabolism and metabolite haptenation in a previously sensitized individual. Mast cell activation occurs when the polyvalent hapten/carrier complex binds to specific IgE. (From Tilles SA, Slatore CG. Hypersensitivity reactions to non- β -lactam antibiotics. Clin Rev Allergy Immunol 2003;24:221–8; with permission.)

As is true for most other antibiotics, sensitization to sulfonamides has been assumed to require drug metabolism and host protein haptenation (Fig. 1). It has been known for almost 20 years that formation of a hydroxylamine intermediate (SMX-NHOH) [12] is associated with hypersensitivity reactions to SMX. This intermediate results from hepatic cytochrome P-450 oxidation of the arylamine at the N4 position. Of interest, sulfonamide nonantibiotics do not have this arylamine group (Figs. 2 and 3). Further oxidation of SMX-NHOH yields a nitroso compound, SMX-NO [13–17]. Fig. 4 schematically depicts this process. SMX-NHOH and SMX-NO have been shown to haptenate endogenous proteins [16,18,19], and this haptenation can be inhibited experimentally by antioxidants.

Recent studies have suggested that other pathophysiologic mechanisms may also contribute to SMX reactions. For example, the SMX-NO intermediate has been shown to be directly cytotoxic to lymphocytes and other immune cells [20]. This observation supports the concept that SMX treatment may result in potentially severe adverse reactions independent of sensitization or immunologic recognition of sulfa epitopes. There are also data suggesting that SMX and its metabolic intermediates haptenate lymphocyte surface proteins without being bound to a soluble carrier [16]. In HIV-infected patients, several factors have been proposed to contribute to the high rate of sulfonamide hypersensitivity, including slow acetylation rates [21–23] and altered levels of thiols, disulfides, and plasma cysteine [24–27].

The complex pathophysiology of SMX adverse reactions may be explained in part by a model called the “danger hypothesis.” The danger hypothesis argues that “co-stimulatory signals” such as infection cause the immune system to become activated, resulting in immune responses to otherwise well-tolerated drugs

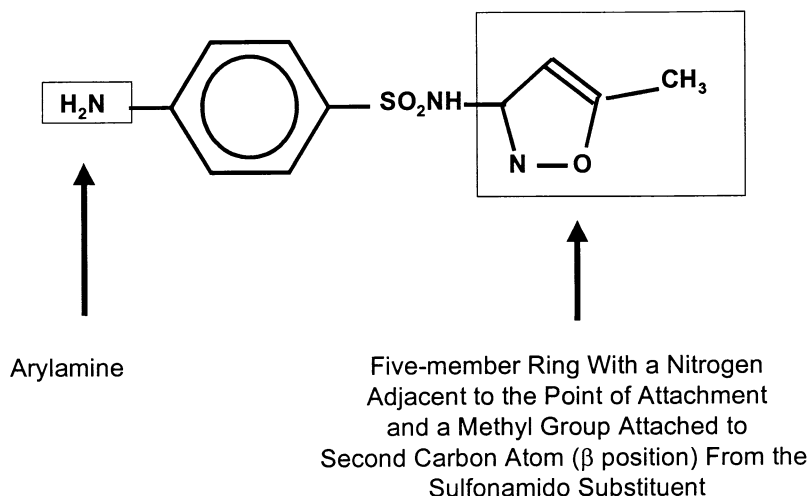
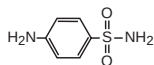
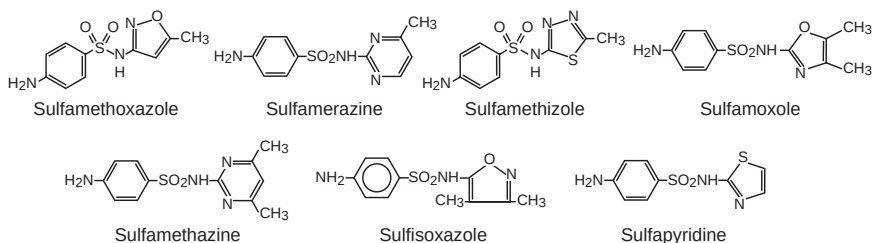


Fig. 2. Structural sites important to sulfonamide-induced hypersensitivity reactions and cross-allergenicity. (From Tilles SA. Practical issues in the management of hypersensitivity reactions: sulfonamides. *S Med J* 2001;94:817–24; with permission.)

