

Sulfonamide cross-reactivity: Is there evidence to support broad cross-allergenicity?

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Approximately 3–6% of the general population is believed to be allergic to sulfonamides, which are synthetic derivatives of *p*-aminobenzenesulfonamide (sulfanilamide).^{1–4} Sulfonamide drugs can be structurally defined by the sulfonamide moiety (SO_2NH_2) and further divided into sulfonamide-containing antibacterials (Table 1) and sulfonamide-containing nonantibacterials.

Sulfonamide antibacterials include sulfacetamide, sulfadiazine, sulfamerazine, sulfamethoxazole, sulfanilamide, sulfapyridine, sulfasalazine, sulfathiazole, and sulfisoxazole. These agents contain a five- or six-membered nitrogen-containing ring attached to the N1 nitrogen of the sulfonamide group and an arylamine group (H_2N) at the N4 position of the sulfonamide group.^{1,3,4,11–17} The N1 and N4 substituents have been found to be predictors of immunologic response (Figures 1 and 2). The prescribing information for many of these agents includes recommendations related to sulfonamide allergy (Table 1).

Purpose. Published and manufacturer-provided data regarding potential cross-reactivity between antibacterial and nonantibacterial sulfonamide agents are reviewed.

Summary. An estimated 3–6% of the general population is allergic to sulfonamides and thus at risk for type I and other hypersensitivity reactions to sulfamethoxazole and other sulfonamide antibacterial agents. Concerns have been raised that a history of sulfa allergy may be associated with an increased risk of adverse reactions to a wide range of nonantibacterial sulfonamides, including certain antivirals, carbonic anhydrase inhibitors, cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs, loop and thiazide diuretics, and sulfonylureas; concerns have also been raised that patients who have experienced an allergic reaction to one nonantibacterial sulfonamide may be at risk for an adverse reaction to others. Structurally, none of the nonantibiotic sulfonamides exhibit both of the features shown to be responsible for

sulfonamide reactions (i.e., an N-containing ring attached to the N1 nitrogen of the sulfonamide group and an arylamine group at the N4 position), and only two agents (amprenavir and fosamprenavir) have the latter characteristic. A comprehensive literature search (1966–December 2011) identified nine case reports indicating possible cross-reactivity to sulfonamide medications; however, in most cases, adequate patient testing was not conducted to firmly establish either sulfa allergy or sulfonamide cross-sensitivity. The weight of evidence suggests that withholding nonantibacterial sulfonamides from patients with prior reactions to antibacterial sulfonamides or other nonantibacterial sulfonamides is not clinically justified.

Conclusion. A review of the professional literature and manufacturer-provided data did not find convincing evidence of broad cross-reactivity between antibacterial and nonantibacterial sulfonamide agents.

Am J Health-Syst Pharm. 2013; 70:1483–94

Most of the nonantibacterial sulfonamides (Table 2), such as loop diuretics, thiazide diuretics, carbonic anhydrase inhibitors, cyclooxygenase (COX)-2-selective nonsteroidal antiinflammatory drugs (NSAIDs), 5-hydroxytryptamine receptor ago-

nists, sulfonylureas, and antivirals, do not contain either of these structural features. None of the nonantibacterial sulfonamides have an N-containing ring attached to the N1 nitrogen of the sulfonamide group, and only amprenavir and fosampre-

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Christine Sommer, Pharm.D., and Mark Hogan, Pharm.D., are acknowledged for their review of the manuscript.

The authors have declared no potential conflicts of interest.

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DOI 10.2146/ajhp120291

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navir have an arylamine group at the N4 position.^{1,11,13,16,19}

The allergic reactions associated with sulfonamide antibacterials include the entire Gell–Coombs spectrum of hypersensitivity reactions.^{1,11,13} Type 1 reactions are immunoglobulin E (IgE)-mediated reactions such as urticaria, angioedema, and anaphylaxis. Patients who have had a type 1 reaction to a sulfonamide antibacterial have been found to have IgE antibodies to the parent drug, with the N1 heterocyclic ring found to be the immunogen recognized by IgE.^{1,11-15,20} IgE has the highest affinity for a 5-methyl-3-isoxazolyl heterocyclic ring at the N1 position, especially if a methyl group is in the β position on the isoxazole ring.²⁰⁻²² IgE has not been found to bind to the sulfonamide group.

There are three possible mechanisms by which a non-type-1 hypersensitivity reaction may be initiated.^{1,11} First, a parent sulfonamide antibacterial or reactive metabolite may bind to a native protein, stimulating a cellular or humoral immune response. Second, a parent sulfonamide antibacterial or reactive metabolite may bind to a cellular protein, causing direct cytotoxicity. Third, a parent sulfonamide antibacterial or metabolite could stimulate T cells to produce an immune response without haptentation or antigen presentation.

Non-type-1 hypersensitivity reactions to sulfonamide antibacterials are believed to be caused by metabolites of the antibiotics.^{1,2,4,11-13,15,17,20} Sulfonamide antibacterials undergo acetylation at the N4 nitrogen, which is mediated by the nonpolymorphic *N*-acetyltransferase (NAT) 1 enzyme.^{1,2,11,17} The sulfonamide antibacterials are also glucuronidated at the N1 sulfonamide nitrogen and hydroxylated at the C5 methyl group (at N1) and at the N4 position by cytochrome P-450 isoenzyme 2C9. The N4 hydroxylated metabolite is believed to be responsible for the initiation of many hypersensitivity reactions seen with sulfonamide antibacterials by forming a haptent.^{2,12,13,17}

This metabolite can oxidize to a reactive nitroso compound, which is acetylated by the NAT 2 enzyme or reduced by reaction with glutathione.

