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Sulfa Drugs and the Sulfa-allergic Patient

Health Canada Product Labeling Listed by Exception

(Last modified September 2008)

Sulfonamide-Containing Agents: Summary of Cross-Reactivity Information

Drug	FDA Product Labeling Recommendations in Sulfonamide Allergy[1,2,12]	Comments[1,2,12]
Sulfonylarylamines		
Antibiotics		
Sulfadiazine, Sulfamethoxazole, Sulfisoxazole, Sulfapyridine	Contraindicated	Contraindications include ophthalmic (sodium sulfacetamide), topical (silver sulfadiazine [*SSD, Silvadene*]), and vaginal products (triple sulfa, sulfanilamide) in addition to oral and parenteral preparations.
Protease Inhibitors		
Amprenavir (*Agenerase*)	Precaution[6]	Labeling cautions that the potential for cross-sensitivity with these agents and sulfonamides is unknown. These agents should be used with caution in patients with a sulfonamide allergy.[6,7]
Fosamprenavir (*Lexiva*) (*Telzir* – Canada)	Precaution[7]	
Nonsulfonylarylamines		
Carbonic Anhydrase Inhibitors		
Acetazolamide (*Diamox*)	Contraindicated, also listed in warnings (Precaution-Health Canada)[14]	Labeling warns that due to severe reactions to sulfonamides, sensitizations may recur when a sulfonamide is readministered regardless of route of administration. This warning includes the ophthalmic preparations (brinzolamide and dorzolamide) because they are absorbed systemically. Two case reports suggest a connection between an anaphylactic reaction with acetazolamide and sulfonamide allergy.
Brinzolamide *(Azopt*)	Warning	
Dorzolamide (*Trusopt*)	Warning	
Methazolamide (*Neptazane*) (*Apo-Methazolamide* – Canada)	Warning (Precaution – Health Canada)	

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Drug	**FDA Product Labeling Recommendations in Sulfonamide Allergy**[1,2,12]	**Comments**[1,2,12]
Nonsulfonylarylamines (cont.)		
Cyclooxygenase 2 (COX-2) Inhibitors		
Celecoxib (*Celebrex)*	Contraindicated	In case reports, celecoxib and valdecoxib have been suggested to cross-react with other sulfonamides. Incidence of allergic reactions to celecoxib was evaluated in three meta-analyses. Combined findings concluded that the risk of cross-reactivity between celecoxib and other sulfonamides is no greater than that seen with placebo or other comparators. Rofecoxib is a sulfone, not a sulfonamide, cross-sensitivity is likely not a concern.
Valdecoxib (*Bextra*)	Contraindicated	
Loop Diuretics		
Bumetanide (*Bumex*) (*Burinex* – Canada)	Warning (Contraindicated and also listed as warning by Health Canada)	Some sources recommend that if a diuretic is used in a patient with a history of sulfonamide allergy, the first dose should be reduced and given under medical supervision. Referral to an allergist may be warranted for patients who have had a severe allergic reaction to a sulfonamide. Ethacrynic acid does not contain a sulfa group and is a possible alternative in sulfonamide-allergic patients. Bumetanide and furosemide product labeling contain statements that patients may also be allergic to these drugs if they are allergic to sulfonamides. One case report suggests cross-sensitivity between furosemide and other sulfonamides. Torsemide is contraindicated in patients allergic to sulfonylureas because its chemical structure is a pyridine sulfonylurea. However, none of the product labeling for sulfonylureas contain statements regarding the use of torsemide. One patient that developed angioedema with torsemide treatment was later found to be sulfonamide-allergic.
Furosemide (*Lasix*)	Precaution	
Torsemide (*Demadex*)	Contraindicated in patients allergic to sulfonylureas	