Sulfanilamide (basic sulfonamide structure)



Structures of sulfonamide antimicrobials (all contain an arylamine group)



Structures of other sulfonamide-containing compounds (none contain an arylamine group)

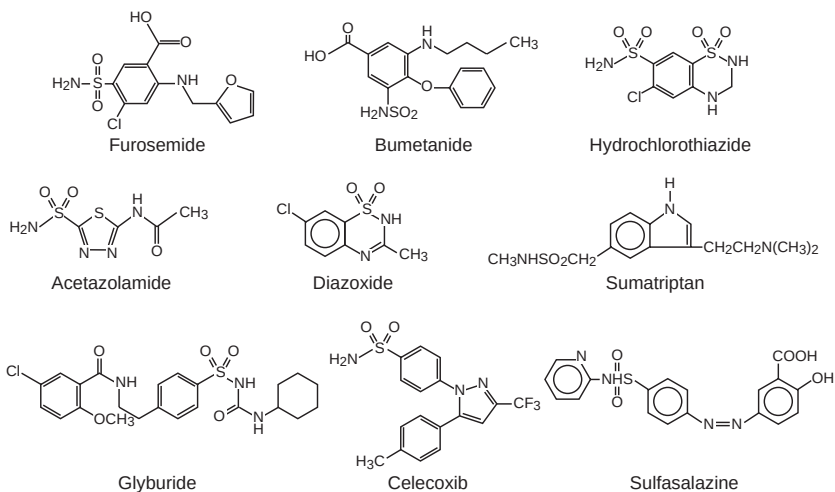


Fig. 3. Sulfanilamide and structurally related drugs. (From Tilles SA, Slatore CG. Hypersensitivity reactions to non-β-lactam antibiotics. *Clin Rev Allergy Immunol* 2003;24:221–8; with permission.)

[28]. The rash that is seen with administration of ampicillin to a patient with infectious mononucleosis (Epstein-Barr virus infection) is a well-known example [29] of this phenomenon. Binding of reactive SMX metabolites to host cells may also serve as a danger signal. Fig. 4 summarizes a variety of proposed mechanisms of SMX hypersensitivity.

Clinical manifestations of sulfonamide hypersensitivity

Sulfonamide hypersensitivity is classically characterized by fever, a generalized maculopapular rash, and toxicity of one or more internal organs (which may