Individuals with a slow-acetylator phenotype or glutathione deficiency may be at an increased risk for sulfonamide antibacterial hypersensitivity.^{2,12} The nitroso metabolite can cause direct cytotoxicity or bind to T cells to induce an immune response responsible for skin exanthems like Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^{1,11,15} Sulfonamide nonantibacterials do not contain the same molecular structures and therefore do not produce similar metabolites.^{1,11,13,15,17,21}

The remainder of this article reviews the evidence for sulfonamide cross-reactivity found in the literature and discusses the practical likelihood of such cross-reactivity.

Literature review

In order to assess the level of published support for sulfonamide cross-reactivity, a comprehensive search of PubMed and MEDLINE covering the period 1966–December 2011 was conducted using the MeSH terms *allergy, hypersensitivity, immediate hypersensitivity, drug hypersensitivity, cross-reaction, sulfonamide, carbonic*

Table 1.

Sulfonamide Antibacterial Manufacturers' Recommendations Concerning Sulfonamide Allergies^{5-10,a}

Drug	Recommendations (in Contraindications Labeling Section)	Yr Labeling Approved by FDA
Sulfacetamide ⁵	Contraindicated in individuals who have a hypersensitivity to sulfonamides. Precautions: cross-sensitivity between different sulfonamides may occur.	1945
Sulfadiazine ⁶	Contraindicated in the following circumstances: hypersensitivity to sulfonamides.	1941
Sulfamethoxazole ⁷	Contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides.	1973
Sulfanilamide ⁸	Should not be used in patients known to be sensitive to this product or to the sulfonamides.	1965
Sulfasalazine ⁹	Contraindicated in patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates.	1950
Sulfisoxazole ¹⁰	Contraindicated in the following patient populations: patients with a known hypersensitivity to sulfonamides.	1953

^aFDA = Food and Drug Administration.

anhydrase inhibitor, COX-2 inhibitor, loop diuretic, sulfonylurea, thiazide, triptan, indapamide, tamsulosin, zonisamide, amprenavir, tipranavir, darunavir, probenecid, and mafenide. Relevant references from MEDLINE articles were also examined. Food and Drug Administration (FDA)-approved labeling for various drugs was reviewed for supporting data. Articles in foreign languages were omitted. The references of relevant articles were reviewed and included when appropriate. In addition to the more detailed information below, summary data on the literature reviewed are provided in an eAppendix (available with the full-text version of the article at www.ajhp.org).

Sulfonamide antibiotics and non-antibiotics. The literature search identified 17 articles on research pertaining to potential cross-reactivity among sulfonamide antibiotics and nonantibiotics and various drugs from other medication classes.

Strom et al. The investigators conducted a retrospective cohort study to examine the risk of allergic reactions within 30 days after the receipt of a sulfonamide nonantibacterial.³ The United Kingdom General Practice Research Database (UKGPRD) was used to collect data. Patients were included if they had received a systemic sulfonamide antibacterial and a prescription for a sulfonamide nonantibacterial within 60 days. The study group consisted of patients who contacted their doctor within 30 days if they believed they experienced an allergic reaction to the sulfonamide nonantibacterial. Ninety-six of 969 patients (9.9%) reported an allergic reaction after receiving a sulfonamide nonantibacterial. Only 1.6% of patients (315 of 19,257) without a previous allergy to sulfonamide antibacterials reported experiencing an allergic reaction to a sulfonamide nonantibacterial. Patients with a sulfonamide antibacterial allergy also had a greater risk of allergic reaction when receiving

Figure 1. The structure of sulfamethoxazole, a sulfonamide antibacterial.¹⁴

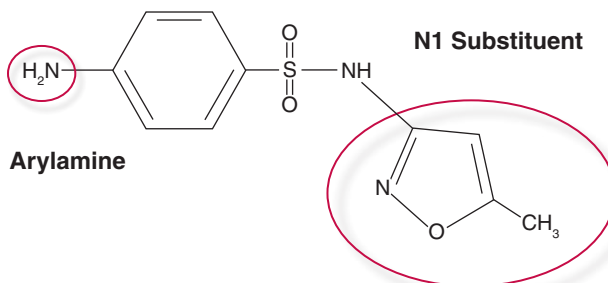
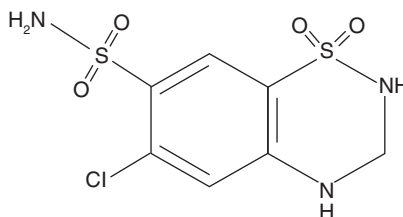


Figure 2. The structure of hydrochlorothiazide, a nonantibacterial sulfonamide. Hydrochlorothiazide does not have a five- or six-membered N-containing ring as the N1 substituent or an N4 arylamine.¹⁴



penicillin as opposed to a sulfonamide nonantibacterial (adjusted odds ratio [OR], 0.7; 95% confidence interval [CI], 0.5–0.9). Patients with a penicillin allergy were more likely to have an allergic response to a sulfonamide nonantibacterial (adjusted OR, 0.6; 95% CI, 0.5–0.8). Strom et al. concluded that while associations between hypersensitivity and both sulfonamide antibacterials and sulfonamide nonantibacterials exist, the associations appear to be due to a predisposition to allergic reactions rather than to cross-sensitivity with sulfonamide-containing drugs.

Hemstreet and Page. In a prospective observational study, the investigators sought to determine the frequency and nature of adverse drug reactions in patients with a sulfonamide allergy who received a potential cross-reacting drug. Ninety-four hospitalized patients with reported

sulfonamide allergies were included in the study. All of the patients were admitted to the University of Colorado Hospital from January to May 2002. The majority of patients were prescribed furosemide, hydrochlorothiazide, or a sulfonylurea. None of the patients experienced an adverse drug event during the study period. Forty patients (43%) had already been using a sulfonamide nonantibacterial for a mean of 6.2 years. Eight (20%) of the 40 patients were taking more than one sulfonamide nonantibacterial.