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Drug	**FDA Product Labeling Recommendations in Sulfonamide Allergy**[1,2,12]	**Comments**[1,2,12]
Nonsulfonylarylamines (cont.)		
Sulfonylureas		
Chlorpropamide (*Diabinese*) (*Apo-Chlorpropamide* – Canada)	None	There is one case report of contact dermatitis with tolbutamide in a patient with sensitivity to sulfanilamide vaginal cream. After discontinuation of tolbutamide, therapy was changed to chlorpropamide which was tolerated without difficulty. There is also one case report which describes an allergic reaction to glyburide in a patient with a known allergy to sulfamethoxazole.
Glimepiride (*Amaryl*)	None	
Glipizide (*Glucotrol*)	None	
Glyburide (*Diabeta, Micronase*)	None	
Tolbutamide (*Orinase*) (*Apo-Tolbutamide* – Canada)	None	
Tolazamide (*Tolinase*)	None	
Thiazides and Related Compounds		
Chlorothiazide (*Diuril)*	Contraindicated	Some sources recommend that if a diuretic is used in a patient with a history of sulfonamide allergy, the first dose should be reduced and given under medical supervision. Referral to an allergist may be warranted for patients who have had a severe allergic reaction to a sulfonamide. Ethacrynic acid does not contain a sulfa group and is a possible alternative in sulfonamide-allergic patients. Case reports suggest cross-reactivity between indapamide and sulfonamide antibiotics.
Chlorthalidone (*Hygroton*) (*Apo-Chlorthalidone* – Canada)	Contraindicated	
Hydrochlorothiazide	Contraindicated (Also listed as warning and precaution for Canada)	
Indapamide (*Lozol*) (*Lozide* – Canada)	Contraindicated	
Metolazone (*Mykrox, Zaroxolyn*)	Warning (In precaution category for Canada)	
Other Agents		
Probenecid (*Benemid*) (*Benuryl* – Canada)	None	--
Sulfasalazine (*Azulfidine*) (*Salazopyrin* – Canada)	Contraindicated (Also in Health Canada precautions)	Sulfasalazine is broken down in the gut into sulfapyridine and 5-aminosalicylic acid (mesalamine). Sulfasalazine is contraindicated because sulfapyridine is a sulfonylarylamine that is systemically absorbed.

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Drug	**FDA Product Labeling Recommendations in Sulfonamide Allergy**[1,2,12]	**Comments**[1,2,12]
Nonsulfonylarylamines (cont.)		
Other Agents (cont.)		
Tamsulosin (*Flomax*)	Precaution[13]	Cross-reactivity in sulfa-allergic patient rarely reported. Cautious use recommended with serious or life-threatening sulfa allergy.[13]
Tipranavir (*Aptivus*)	Precaution[10]	The potential for cross-sensitivity between drugs in the sulfonamide class and tipranavir (a protease inhibitor) is unknown.[10]
Sulfonamide Moiety-Containing Drugs		
5-HT Antagonists		
Naratriptan (*Amerge*)	None (Warning by Health Canada)	Sulfonamide group not on benzene ring, FDA concluded no risk of cross-reactivity. A retrospective chart review evaluated patients with a sulfonamide allergy receiving sumatriptan. No allergic reactions were reported during sumatriptan therapy.
Sumatriptan (*Imitrex*)	None (Warning by Health Canada)	
Other Agents		
Ibutilide (*Corvert*)	None	--
Sotalol (*Betapace*) (*Sotacor* – Canada)	None	--
Topiramate (*Topamax)*	None	--
Zonisamide (*Zonegran*)	Contraindicated[11]	One small study showed no risk of cross-reactivity when zonisamide was used in patients allergic to sulfonylarylamines.

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Cross-Reactivity of Sulfonamide Drugs

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Background

An estimated 3% of patients develop allergic reactions to sulfonamide antibiotics.[1] The most common type of reaction is a maculopapular rash. Rarely, patients develop life-threatening reactions like anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrosis. For many years, there has been debate in the medical community whether all sulfa drugs should be avoided in patients allergic to sulfonamide antibiotics.

How are Sulfa Drugs Classified?

A sulfonamide is any compound that contains a SO_2NH_2 moiety.[2] Sulfonamides are divided into three different groups based on chemical structure. The first group, the sulfonylarylamines, have a sulfonamide moiety directly attached to a benzene ring with an unsubstituted amine ($-NH_2$) moiety at the N4 position.[2] This group consists primarily of the sulfonamide-type antibiotics as well as two protease inhibitors (amprenavir [*Agenerase*] and fosamprenavir [*Lexiva*]). The second group, the nonsulfonylarylamines, also have a sulfonamide moiety attached to a benzene ring or other cyclic structure, but they do not have an amine group at the N4 position. The third group, known as the sulfonamide-moiety containing drugs, have a sulfonamide group that is not connected to a benzene ring like in the other groups. The specific agents included in these three groups are summarized in the attached table.