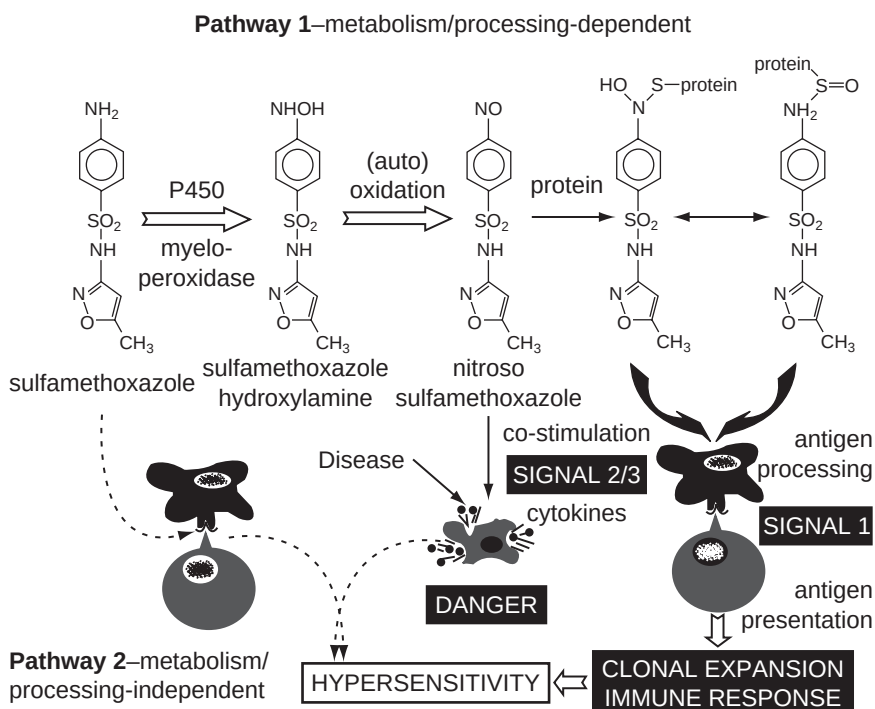


Fig. 4. Proposed mechanisms of SMX hypersensitivity reactions. Pathway 1 involves sequential oxidation to the reactive nitroso metabolite that can bind irreversibly to thiol groups of circulating or cell surface proteins. Pathway 2 suggests that SMX stimulates T-cell proliferation, in the absence of drug metabolism and antigen processing, via a direct reversible interaction between the parent drug and the antigenic peptide embedded within the major histocompatibility complex binding groove of antigen-presenting cells. (From Naisbitt DJ, Gordon SF, Pirmohamed M, Burkhart C, Cribb AE, Pichler WJ, et al. Antigenicity and immunogenicity of sulfamethoxazole: demonstration of metabolism-dependent haptenation and T-cell proliferation in vivo. *Br J Pharmacol* 2001;133:295–305; with permission.)

be asymptomatic). This reaction usually develops 7 to 14 days after initiating therapy [30] and similarly resolves 7 to 14 days after the offending agent's discontinuation [31]. Anaphylactic and anaphylactoid reactions also occur but are much less frequent [30]. SMX reactions result in TEN and Stevens-Johnson syndrome [7] only rarely, although they account for the largest percentage of the 10 cases per million persons per year of antibiotic-induced cases. Additionally, a "hypersensitivity syndrome" characterized by hypotension, fever, rash, and pulmonary infiltrates has been described and usually resolves with supportive therapy. The most common manifestation of SMX reactions in HIV-infected patients is a fixed drug eruption, although erythema multiforme, TEN, Stevens-Johnson syndrome, and anaphylactoid reactions have also been reported [11]. Table 1 describes some of the more common immunologically mediated reactions [30–35].

Table 1

Spectrum of cutaneous manifestations of sulfonamide hypersensitivity

Reaction	Typical presentation
Anaphylaxis or anaphylactoid reactions	Occurs within 30 minutes. Occurs most commonly after parenteral drug administration but may occur with other routes of administration. Symptoms may include: pruritus; urticaria; angioedema; respiratory distress as a result of laryngeal edema, bronchospasm, or laryngospasm; wheezing; stridor; respiratory obstruction; hypotension; cardiovascular collapse; and abdominal or uterine cramping. Mortality rate is highly dependent on the rapid response to appropriate treatment.
Isolated angioedema/urticaria	Occurs minutes to days after the initiation of therapy. Symptoms may include: mucosal lesion involvement, urticaria, swelling of central part of face, respiratory distress, and cardiovascular collapse.
Serum sickness or serum sickness-like reactions	Occurs 1 to 2 weeks after initiation of therapy. The onset of symptoms is delayed to reflect the time required to form immune complexes. Symptoms may include fever, arthralgia, and morbilliform lesions sometimes with urticaria. Mortality rate is less than 5%.
Stevens-Johnson syndrome	Occurs 1 to 3 weeks after initiation of therapy. Symptoms may include erosions at ≥ 2 mucosal sites, small blisters on dusky purpuric macules or atypical targets, rare areas of confluence, and detachment of $< 10\%$ of body surface area; 10% to 30% of cases involve fever and lesions of the respiratory and gastrointestinal tracts. With prompt use of corticosteroids, the mortality rate is less than 5%.
Toxic epidermal necrolysis	Occurs 1 to 3 weeks after initiation of therapy. Symptoms may include erosions at ≥ 2 mucosal sites, individual lesions similar to those of Stevens-Johnson syndrome, confluent erythema, outer layer of epidermis separates readily from basal layer with lateral pressure, large sheets of necrotic epidermis, and total detachment of $> 30\%$ of body surface area. Nearly all cases involve fever, systemic consequences of widespread injury to the skin, leukopenia, and lesions of the respiratory and gastrointestinal tracts. Mortality rate ranges from 1% to 30%. Sepsis is the most common cause of death.
Fixed drug eruption	Occurs 0.5 to 8 hours after re-exposure to a drug. Unlike other skin eruptions, fixed drug eruptions are considered characteristic of drug hypersensitivity reactions. Lesions are well delineated, round or oval, a few millimeters to 25 to 30 cm in size, and tend to recur at the same site with each subsequent exposure. Initially, the lesion appears edematous, followed by erythema, which later darkens to a deep reddish to purple color. Occasionally, lesions may appear eczematous, urticarial, vesiculobullous, hemorrhagic, or nodular. The mucus membranes are occasionally involved. Lesions usually resolve in 2 to 3 weeks after withdrawal of the suspected agent.