Tornero et al. In a clinical trial conducted to investigate the cross-reactivity between sulfonamide derivatives and *p*-amino compounds, Tornero et al.¹⁵ studied 28 patients with a history of fixed drug eruptions (FDEs) due to sulfonamide antibacterials. Patch testing was done with sulfamethoxazole and sulfadiazine;

Table 2.
Nonantibacterial Sulfonamides Marketed in the United States,
by Class^{18,a}

Drug	Yr Approved by FDA
Antivirals	
Amprenavir	1999
Darunavir	2006
Fosamprenavir	2003
Tipranavir	2005
Carbonic anhydrase inhibitors	
Acetazolamide	1953
Brinzolamide	1998
Dorzolamide	1994
Methazolamide	1959
COX-2 inhibitors	
Celecoxib	1998
Rofecoxib	1999
Valdecoxib	2001
Loop diuretics	
Bumetanide	1983
Furosemide	1966
Torsemide	1993
Sulfonylureas	
Acetohexamide	1964
Chlorpropamide	1958
Glimepiride	1995
Glipizide	1984
Glyburide	1984
Tolazamide	1966
Tolbutamide	1961
Thiazide diuretics	
Bendroflumethiazide	1959
Benzthiazide	1960
Chlorothiazide	1961
Chlorthalidone	1960
Cyclothiazide	1982
Hydrobenzthiazide	1959
Hydrochlorothiazide	1959
Hydroflumethiazide	1960
Methyclothiazide	1961
Polythiazide	1963
Quinethazone	1960
Triptans (5-HT₃ receptor agonists)	
Almotriptan	2001
Eletriptan	2002
Frovatriptan	2001
Naratriptan	1998
Rizatriptan	1998
Sumatriptan	1992
Zolmitriptan	1997
Miscellaneous	
Diazoxide	1973
Indapamide	1983
Metolazone	1973
Probenecid	1951
Tamsulosin	1997
Zonisamide	2000

^aCOX = cyclooxygenase, 5-HT₃ = 5-hydroxytryptamine type 3.

results were considered positive if an FDE lesion persisted for at least six hours. Patients also underwent controlled oral challenge testing (COCT) with sulfamethoxazole, sulfadiazine, sulfamethizole, furosemide, procaine, and glipizide; 42.8% of patients (6 of 14) and 31.8% of patients (7 of 22) with an FDE after sulfamethoxazole administration also reacted to COCT with sulfamethizole and sulfadiazine, respectively. The other drugs did not elicit an allergic response. Results showed that there is variability in cross-reactivity among the various sulfonamide antibacterials and that there is no cross-reactivity between sulfonamide antibacterials and other sulfonamide derivatives of *p*-amino drugs. The authors also stated that non-aromatic-containing sulfonamides, such as celecoxib, do not contain the essential arylamine to exhibit cross-reactivity with sulfonamide antibacterials.

Verdel *et al.* A case-control study by Verdel *et al.*¹⁶ evaluated how differences in the chemical structures of the sulfonamide drugs influence the risk of an allergic event. The authors used the UKGPRD to collect information on patients with a diagnosis of diabetes mellitus or a prescription for a drug with a diabetes mellitus indication ($n = 141,164$). Within this study population, a nested case-control study was conducted to find patients with at least one diagnosis of hypersensitivity or allergic reaction during the study period ($n = 3,362$); the date of their last recorded hypersensitivity or allergy event was recorded as the index date. The study population was reviewed for patients who had received a prescription for a sulfonamide drug in a 14-day time window prior to the index date and also for patients who had received a sulfonamide within one year before the index date (1,353 patients had or were taking a sulfonamide). The prevalence of current sulfonamide drug use was found to be higher among cases relative to the control

group (40.2% versus 28%; crude OR, 2.16; 95% CI, 1.92–2.43). The sulfonamides were all classified according to the presence or absence of the N1 substituent and the N4 arylamine. The results showed that sulfonamides with both the N1 substituent and an arylamine at the N4 position were clearly associated with allergic reactions (adjusted OR, 3.71; 95% CI, 1.40–9.81).

Naisbitt et al. The researchers conducted a study to determine if bioactivation of sulfamethoxazole to chemically reactive metabolites and subsequent protein conjugation are involved in sulfamethoxazole hypersensitivity.¹⁷ Flow cytometry showed binding of *N*-hydroxy and nitroso metabolites of sulfamethoxazole to the surface of white blood cells (WBCs). The parent drug did not bind to WBCs. Cellular haptenation of a sulfamethoxazole–nitroso metabolite was found to be reduced by the presence of glutathione. The authors found that if an imbalance between oxidation of sulfamethoxazole and the reduction of toxic metabolites generated occurs, the toxic metabolites haptenate on body proteins and can possibly cause drug hypersensitivity.

Carrington et al. The investigators hypothesized that patients with an immediate hypersensitivity reaction to sulfonamides express IgE that can bind to an N4-sulfonamidoyl determinant.²⁰ They tested the serum of 10 patients with a history of hypersensitivity to sulfonamides. Significant binding was seen in 3 patients with a sulfonamide allergy. The N4-sulfonamidoyl determinant was the major determinant recognized by IgE. The *p*-aminophenyl group was not the dominant feature of the determinant. Sulfanilic acid was not found to inhibit binding. The substituted sulfonamide region was found to be the dominant feature of the ligand.

Harle et al. After developing an immunoassay to detect sulfamethoxazole-

reactive IgE antibodies in the serum of patients who experienced anaphylaxis after ingesting sulfamethoxazole–trimethoprim, Harle et al.²² conducted inhibition experiments with various sulfonamides to determine the structural specificity of sulfamethoxazole-reactive IgE antibodies in three patients. The parent sulfonamide, sulfanilamide, was found to be a very poor inhibitor, whereas sulfamethoxazole, sulfamerazine, and sulfamethizole were more potent inhibitors. The 5-methyl-3-isoxazolyl group on sulfamethoxazole was found to be the antigenic determinant for all three patients. The 5-methyl group was especially important for IgE antibody recognition.