The Cross-Reactivity Controversy

Several case reports suggest patients that are allergic to sulfonamides from one group (e.g., sulfonylarylamines) may be at increased risk for developing an allergic reaction to a sulfonamide from another group.[2] This is known as cross-reactivity. However, there is no data from well designed trials that show that sulfonamides from different groups cross-react. An alternative theory to sulfonamide cross-reactivity is that patients allergic to one drug may be at higher risk for being allergic to other, even structurally unrelated, drugs.[3]

This hypothesis was tested in a retrospective cohort study by Strom et al (n=20,226) that evaluated the incidence of allergic reactions following initiation of sulfonamide nonantibiotic drugs.[3] Patients that had previously experienced an allergic reaction to a sulfonamide antibiotic had a higher occurrence of allergic reactions than did patients with no history of hypersensitivity to sulfonamide antibiotics (9.9% versus 1.6%, adjusted odds ratio 2.8; 95% confidence interval, 2.1 to 3.7). However, patients with a prior sulfa allergy were even more likely to have an allergic reaction to penicillin, obviously a structurally unrelated drug, than they were to a sulfonamide nonantibiotic. Additionally, the risk of an allergic reaction after receiving a sulfonamide antibiotic was HIGHER in patients with a history of penicillin allergy than in those with a history of hypersensitivity to sulfonamide antibiotics.

Some experts also argue that cross-reactivity isn't possible between the sulfonylarylamines and the other types of sulfonamides because of structural differences.[2,4] The one structural similarity found among the three groups, the SO_2NH_2 moiety, hasn't been shown to interact with the immune system.[4] However, there are at least two known types of allergic reactions related to the sulfonylarylamine structure that require functional groups NOT present in the nonsulfonylarylamines or sulfonamide moieties.

The first, type 1 immunological reaction, requires the presence of a heterocyclic ring at the sulfonamide-N1 position.[2,4] This reaction is immunoglobulin (Ig) E mediated and presents usually within one to three days after initiation of medication and is commonly associated with a maculopapular eruption or an urticarial rash.[2] More serious reactions including angioedema, hypotension, and anaphylaxis may also occur, especially with repeat exposure.[2,4]

The second, more common hypersensitivity reaction, requires the presence of an unsubstituted amine group at the N4 position.[2,4,5] Cytochrome P-450 oxidation of the N4 arylamine results in the formation of cytotoxic or immunogenic hydroxylamine and nitrosoamine metabolites.[4,5] This reaction usually develops seven to 14 days after initiation of drug therapy and resolves upon discontinuation of medication.[2] Presentation consists of a fever and a nonurticarial rash that may

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progress to erythema multiforme and multi-organ toxicity.

The difference in chemical structure between the sulfonylarylamines and other types of sulfonamides implies that cross-reactivity is unlikely. However, T-cell mediated immune response to the unmetabolized, nonhaptenated parent sulfonamide antibiotic has been reported to occur occasionally.[4] It is unknown whether T-cell recognition is related to the sulfonamide moiety or some other functional group. Until the mechanism behind T-cell recognition is more clearly understood, cross-reactivity between sulfonylarylamines and the other types of sulfonamides remains theoretically possible.

The protease-inhibitors amprenavir and fosamprenavir are sulfonamides with an N4 arylamine, like the sulfonylarylamine antibiotics. The product labeling for these agents state that the potential for cross-sensitivity with other sulfonamides is unknown, but they should be used with caution in people with sulfonamide allergy.[6,7] In initial clinical trials, 16 patients with a history of sulfonamide allergy were prescribed amprenavir.[2] Five (31%) of these patients developed a rash which resulted in discontinuation of amprenavir in two patients. In a clinical study with fosamprenavir used as the only protease inhibitor, rash occurred in 20% of patients with a history of sulfonamide allergy compared to 33% of patients with no history of sulfonamide allergy.[7]

