



Therapeutic options

UPDATE ON SULFONAMIDE ALLERGY AND CROSS-REACTIVITY

Sulfonamides comprise a broad range of therapeutic agents, and concerns about cross-reactivity—particularly between antibiotic sulfonamides and non-antibiotic sulfonamides—continue to complicate pharmacotherapy and cause confusion for clinicians.¹⁻³ Sulfonamide antibiotics are among the most common causes of allergic-type adverse drug reactions, and such reactions are associated with substantial morbidity and mortality and increased health care costs.^{2,4,5} As such, pharmacists need to be aware of current evidence regarding sulfonamide cross-reactivity so they can identify susceptible patients and make appropriate recommendations for medication management.

CLINICAL PRESENTATION

Following gastrointestinal complaints, immune-mediated rashes and fixed drug eruptions are the most common adverse reactions associated with sulfonamide antibiotics.⁶ These dermatological reactions have been reported to occur in 1.5% to 3% of immunocompetent individuals, and up to 30% or more of patients infected by the human immunodeficiency virus (the higher incidence in HIV-positive patients may be related to immunologic variables, altered drug metabolism, decreased glutathione levels, and/or frequent exposure, among other factors).^{2,4,5,7}

Rashes are usually maculopapular in nature and spread to varying degrees over the trunk and extremities; they may or may not be accompanied by pruritis.⁶ Urticarial rashes are also relatively common.³ These allergic rashes typically occur days to weeks after initial drug exposure (during which sensitization occurs), but often develop much sooner on secondary exposure (e.g., within minutes to hours).⁵ Although such rashes may resolve spontaneously

upon drug discontinuation, they should not be taken lightly as anaphylaxis may develop with repeat exposure (particularly with urticarial rashes).^{3,6}

Fixed drug eruptions appear as well-circumscribed red or scarlet lesions that often leave hyperpigmentation with healing, and they may recur at the same site with re-exposure to the offending drug.⁶

While the above-mentioned cutaneous reactions are the most common physical manifestations of allergic-type reactions to sulfonamides, many additional reactions affecting the skin and other organ systems have been reported. Some of the less common hypersensitivity reactions to sulfonamides are listed in Box 1.

DIAGNOSIS

At present, sulfonamide allergy remains primarily a clinical diagnosis, as no confirmatory immunologic test has been proven to be reliable, valid, and practical for routine use.⁸ Provocation testing (which involves giving patients increasing doses of the drug under consideration until a therapeutic dose is reached) may be used to confirm immediate ("type 1") immunoglobulin E (IgE)-mediated hypersensitivity reactions (e.g., urticaria, angioedema, anaphylaxis); however, such testing carries a significant risk of inducing a reaction similar to the original reaction.⁵ Of note, repeat administration of a drug suspected of causing a life-threatening reaction not mediated by IgE (e.g., Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], drug rash with eosinophilia and systemic symptoms [DRESS], hepatitis, or hemolytic anemia) is generally contraindicated.^{4,5}

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Box 1 – Less common hypersensitivity reactions to sulfonamides^{3,4,6}

Cutaneous

Angioedema, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis

Hematologic

Hemolytic anemia, granulocytopenia/neutropenia, thrombocytopenia

Hepatic

Cholestatic jaundice, hepatitis

Pulmonary

Pneumonitis

Renal

Interstitial nephritis, membranous glomerulonephritis, renal tubular necrosis

Multi-organ reactions

Anaphylaxis*
 DRESS syndrome†
 Serum sickness syndrome‡
 Sulfonamide hypersensitivity syndrome§
 Vasculitis

DRESS = drug rash with eosinophilia and systemic symptoms

* Anaphylaxis clinical features include urticaria/angioedema, bronchospasm, gastrointestinal symptoms, and hypotension, with potential for cardiovascular collapse.^{4,6}

† DRESS syndrome clinical features include cutaneous eruption, fever, eosinophilia, hepatic dysfunction, and lymphadenopathy.⁴

‡ Serum sickness syndrome clinical features include fever, vasculitis, lymphadenopathy, arthralgias, and rashes/urticaria.^{4,6}