Nassif et al. The investigators showed that sulfamethoxazole initiated T-cell activation in patients who had TEN after exposure to trimethoprim–sulfamethoxazole.²³ T-cell activation resulted in direct cytotoxicity against keratinocytes, resulting in cell lysis at normal sulfamethoxazole concentrations. The hydroxylamine and nitroso metabolites were not found to cause T-cell activation at normal concentrations. Nine other sulfonamides were tested to evaluate the potential for cross-reactivity. Sulfamethizole, sulfisoxazole, and sulfadiazine showed significant cross-reactive cytotoxicity, but the six other sulfonamides (sulfapyridine, sulfasalazine, tolbutamide, chlorpropamide, glyburide, and hydrochlorothiazide) did not. The three-dimensional structure of the three cross-reacting drugs was found to be essential in allowing the major histocompatibility complex drug complex to interact with the T-cell receptor.

Morgan et al. Eight years of inpatient and outpatient records for patients with a reported sulfonamide allergy who had received a sulfonamide nonantibacterial were examined; 215 patients' records were studied, and 247 drug dispensations meeting the search criteria

were found.²⁴ Twenty-five patients (11.6%) received more than one class of sulfonamide nonantibacterial. Only 4 (1.6%) minor adverse reactions were listed (due to glyburide, sumatriptan, furosemide, and celecoxib); 80% of the prescriptions were refilled, which suggests that the drugs were well tolerated.

Schnyder et al. The researchers analyzed the proliferative response of peripheral blood mononuclear cells and T-cell clones from patients with allergy to sulfamethoxazole, sulfamethoxazole–hydroxylamine metabolites, and sulfamethoxazole–nitroso compounds.²⁵ Most of the T-cell clones were specific for the unbound sulfamethoxazole. Only a small fraction of the T-cell clones responded to the reactive metabolites or were cross-reactive. T-cell clones were found to be able to recognize both bound and unbound sulfamethoxazole but were more apt to recognize unbound sulfamethoxazole.

Depta et al. The investigators examined whether chemically inert drugs can stimulate T cells through their T-cell receptor (TCR) and if cross-reactivity to various related compounds is possible.²⁶ T-cell clones isolated from a patient with hypersensitivity to sulfamethoxazole were used for the experiments. The T-cell clones reacted to sulfamethoxazole only when antigen-presenting cells were present. Cross-reactivity was found to be dependent on the degree of TCR expression. High T-cell expression increased the likelihood of structurally related compounds cross-reacting. On the other hand, sulfamethoxazole-specific T-cell clones did not cross-react with sulfonamide derivatives such as celecoxib, furosemide, and glyburide. The clones only reacted with sulfonamides having the sulfanilamide core. T-cell reactivity to drugs was found to be solely determined by the TCR, with the density of the TCR directly correlated with the cross-reactivity of structurally similar compounds.

Britschgi et al. In a study to investigate the involvement of T cells in drug-induced acute generalized exanthematous pustulosis, Britschgi et al.²⁷ examined four patients with various allergies. One patient had generalized erythema, pustules, and a fever after taking sulfamethoxazole-trimethoprim and clarithromycin. Another patient had generalized erythema and pustules after ingesting celecoxib. The other patients were allergic to nonsulfonamide substances. T-cell cultures and proliferation assays were conducted on all patients. Three patients were found to have a strong T-cell sensitization to amoxicillin and sulfamethoxazole. Britschgi et al. also analyzed the T cells to determine if there was cross-reactivity between celecoxib and sulfamethoxazole. They found that there was no cross-reactivity between peripheral blood mononuclear cells in over 200 sulfamethoxazole-specific T-cell clones from a sulfamethoxazole-allergic patient. The sulfonamide structure was not found to account for T-cell-mediated cross-reactivity.

Ahmad et al. The researchers conducted a study to examine the cross-reactivity of drugs and antibodies in order to predict if structures share the same antigenic potential toward a sensitized individual.²⁸ A biosensor was used to test the binding of sulfamethazine and furosemide to antisulfamethazine or antifurosemide antibody in the presence of other structurally related sulfonamides. A total of 13 other sulfonamides were tested for cross-reactivity. It was determined that a five- or six-membered aromatic substituent on the sulfonamide group was a prerequisite for antibody binding. The diuretics (diazoxide, furosemide, acetazolamide, bumetanide, and hydrochlorothiazide), hypoglycemics (tolazamide), and sulfanilamides did not cross-react with the sulfamethazine antibodies. Only sulfamethizole and sulfamerazine showed possible cross-reactivity. The investigator noted

that the type and size of the heterocyclic atom were important for five-membered aromatic substituents. The sulfonamide-containing moiety was not found to be a potent indicator of drug cross-reaction and antigenic potency. The results showed that predicting a cross-reaction solely on the basis of the molecule having a sulfonamide moiety is not likely.