From Tilles SA. Practical issues in the management of hypersensitivity reactions: sulfonamides. *S Med J* 2001;94:817–24; with permission.

A myriad of potential adverse effects of sulfonamides are not thought to be immunologically mediated. This list is too extensive to review in detail, but every organ system can sustain adverse effects. Some examples include nausea and vomiting, hepatitis, arthritis, and electrolyte abnormalities [36]. Hematologic complications are uncommon but can be life threatening.

Diagnosis

A useful classification system has been developed for categorizing adverse drug reactions [37]. The first category accounts for common and predictable reactions, including side effects (eg, sedation with antihistamines), toxicity (anticipated effects owing to overdosage), and drug interactions. The second and smaller category is designated uncommon and unpredictable and includes intolerances and idiosyncratic and hypersensitivity reactions. Of these effects, only hypersensitivity includes reactions involving immunologic sensitization and resultant highly specific antigen-provoked effector responses by lymphocytes or antibodies. Although this classification system is simple in theory, accurately classifying reactions in real-world practice is often challenging.

A detailed history is the most critical step in the diagnosis of a sulfonamide hypersensitivity reaction. Important information includes determining the timing and nature of symptoms, the history of previous exposure to the offending agent, and the outcome of possible re-challenge with the same or similar medication. A detailed description of sulfonamide-induced symptoms should be elicited, including whether there was any mucous membrane involvement. It is also important to list all of the medications regularly and intermittently taken by the patient, as well as other general medical problems. A review of the medical record may add useful information regarding the possible etiology and response to management (eg, emergency department documentation of urticaria with angioedema treated with epinephrine versus anxiety with flushing treated with a benzodiazepine) [38,39].

After a thorough history, the ideal next step in the diagnosis of a possible drug hypersensitivity reaction is objective testing; unfortunately, there is no well-validated testing method to confirm the diagnosis of sulfonamide hypersensitivity. Skin testing is impractical, because there are likely multiple relevant haptens, and previous attempts to develop sensitive skin-testing reagents have been unsuccessful [40].

The lymphocyte toxicity assay (LTA) is a potential tool for the diagnosis of sulfonamide hypersensitivity. This test involves incubating the drug with rodent hepatocytes and then adding lymphocytes from the patient. In theory, the percentage of dead cells correlates with the occurrence and severity of the patient's hypersensitivity reaction. In patients with sulfonamide hypersensitivity, a recently described LTA reported a sensitivity and specificity of 98% and 89%, respectively [41]. The associated and more clinically relevant positive and negative predictive values were 90% and 67%, respectively. Subsequent studies in HIV-infected

subjects revealed positive and negative predictive values of 80% and 75%, respectively [42]. Further validation studies and improvements in the assay's sensitivity and reproducibility would be necessary before its widespread use.

Desensitization

When a patient reports a previous adverse reaction to an antibiotic, it is usually clinically appropriate, although increasingly problematic from an economic and public health point of view, to prescribe a different class of antibiotic. Nevertheless, in some circumstances, the risks of avoiding a specific antibiotic outweigh the risks of reintroducing it to a patient in whom the drug previously caused an adverse drug reaction. A common example is the treatment of patients with HIV. TMP-SMX is the drug of choice for patients infected with *Pneumocystis carinii*. The serious nature of this disease combined with the absence of convenient alternative treatments may result in a risk-benefit ratio favoring a careful attempt to use the medication despite a history of a prior reaction. TMP-SMX desensitization should be undertaken very cautiously, although a variety of desensitization protocols have been studied and enable most sulfa-sensitive, HIV-infected patients to receive the drug safely. TMP-SMX desensitization in non-HIV-infected patients has not been well studied; therefore, the safety of this procedure in these patients is not known.