§ Sulfonamide hypersensitivity syndrome clinical features include serum sickness, fever, rash, and either organ dysfunction or drug-induced lupus erythematosus; patients may exhibit hepatotoxicity, aseptic meningitis, acute interstitial nephritis, pneumonitis, myocarditis, serum sickness polyarthritides, or rashes that can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis.⁶

MECHANISM OF REACTIONS & CROSS-REACTIVITY

Among Sulfonamides

Broadly, sulfonamides are defined as drugs that contain the basic chemical structure shown in Figure 1. Sulfonamide antibiotics contain two structural characteristics that distinguish them from non-antibiotic sulfonamides: (1) an arylamine group at the N4 position of the sulfonamide moiety; and (2) a nitrogen-containing heterocyclic ring attached to the N1 nitrogen of the sulfonamide group.^{1,5,6} These characteristics are outlined in Figure 2, which shows the chemical structure for sulfamethoxazole.

Most hypersensitivity reactions to sulfonamide antibiotics are believed to be directly related to the specific side chains mentioned above, and not to the sulfonamide functional group itself.^{1,5,6} Type 1

reactions to antibacterial sulfonamides appear to be directed at the N1 heterocyclic ring, and many other non-type I hypersensitivity reactions (e.g., sulfonamide hypersensitivity syndrome, SJS, TEN) appear to be mediated by reactive hydroxylamine or nitrosoamine metabolites of the N4 arylamine group that cause either direct cytotoxicity or an immunologic response.^{1,2,6}

As the majority of hypersensitivity reactions to sulfonamide antibiotics appear to be related to the N1 heterocyclic ring or N4 arylamine group, cross-reactivity with non-antibiotic sulfonamides is highly unlikely.^{1,2} Therefore, routine avoidance of non-antibiotic sulfonamides (see Box 2) in patients who report allergies to sulfonamide antibiotics seems unjustified, with the exception of sulfasalazine (which is cleaved *in vivo* to sulfapyridine and 5-aminosalicylic acid) and, possibly, the sulfonilarylamine protease inhibitors (e.g., amprenavir/fosamprenavir, darunavir; these agents are sulfonamides that contain an N4 arylamine group).^{6,9-11} In contrast, patients who have experienced a hypersensitivity reaction to one sulfonamide antibiotic should avoid other sulfonamide antimicrobials (including topical preparations; see Box 3), even though cross-reactivity is not universal.^{1,2}

Although there is an association between allergy to sulfonamide antibiotics and subsequent reactions to non-antibiotic sulfonamides, it is most likely attributable to a predisposition to allergic reactions in general rather than true cross-reactivity.^{1,2,12} In fact, patients who are allergic to one antimicrobial drug have at least a 10-fold increased risk of reacting to other structurally unrelated drugs.²

Figure 1 – Sulfonamide functional group chemical structure⁶

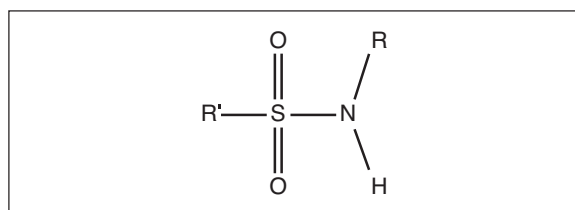
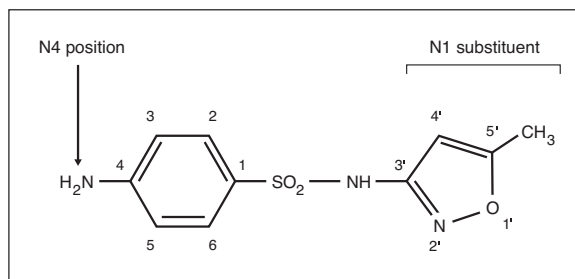


Figure 2 – Sulfamethoxazole chemical structure⁶



Box 2 – Non-antibiotic sulfonamides available in Canada† 1-3,6,12-16**

Anti-inflammatory agents	Carbonic anhydrase inhibitors	Diuretics	Hypoglycemics (sulfonylureas)	Migraine therapy	Miscellaneous
Celecoxib	Acetazolamide Brinzolamide Dorzolamide Methazolamide	Bumetanide Chlorthalidone Furosemide Hydrochlorothiazide Indapamide Metolazone	Chlorpropamide Gliclazide Glimepiride Glyburide Tolbutamide	Naratriptan Sumatriptan	Diazoxide Ibutilide Probenecid Sotalol Tamsulosin Tipranavir Topiramate

* Darunavir, fosamprenavir, and sulfasalazine are also non-antibiotic sulfonamides available in Canada; however, these agents may cross-react in patients with an allergy to a sulfonamide antibiotic (see text for details).