Roujeau et al. A case-control study was conducted to quantify the risk of SJS or TEN with the use of specific drugs.²⁹ Two hundred forty-five patients with SJS or TEN and 1147 control patients who were hospitalized for other reasons were studied. An increased risk for SJS or TEN was noted in association with drugs that are used for short periods of time, such as sulfamethoxazole-trimethoprim (relative risk [RR] estimate, 160), other sulfonamide antibacterials (crude RR, 172; 95% CI, 75–396), chlormezanone (crude RR, 62; 95% CI, 21–188), aminopenicillins (multivariate RR, 6.7; 95% CI, 2.5–18), quinolones (multivariate RR [estimated only in cases involving at least 3 exposed case patients and controls], 10; 95% CI, 2.6–38), and cephalosporins (multivariate RR, 14; 95% CI, 3.2–59). Another high-risk medication category was drugs used for months or years, such as carbamazepine (multivariate RR, 12; 95% CI, 3.5–3.8), phenobarbital (multivariate RR, 8.7; 95% CI, 3.2–23), phenytoin (multivariate RR, 8.3; 95% CI, 1.5–45), valproic acid (multivariate RR, 8.3; 95% CI, 1.8–40), oxicam NSAIDs (multivariate RR, 22; 95% CI, 6.2–74), allopurinol (multivariate RR, 5.5; 95% CI, 2.0–15), and corticosteroids (multivariate RR, 4.4; 95% CI, 1.9–10). Thiazide diuretics (multivariate RR, 1.4; 95% CI, 0.5–2.8), furosemide (multivariate RR, 0.3; 95% CI, 0.05–1.6), and sulfonylureas (multivariate RR, 0.7; 95% CI, 0.1–3.2) were not associated with a significant increase in risk.

Naisbitt et al. The site of antigen formation for sulfamethoxazole was

investigated in an animal study.³⁰ Male Wistar rats were given sulfamethoxazole, sulfamethoxazole-hydroxylamine, or nitroso-sulfamethoxazole. Flow cytometry was used to determine antigen formation on the cell surface, and ex vivo T-cell proliferation was assessed to determine the immunogenicity of sulfamethoxazole. Antigen formation on the surface of lymphocytes occurred only with administration of nitroso-sulfamethoxazole. Bioactivation of sulfamethoxazole to the reactive nitroso metabolite appears to be critical for the development of a primary cellular immune response.

Gruchalla and Sullivan. The researchers skin tested (via prick and intradermal tests) 44 patients with a history of sulfonamide allergy and 6 patients who had been exposed to sulfamethoxazole without a reaction.³¹ The major antigenic determinant for sulfamethoxazole is believed to be the N4 sulfonamidoyl group. A multivalent N4 sulfonamidoyl-substituted poly-L-tyrosine carrier used in the skin tests produced reactivity, indicating that IgE antibodies to the N4-sulfonamidoyl determinant are present in patients with a sulfamethoxazole allergy.

Cribb and Spielberg. The oxidation of sulfamethoxazole to its hydroxylamine metabolite by human liver microsomes was investigated in vitro as well as in vivo (by detection in the urine).³² Three healthy volunteers were given 1000 mg of sulfamethoxazole. Analysis of 24-hour urine samples showed that the sulfamethoxazole-hydroxylamine metabolite constituted a mean $\pm$ S.D. of $3.1\% \pm 0.7\%$ of the drug excreted in the urine during the study period, confirming that it is an in vivo metabolite of sulfamethoxazole. Two human livers were used to show that sulfamethoxazole is oxidized to the hydroxylamine by liver microsomes in a nicotinamide adenine dinucleotide phosphate-dependent process.

Carbonic anhydrase inhibitors. Three case reports and one case series were found for carbonic anhydrase inhibitors and sulfonamide allergies.³³⁻³⁶ Gallerani et al.³³ presented the case of a patient who developed anaphylactic shock after ingesting acetazolamide even though he had been taking hydrochlorothiazide without problems and later tolerated therapy with furosemide. In another case report, by Mancuso and Berdondini,³⁴ a patient developed severe erythema, edema, and exudation of his eyelids and upper cheeks, as well as conjunctival hyperemia, after application of dorzolamide ophthalmic drops; patch tests with sulfonamide antibacterials were negative. In another case, reported by Tzanakis et al.,³⁵ a patient developed nausea, cyanosis, and acute respiratory failure after receiving acetazolamide. The patient later had a positive result on a skin test using a "sulfonamide skin solution." Of the three case reports, only the last suggested cross-reactivity of carbonic anhydrase inhibitors and sulfonamide antibacterials; however, the evidence for cross-reactivity was not strong because the patient was only tested once using a single solution of sulfonamide.³⁵

Lee et al.³⁶ conducted a retrospective case-series study to determine if acetazolamide or furosemide could produce an allergic cross-reaction in patients with self-reported sulfa allergy. All charts indicating the presence of intracranial hypertension and sulfa allergy in patients treated with either acetazolamide or furosemide at one medical center during the period 1972–2003 were reviewed. Of the 363 charts reviewed, only 34 documented patient reports of sulfa allergy. Thirteen of the patients were treated with acetazolamide, 7 patients were treated with furosemide, and 14 patients received both drugs. Ten patients (37%) given acetazolamide had no documented allergic cross-reactions to sulfonamides, and only 2 patients' charts had documentation

of urticaria after acetazolamide use. The other 15 cases (55%) involved other types of predictable adverse reactions to acetazolamide (e.g., paresthesias, fatigue). The 7 patients treated with furosemide had no recorded unpredictable adverse drug reactions or allergic cross-reactions. The 14 patients who received both drugs were without documented adverse effects.

COX-2-selective NSAIDs. Eleven case reports,³⁷⁻⁴⁷ one case series,⁴⁸ one meta-analysis,⁴⁹ and one cross-reactivity study⁵⁰ regarding potential cross-reactivity of COX-2-selective NSAIDs and sulfonamide allergies were found in the primary literature. Although there are a handful of relevant case reports pertaining to the COX-2-selective NSAIDs, only one (from Glasser and Burroughs³⁷) indicated possible cross-reactivity. Two case reports (from Schuster and Wüthrich³⁸ and Ernst and Egge³⁹) were inconclusive; one case report (from Kaur et al.⁴¹) involved rofecoxib, which has a methylsulfone moiety but not a sulfonamide moiety; two case reports (from Galan et al.⁴⁴ and Carrillo-Jimenez and Nurnberger⁴⁵) involved celecoxib-induced cholestatic hepatitis. In the case reported by Galan et al., the patient was also taking other medications known to be hepatotoxic (indapamide, glyburide, conjugated estrogens, and atorvastatin), and two of her longstanding medications (indapamide and glyburide) were sulfonamide nonantibacterials. The labeling for celecoxib (Celebrex, G.D. Searle LLC, Division of Pfizer Inc.) states in the precautions section that there are postmarketing reports of fulminant hepatitis and elevated liver enzymes; it does not mention those effects in relation to the drug being a sulfonamide.⁵¹