As is true for all medical procedures, informed consent should be obtained before beginning desensitization. A history of TEN or Stevens-Johnson syndrome is an absolute contraindication to reintroducing the drug, because these reactions are potentially life threatening and not easily aborted. If dosing of the

Table 2

Sample rapid oral desensitization protocol for trimethoprim-sulfamethoxazole (dosed every 15 minutes) in HIV-infected patients

Concentration	Volume (mL)	Dose (mg)
10 ng/mL	1, 2, 4	0.00007
1000 ng/mL	$\frac{1}{2}$, 1, 2, 4	0.00075
1 μ g/mL	$\frac{1}{2}$, 1, 2, 4	0.0075
10 μ g/mL	$\frac{1}{2}$, 1, 2, 4	0.075
100 μ g/mL	$\frac{1}{2}$, 1, 2, 4	0.75
1 mg/mL	$\frac{1}{2}$, 1, 2, 4	7.5
10 mg/mL	$\frac{1}{2}$, 1, 2, 4	75.0
40 mg/mL	2, 4, 8	560.0
DS tablet	1	800.0

Begin dosing 2 DS tablets every 6 hours after last step.

Abbreviations: DS, double strength.

From Moreno JN, Poblete RB, Maggio C, et al. Rapid oral desensitization for sulfonamides in patients with acquired immunodeficiency syndrome. *Ann Allergy Asthma Immunol* 1995;74:140–6; with permission.

Table 3

Sample oral ambulatory desensitization protocol for trimethoprim-sulfamethoxazole (dosed three times daily) in HIV-infected patients

Day	Concentration (mg/mL)	Volume (mL)	Dose (mg)
1	0.00002	1, 3, 7	0.00007
2	0.0002	1, 3, 7	0.00075
3	0.002	1, 3, 7	0.0075
4	0.02	1, 3, 7	0.075
5	0.2	1, 3, 7	0.75
6	2.0	1, 3, 7	7.5
7	20.0	1, 3, 7	75.0
8	40.0	5, 10, 20	560.0
9	DS tablet	NA	800.0

Begin dosing 1 DS tablet daily after last step.

Abbreviations: DS, double strength; NA, not applicable.

From Rich JD, Sullivan T, Greineder D, et al. Trimethoprim/sulfamethoxazole incremental dose regimen in human immunodeficiency virus–infected persons. *Ann Allergy Asthma Immunol* 1997; 79:409–14; with permission.

drug following desensitization is interrupted, desensitization must be repeated before reintroducing the drug [43].

Desensitization involves the progressive administration of increasing doses of the offending medication. Premedication with antihistamines or corticosteroids is generally not recommended, because these drugs have not been shown to prevent reactions and may mask early signs of anaphylaxis [2]. Multiple SMX desensitization protocols have been published, and all yield similar results [44–48]. Tables 2 and 3 [46,47] describe rapid and slow desensitization schemes for HIV-infected patients, respectively. Several investigators report that it is reasonable to have HIV-infected patients administer the slow protocol at home, as long as necessary safeguards are taken, such as the assurance of immediate access to an emergency response system and the patient's understanding of the warning signs of a serious reaction.

Cross-reactivity

Many medications other than SMX have a sulfonamide moiety (see Fig. 2), including some of the most widely prescribed drugs, such as diuretics, sulfonylureas, and the recently introduced cyclooxygenase-2 (COX-2) inhibitor celecoxib. A fundamental difference between sulfonamide-containing antibiotics and nonantibiotics is the presence or absence of an arylamine group at the N4 position. This group is present only in the sulfa antibiotics, and, given the evidence implicating the arylamine group in the SMX hypersensitivity reaction, the absence of this group should reduce the likelihood of cross-reactivity with sulfonamide nonantibiotics. This question has become controversial, because some