† Dapsone is a sulfone antibiotic that closely resembles the sulfonamide antibiotics; cross-reactivity is well documented.²

‡ This list may not be all-inclusive.

Box 3 – Antibiotic sulfonamides available in Canada* 15

Silver sulfadiazine
Sulfacetamide (including combinations)
Sulfamethoxazole (including combinations)
Sulfisoxazole (including combinations)

*This list is not all-inclusive; veterinary products were specifically excluded.

Between Sulfonamides and Other Agents

Given the proposed mechanism of hypersensitivity to sulfonamide antibiotics discussed above, the question of cross-reactivity between sulfonamide antibiotics and non-sulfonamide drugs containing a para-aminobenzyl (arylamine) group similar to the antibiotic N4 substituent merits consideration.² Drugs with this structure include acebutolol, benzocaine, and procainamide.² Available evidence suggests that cross-reactivity is unlikely; therefore, patients who report hypersensitivity reactions to sulfonamide antibiotics need not generally avoid such arylamine-containing medications.^{2,6}

Similarly, patients with reported sulfonamide hypersensitivity need not routinely avoid sulfur-, sulfate-, or sulfite-containing compounds.^{6,8}

MANAGEMENT

The most important step in properly managing patients with a reported “sulfa” allergy is to obtain a careful, thorough, and detailed history about their reaction, including the exact agent associated with the reaction, the precise nature and severity of the reaction, the timing of onset of the reaction, and use of any concurrent medications at the time of the reaction.⁸ Once these details are known and true drug allergy is suspected or confirmed, major management options include use of an alternative

non-cross-reactive medication, consideration of carefully monitored test dosing, or a trial of a medication desensitization protocol.⁸

Avoidance/Use of Alternative Medications

As noted above, hypersensitivity to a sulfonamide antibiotic generally warrants avoidance of the implicated agent and all other sulfonamide antimicrobials, but not non-antibiotic sulfonamides (except sulfasalazine and, possibly, fosamprenavir and darunavir) or non-sulfonamide arylamines. Nonetheless, some clinicians advise against using any sulfonamide in patients with a history of anaphylaxis or another serious reaction (unless it is an emergency and no alternatives exist),¹³ but such an approach does not appear to be supported by high-quality evidence.

Where the reported allergy is to a non-antibiotic sulfonamide, use of non-sulfonamide alternatives may be advisable. For example, if the reported allergy is to a sulfonamide diuretic, ethacrynic acid or potassium-sparing diuretics (e.g., amiloride, eplerenone, spironolactone) could be used.

Test Dosing or Desensitization

In instances where acceptable alternatives are not available, test dosing or drug desensitization protocols can be considered.⁸ Test dosing, or “graded drug challenges” (which are equivalent to provocation testing; see Diagnosis, above), may be appropriate when the apparent drug reaction was relatively mild (e.g., maculopapular eruption).^{5,8} Where previous reactions are presumed to be IgE-mediated (e.g., anaphylaxis, angioedema, urticaria), or in HIV-positive patients with typical reactions (maculopapular eruptions with pruritis and fever), drug desensitization protocols may be an option.^{4,5,8} Since maintenance of a desensitized state requires the continuous presence of drug, patients should be

informed that desensitization would need to be repeated if more than 24 to 48 hours elapses without drug administration.^{5,8}

Both test dosing and drug desensitization should only be performed in an appropriate medical setting, with proper monitoring and immediate

availability of rescue medications and equipment.⁸ Furthermore, neither of these approaches should generally be considered if the reaction history is consistent with a severe non-IgE-mediated reaction such as SJS, TEN, DRESS, hepatitis, or hemolytic anemia.^{4,8}

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