Patterson et al.⁴⁹ conducted a meta-analysis to investigate the incidence of allergic reactions due to celecoxib in patients with a history of hypersensitivity reactions to sulfonamides or currently taking a sulfon-

amide. Fourteen international arthritis trials were examined, and a total of 11,008 patient cases meeting the study criteria were identified. Three analyses were conducted: (1) a comparison of the incidence of allergic reactions in sulfonamide-hypersensitive patients receiving celecoxib versus a placebo or an active comparator, (2) a comparison of the incidence of allergic reactions in patients taking celecoxib with and without other sulfonamide-containing medications (diuretics, sulfonylureas), and (3) a comparison of the incidence of allergic reactions in patients using celecoxib relative to patients receiving nonsulfonamide NSAIDs. A subset of patients with a history of sulfonamide hypersensitivity were found to have a threefold to sixfold higher chance of a dermatological reaction relative to the entire study cohort. The trend was found to be consistent for all three groups (those receiving celecoxib, those receiving nonsulfonamide-containing NSAIDs, and placebo users). The potential for cross-sensitivity of celecoxib and other sulfonamide-containing medications appeared comparable to that of a placebo and nonsulfonamide-containing NSAIDs.

Shapiro et al.⁵⁰ conducted a study to assess the cross-reactivity of sulfonamide antimicrobials and celecoxib in patients with a known allergy to sulfonamide antimicrobials. All patients ($n = 28$) underwent skin-prick tests, intradermal tests, lymphocyte toxicity assays, or oral-challenge tests to determine if they demonstrated a hypersensitivity reaction to sulfamethoxazole–trimethoprim or celecoxib. All patients were able to tolerate an oral challenge with celecoxib. Fifteen patients continued to take celecoxib without any problems. Moreover, differences in structure, metabolism, and site specificity suggest a low rate of cross-sensitivity to celecoxib and sulfonamide antimicrobials.

Clinical trial data from the manufacturer of valdecoxib (Pharmacia

Corporation, merged with Pfizer Inc. in 2003) indicated that patients with a sulfa allergy did not have an increased incidence or severity of cutaneous or systemic allergic reactions when compared with users of other NSAIDs (Dixon M, Pharmacia Corporation, personal written communication, 2002 May 10). Other clinical data on file with the manufacturer regarding 500 patients with self-described sulfonamide allergy did not demonstrate any significant differences between valdecoxib or other NSAIDs and placebo use for any allergy-related adverse drug reaction. The information provided stated that valdecoxib lacks an arylamine group at the N4 position and a heterocyclic ring with an N1 methyl group and, therefore, should not be expected to form active metabolites associated with sensitization. Given the weight of available evidence, nonarylamine sulfonamides (the COX-2 inhibitors valdecoxib and celecoxib, as well as furosemide and acetazolamide) should not be expected to cross-react with sulfonamide antimicrobials in clinical practice.

Loop diuretics. The literature search revealed six case reports involving loop diuretics and sulfonamide allergies.⁵²⁻⁵⁷ Two case reports (from Dominguez-Ortega et al.⁵² and Alim and Patel⁵³) indicated possible cross-reactivity. In one of these reported cases, a woman developed anaphylaxis after taking furosemide.⁵³ Transdermal skin tests with furosemide and sulfamethoxazole were positive; however, skin testing is not always accurate, and the patient did not have any other tests done or undergo skin testing with any other sulfonamides. The evidence presented in two other relevant case reports^{54,55} was inconclusive. Wall et al.⁵⁵ discussed a patient with a history of SJS after receiving trimethoprim-sulfamethoxazole and the development of a rash on separate occasions after being given furosemide and

glyburide. The patient underwent a graded-dose challenge with torsemide but did not have any signs of an allergic reaction and tolerated torsemide 40 mg/day. The other case, reported by Hansbrough et al.,⁵⁵ involved a patient who the authors postulated was originally sensitized to hydrochlorothiazide because he developed anaphylaxis after his first dose of furosemide. However, although he reacted to many other drugs when undergoing prick and intradermal tests, he was never tested with hydrochlorothiazide. In the remaining two case reports, both involving the same patient and reported by Juang et al.,^{56,57} a woman who received furosemide developed pancreatitis, which is not a typical sign of an allergic reaction.

Sulfonylureas. There have been three case reports involving sulfonylureas and possible sulfonamide cross-reactivity.⁵⁹⁻⁶¹ Bretza⁵⁹ reported on a patient with a history of allergy to tolbutamide (manifested by petechial rash and thrombocytopenia) who developed hypotension, tachycardia, petechial eruptions, and thrombocytopenia after taking hydrochlorothiazide. However, thrombocytopenia is not a typical allergic reaction. Bukhalo et al.⁶⁰ discussed the case of a 33-year-old man who was diagnosed with leukocytoclastic vasculitis (LCV) associated with glyburide use. He had a history of allergy to sulfamethoxazole-trimethoprim (generalized cutaneous eruption); however, he was currently taking furosemide without problems. The authors of the case report noted that LCV is typically caused by drugs in only 13% of cases and that it usually develops 7–10 days after treatment is started. In this case, LCV appeared 2 days after the initiation of treatment. In another case report, published by Fisher,⁶¹ a patient tolerated certain sulfonamide nonantibacterials but not others.