Other drugs (e.g., some local anesthetics, dapsone, and procainamide) do not contain a sulfonamide moiety, but like the sulfonylarylamines contain an N4 arylamine.[4] The same is true for sunscreens that contain para-amino-benzoic acid (PABA) derivatives.[1] Although, the significance of this structural similarity is unknown, there have been reports of cross-sensitivity between sulfonamides and dapsone, a sulfone.[1,8]

Cross-reactivity between dapsone and sulfonylarylamines appears to be especially prevalent in human immunodeficiency virus (HIV) infected individuals, who are already at a much higher risk of allergic reaction to sulfonamides.[1,8] The package labeling of dapsone does not address the issue of cross-sensitivity with sulfonamides. However, experts state that dapsone may be considered in HIV-infected patients with mild hypersensitivity reactions to trimethoprim-sulfamethoxazole (*Bactrim, Septra*).[8]

Agents containing sulfur, sulfites, sulfates, and saccharin often confuse clinicians about their potential for cross-reactivity with sulfonamides. Medications that contain sulfur such as amoxicillin (*Amoxil*), captopril (*Capoten*), omeprazole (*Prilosec*), ranitidine (*Zantac*), spironolactone (*Aldactone*), and sulindac (*Clinoril*) are not sulfonamides and do not cross-react.[1] Sulfites (sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite) are used in foods and drugs (e.g., *Epipen*, *Pred Forte*, *Garamycin* injectable, etc.) as antioxidants.[1,9] They are also chemically unrelated to sulfonamides and there is no risk of cross-sensitivity. However, sulfites may cause their own reactions such as dyspnea, wheeziness, and chest tightness in patients with asthma.[9] Sulfates (e.g., zinc sulfate, morphine sulfate, etc) are also not chemically related to sulfonamides. Saccharin is an O-toluene sulfonamide derivative. This artificial sweetener is an ingredient in many liquids and tablets, but is not required to appear in drug labeling.[1,9] Dermatologic reactions and cross-reactivity with sulfonamide antibiotics have been reported. The American Academy of Pediatrics recommends that children with sulfonamide allergy avoid saccharin [Evidence level C, Consensus].[9]

Commentary

The majority of available evidence suggests that nonsulfonylarylamine and sulfonamide moiety-containing drugs need not be routinely avoided in patients with a history of allergy to sulfonylarylamines.[2-4] Although, the nonsulfonylarylamines and sulfonamide moieties may cause allergic reactions themselves, because of the stereospecificity of the reaction associated with sulfonylarylamines, cross-reactivity is unlikely.[4] The question that remains unanswered is the mechanism behind T-cell recognition, and whether it is related to the sulfonamide functional group.[4]

Unfortunately, the product labeling of many nonantibiotic sulfonamide agents does not correlate with what is known scientifically. For instance, many diuretics are either contraindicated or contain warnings regarding their use in patients with a history of sulfonamide allergy (see table).[1,2] The

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inconsistency between product labeling and available evidence is likely because some of these agents (e.g., hydrochlorothiazide) were marketed many years before these newer theories refuting cross-reactivity were developed.

The inconsistency between product labeling and scientific evidence places clinicians in a difficult position. The routine avoidance of sulfonamide-containing drugs in patients with a history of sulfa allergy can unnecessarily complicate or compromise patient care. However, to ignore the product labeling recommendations places clinicians at risk of liability.

Patient-specific factors should be considered when evaluating the risk of an allergic reaction.[1] Allergic reactions may be less common in infants and the elderly, in theory because the immune system is immature or senescent. Factors that may predict drug allergy include a family or personal history of drug allergy, some concurrent illnesses (e.g., HIV), and slow acetylator phenotype.[1] One theory called the "danger hypothesis" suggests that co-stimulatory signals such as genetic predisposition and environmental stress (e.g., infection) cause the immune system to become activated resulting in an immune response to otherwise well-tolerated drugs.[5]

Ultimately, clinicians will need to make the decision of whether to initiate sulfonamide drugs in sulfa allergic patients on a case by case basis. Some experts support using nonsulfonylarylamine and/or sulfonamide moiety-containing medications in patients allergic to sulfonylarylamines if alternative therapy with structurally unrelated compounds is not possible [Evidence level C; expert opinion].[2] Exceptions include patients with serious allergic reactions and/or multiple medication allergies.[2]

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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