Table 4
Summary of literature discussing sulfonamide cross-reactivity

Reaction	Testing	Interpretation
Anaphylaxis after IV furosemide [51]	Positive intradermal skin test with chlorothiazide, TMP-SMX, and furosemide; no oral challenges administered	Differences in structures/ metabolism of these drugs suggest rare immunological cross-reactivity [52]
33 Patients with urticaria/ angioedema or fixed drug eruption[53]	Prick/intradermal skin tests, oral challenges, and/or patch tests to procaine, furosemide, and a sulfonamide antimicrobial	No cross-reactivity between sulfonamide antimicrobials and furosemide or procaine observed
Development of edema, respiratory distress, and hemoglobinuria following acetazolamide administration (for the treatment of CHF) in a patient with a previous history of a 'sulfa' allergy[54]	None	Cross-reactivity between acetazolamide and sulfonamide antimicrobials not confirmed; symptoms possibly secondary to worsening of CHF[54,55]
16 Patients in whom a skin reaction developed following indapamide therapy[56]	11 Patients subsequently took chlorthalidone, hydrochlorothiazide, furosemide, epitizide, or clopamide without a relapse	Cross-reactivity between thiazides rare
Fixed drug eruption after indapamide therapy for hypertension[57]	Positive oral challenge to indapamide, SMX, and sulfadiazine, and negative oral challenge to furosemide	Cross-reactivity may be directed against metabolite of drug
82 Patients on sulfonyleurea; 8 patients had previous history of hypersensitivity reaction to sulfonamide[58]	All patients tolerating sulfonyleurea	Cross-reaction between sulfonamide antibiotics and sulfonyleurea unlikely
Thrombocytopenia after using tolbutamide for 2 years in a woman[59]	Exposed to hydrochlorothiazide 2 years later and within 2 days, thrombocytopenia developed	Does not confirm drug-induced thrombocytopenia
7 Of 34 patients taking oral sulfonyleurea had history or reaction to sulfonamide[58]	One of the patients, mild rash with sulfonyleurea; other 6 patients tolerated the oral antidiabetic agent	Supports hypothesis of low cross-reactivity between sulfonamide antimicrobials and sulfonamides
Fever and pustular eruption in a patient after celecoxib[60]	PBMCs from a SMX-allergic patient and this patient did not cross-react	Suggests that the sulfonamide structure does not account for the reaction
28 Immunocompetent patients with a history of sulfa antibiotic allergy: urticaria (7/28), cutaneous eruptions (9/28), other reactions(12/28)[47]	4/28 Patients had positive skin test to SMX; 2/10 had positive lymphocyte toxicity assay; all 28 tolerated initial dosing of celecoxib; 5/28 stopped celecoxib due to adverse effects	Supports hypothesis of low cross-reactivity between sulfonamide antimicrobials and sulfonamides

Abbreviations: CHF, congestive heart failure; IV, intravenous; PBMCs, peripheral blood mononuclear cells.

Adapted from Shapiro LE, Knowles SR, Weber E, Neuman MG, Shear NH. Safety of celecoxib in individuals allergic to sulfonamide: a pilot study. *Drug Saf* 2003;26:187–95.

patients report histories of reactions to sulfa antibiotics and sulfa nonantibiotics. Table 4 [49] summarizes several case reports and small experimental studies addressing sulfonamide cross-reactivity. In addition, a recently published epidemiologic study [50] addressed the question of sulfonamide cross-reactivity by evaluating the medical records of more than 20,000 patients. The investigators found that, for patients who previously reacted adversely to a sulfonamide antibiotic, the odds ratio for a reaction to another sulfonamide was 6.6; however, this same group of sulfonamide-allergic patients was more likely to report an adverse reaction to penicillin (odds ratio of 7.8). Patients with a history of a penicillin reaction were more likely to react to sulfonamide nonantibiotics than were patients with prior sulfonamide antibiotic reactions. It was concluded that sulfonamide cross-reactivity is unlikely, but that certain individuals have a general predisposition to adverse reactions to multiple drugs.

Summary

Sulfonamides have the potential to elicit many types of adverse drug reactions. Fortunately, severe reactions are uncommon. Significant progress has been made toward understanding the mechanism of hypersensitivity reactions to sulfonamide antibiotics, including the role of metabolic intermediates, the nature of carrier protein substrates, and the possible role of infection and toxic intermediates. There has also been significant progress in addressing the challenge posed by HIV-infected patients who have experienced adverse reactions to sulfonamide antibiotics. Most of these patients can now safely take the drug with the help of a desensitization protocol. Because there are no reliable diagnostic tests to augment the clinical history reported by the patient, for most non-HIV-infected patients presenting with sulfonamide allergy, it is appropriate to counsel indefinite avoidance of the drug. These patients do not necessarily need to avoid all sulfonamide-containing medications, because cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics seems to be uncommon.

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