Thiazides and related diuretics. The literature search revealed a

retrospective chart review and five case reports involving thiazides or related diuretics and sulfonamide allergies.⁶²⁻⁶⁷ In one case, reported by Mineo and Cheng,⁶⁵ a woman with septic shock due to pneumonia was discharged from the hospital and started on furosemide. Her current drug therapy included hydrochlorothiazide, and she had a documented history of allergy to penicillin and sulfamethoxazole. She was later readmitted twice for similar symptoms; however, on the third admission, it was suspected that she had an anaphylactic reaction to hydrochlorothiazide because, unbeknownst to her doctors, the drug had been restarted before the most recent two hospital admissions. The patient never underwent allergy testing to determine if the reaction constituted true anaphylaxis or if hydrochlorothiazide was the drug responsible. De Barrio et al.⁶⁶ presented a case of an FDE involving indapamide. The patient underwent controlled oral challenge tests with various sulfonamides. Tests with sulfamethoxazole and sulfadiazine were positive, but furosemide was tolerated by the patient. Gales and Gales⁶⁷ reported the case of a patient with a history of possible sulfonamide allergy who developed erythema multiforme after receiving indapamide.

Stricker and Biriell⁶² reviewed reported cases of indapamide-related adverse skin reactions in the United Kingdom and the Netherlands. The Netherlands Centre for Monitoring of Adverse Reactions to Drugs presented 16 cases of rash due to indapamide, while the WHO Collaborating Centre for International Drug Monitoring Programme reported 188 cases. In the 16 Netherlands cases, all the reactions occurred the first time that the patient took indapamide. Eleven of these patients tolerated chlorthalidone, clopamide, epitizide, furosemide, and hydrochlorothiazide without any adverse drug reactions. As many drugs with a close structural resemblance to

indapamide were tolerated by the patients, this suggested that the allergic reactions seen with indapamide were directed not against the sulfonamide side chain but possibly against a reactive intermediate.

5-Hydroxytryptamine agonists.

The literature search identified a single retrospective chart review, from Newman et al.,⁶⁸ discussing 5-hydroxytryptamine agonists (i.e., triptans) and sulfonamide cross-reactivity. The study was conducted to determine if the differences in molecular structure between sumatriptan and sulfonamide antibacterials make cross-sensitivity unlikely. Charts at St. Luke's-Roosevelt Headache Institute were reviewed to identify patients with a prior allergic reaction to a sulfonamide antibacterial who later received treatment with sumatriptan. Fifteen patients met the case inclusion criteria, but none had any reported adverse effects from sumatriptan therapy.

Antivirals. There are no published case reports of hypersensitivity to amprenavir or fosamprenavir in patients with a history of sulfonamide allergy. There is one case report (by Kohli-Pamnani et al.⁶⁹) of a patient with late-stage human immunodeficiency virus (HIV) disease who developed a rash after starting amprenavir therapy, but she had previously tolerated long-term therapy with sulfamethoxazole-trimethoprim.

Data from the manufacturer of amprenavir (GlaxoSmithKline, Research Triangle Park, NC) revealed that 16 patients with a sulfonamide allergy were prescribed the protease inhibitor during clinical trials.^{70,71} Five (31%) patients had a rash that resulted in them discontinuing the drug. The manufacturer indicated that abacavir was being taken concurrently during the clinical trials and could have contributed to the rash seen in 2 of the patients. In another study cited in the prescribing information for amprenavir,⁷¹ 65 patients who had previously received

a sulfonamide took amprenavir; 19 of the patients had a history of rash due to sulfonamides. Seven (37%) of those 19 patients developed a rash while taking amprenavir compared with 10 of 46 patients (22%, $p = 0.208$; not significant) without a history of sulfonamide-induced rash; 13 of the 17 patients who developed a rash were also receiving efavirenz, abacavir, or both. It was concluded that the use of amprenavir and a sulfonamide concurrently did not appear to increase the risk of rash in clinical trial participants.

Data from the manufacturer of fosamprenavir (Lexiva, GlaxoSmithKline) indicated that in Phase III trials, the incidence of rash in patients taking fosamprenavir was the same as that in patients with a history of sulfa allergy and those not allergic to sulfonamides (Martinez W, GlaxoSmithKline, personal written communication, 2007 Sep 21). The manufacturer indicated that fosamprenavir was a derivative of sulfanilamide and recommended caution when using the protease inhibitor in patients with a history of sulfa allergy.

Information provided by the manufacturer of tipranavir (Aptivus, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) indicated there is one published article regarding tipranavir cross-reactivity.⁷⁴ The manufacturer of tipranavir recommends caution when using tipranavir in patients with a known sulfa allergy; however, the manufacturer has noted that tipranavir does not contain an arylamine and the potential for cross-sensitivity is unknown (Oakes M, Boehringer Ingelheim Pharmaceuticals, personal written communication, 2007 Sep 24). In support of that position, the manufacturer has cited the results of the RESIST studies,⁷⁴ which evaluated the risk of rash development in patients with a history of a rash due to a sulfonamide while receiving tipranavir with ritonavir.⁷² Among a total of 1400 patients, 135

patients had a history of rash while taking a sulfonamide. Only 12 (8.9%) developed a rash while taking tipranavir and ritonavir combination therapy, as compared with 11 patients (9.4%) taking a comparator protease inhibitor and ritonavir.

Only one pertinent case report involving darunavir was found in the literature.⁷³ A man with HIV infection developed bleeding eruptive lesions of the oral mucosa, maculopapular lesions, conjunctivitis, fever, and odynophagia four months after his antiretroviral regimen had been changed from tenofovir, lopinavir with ritonavir, and nevirapine to darunavir and abacavir with lamivudine. He reported an unspecified allergic reaction to sulfa-based drugs. He was diagnosed with TEN. No testing was done to determine if darunavir or abacavir might have been responsible for the reaction; both of these drugs have been associated with TEN, with abacavir cited in relatively more cases.

Information from the manufacturer of darunavir (Tibotec Therapeutics, renamed Janssen Therapeutics, Division of Janssen Products, LP, Titusville, NJ) stated that the rate of rash observed in patients with a sulfa drug allergy who received darunavir was not different than that observed in control patients with no known sulfa allergy (Portnoy A, Tibotec Therapeutics, personal written communication, 2007 Sep 24).

Miscellaneous nonantibacterial sulfonamides. Data from the manufacturer of tamsulosin (Boehringer Ingelheim Pharmaceuticals) indicated that there are very few post-marketing reports of hypersensitivity to tamsulosin in patients with a documented sulfonamide allergy (Polistena E, Boehringer Ingelheim, personal written communication, 2007 Sep 21). Our literature search did not reveal any case reports of potential cross-reactivity with tamsulosin. Tamsulosin is a nonarylamine sulfonamide derivative. The package

insert does not list a sulfonamide allergy as a contraindication to therapy but recommends caution if the patient has reported a serious sulfonamide allergy.⁷⁴ In the aforementioned personal communication, the manufacturer commented that, based on postmarketing experience and medical literature, it is unclear if sulfonamide cross-reactivity occurs.

The literature search found three pertinent articles on zonisamide: one case report (by McJilton and Ramsay⁷⁵) indicating a lack of sulfonamide cross-reactivity, one retrospective chart review,⁷⁶ and one clinical study.⁷⁷

Ritter et al.⁷⁷ conducted a retrospective chart review that identified 15 adults and children who had reported a sulfa allergy manifesting as a rash and had been treated with zonisamide. None of the patients had a rash or other type of allergic reaction while taking zonisamide.

Neuman et al.⁷⁷ conducted a study to determine if cross-sensitivity exists among zonisamide, other anticonvulsants, and sulfamethoxazole. Patients included in the study had hypersensitivity reactions after receiving antiepileptic drugs (carbamazepine, phenytoin, or phenobarbital) or sulfamethoxazole. A lymphocyte toxicity assay was used for in vitro testing of sulfamethoxazole and the specific anticonvulsant responsible for each reaction. Two patients exhibited a positive assay result when tested with sulfamethoxazole and zonisamide. Both of these patients developed rash, fever, and hepatic involvement.

Two case reports (by Fernandez et al.⁷⁸ and Sanz de Galdeano et al.⁷⁹) indicated a lack of cross-reactivity between sulfanilamide and mafenide (a synthetic anti-infective agent that is closely related chemically but not pharmacologically to the sulfonamides). Patients in both case reports developed erythematous lesions after using an ointment containing both mafenide and sulfanil-

amide. The results of patch testing with all of the ingredients of the ointment were positive for mafenide but not for sulfanilamide.

Discussion

Nine single-case reports suggest a possible cross-sensitivity between the sulfonamide antibacterials and non-antibacterial sulfonamides. However, in many of these case reports, testing was not conducted to precisely determine the cause of the allergic reaction or to determine if the patient exhibited cross-sensitivity or if the reactions to two sulfonamide derivatives were merely coincidental. It has been suggested that patients who are allergic to multiple drugs may have a "multiple drug allergy syndrome," in which a person who is allergic to one drug is more likely to be allergic to other drugs.³

There is still a question as to whether or not the unmetabolized, nonhaptened parent drug can elicit a humoral immune response.^{1,11,24} Most studies have shown that patients usually do not produce immunoglobulin G or M antibodies against the parent sulfonamide antibacterial. While it may be possible for the sulfonamide antibacterials and nonantibacterials to stimulate T cells via recognition of a common hapten, it is not likely that T cells can recognize the sulfonamide moiety. This is a potential concern, as many severe cutaneous reactions are mediated by T cells. Mechanistic and observational evidence suggests that a shared T-cell mechanism is not likely due to the stereospecificity required for an interaction with a T-cell receptor.^{1,11,23,25-27}

Many of the sulfonamide non-antibacterials have been available for many years (Table 2). The non-antibacterial sulfonamides are often called sulfonamide derivatives because they were derived from the original sulfonamide antibacterials.

When these drugs were first approved for marketing, the hapten re-

sponsible for the IgE-mediated or idiosyncratic reactions was not known, and it appears that it was common practice to include a broad general warning in the prescribing information if a drug had a sulfonamide in its structure.¹⁴ The prescribing information for these drugs has never been updated to reflect a lack of evidence to support the inclusion of these warnings; this all-inclusive approach may be taken for legalistic purposes. There are no studies to support the contraindications and warnings seen in the current prescribing information for nonantibacterial sulfonamides, and new drugs with sulfonamide structures are frequently given a "sulfa class effect" warning.¹⁴

Although FDA-approved prescribing information is periodically updated, there appears to be a lack of incentive to update the information and change warnings regarding sulfonamide cross-reactivity. It is also unlikely that any manufacturer would conduct allergy challenge tests in patients who have experienced a prior serious hypersensitivity reaction to a sulfa antibiotic. However, the reluctance to update the labeling of sulfonamide nonantibacterials on the basis of actual evidence versus theoretical suppositions has a significant effect on health care delivery. An increased number of allergy alerts involving sulfonamides are generated through automated clinical decision-support systems; these alerts are often ignored and may be a factor in creating alert fatigue. More broadly, valuable therapeutic options may be avoided in patients because of unsubstantiated beliefs that all sulfonamides are cross-reactive.

Practitioners should be aware of the relative lack of evidence to support cross-reactivity and educate colleagues on the need for improved documentation of allergies to specific compounds. In our view, nine case reports over 20 years, primarily related to diuretics, do not constitute a strong clinical justification to deny

nonantibacterial sulfonamides to patients who are allergic to sulfonamide antibacterials or other nonantibacterial sulfonamides.

Conclusion

A review of the professional literature and manufacturer-provided data did not find convincing evidence of broad cross-reactivity between antibacterial and nonantibacterial sulfonamide.

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