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Acetazolamide and Sulfonamide Allergy: A Not So Simple Story

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Abstract

Kelly, Thomas E., and Peter H. Hackett. Acetazolamide and sulfonamide allergy: a not so simple story. *High Alt. Med. Biol.* 11:319–323, 2010.—Allergies and adverse reactions to sulfonamide medications are quite common. Two distinct categories of drugs are classified as sulfonamides: antibiotics and nonantibiotics. The two groups differ in their chemical structure, use, and the rate at which adverse reactions occur. Cross-reactivity between the two groups has been implied in the past, but is suspect. Acetazolamide, from the nonantibiotic group, is routinely used in the prevention and treatment of high altitude issues and may not need to be avoided in individuals with a history of sulfonamide allergy. This review addresses the differences between the groups and the propensity for intergroup and intragroup adverse reactions based on the available literature. We also examine the different clinical presentations of allergy and adverse reactions, from simple cutaneous reactions with no sequelae through Stevens–Johnson syndrome and anaphylaxis, with risk for significant morbidity and mortality. We offer a systematic approach to determine whether acetazolamide is a safe option for those with a history of allergy to sulfonamides.

Key Words: sulfa allergy; sulfonamide; acetazolamide; acute mountain sickness; high altitude; acclimatization

Introduction

WHAT EXACTLY DOES SULFA allergy mean and how does it apply to the use of acetazolamide for high altitude conditions? Sulfa drug is a vague term typically referring to medications containing a sulfonamide component. Historically, it most often refers to sulfonamide antibiotics (Tilles, 2001). However, numerous nonantibiotic medications in common use today also contain a sulfonamide moiety. Agents in this group include hypoglycemics, antihypertensives, anti-inflammatories, diuretics, and acetazolamide (Table 1). The carbonic anhydrase inhibitor acetazolamide is used to speed acclimatization to high altitude, prevent or treat acute mountain sickness and periodic breathing, and improve sleep at altitude. The medication is effective and well tolerated; avoiding its use because of a history of sulfonamide allergy, as suggested in previous literature (Hackett and Roach, 2001) may, however, not be warranted. In light of new evidence and new recommendations from the allergy literature, we examine whether acetazolamide may indeed be safe to use in those with a history of sulfonamide allergy. With some insight to the specifics of the adverse reaction and the agents involved,

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Table 1. Common Sulfonamide-Containing Medications

Antimicrobial sulfonamides	*Nonantimicrobial sulfonamides*
Sulfamethoxazole	Acetazolamide, brinzolamide, dichlorphenamide, dorzolamide, methzolamide
Sulfamethizole	Furosemide, bumetanide
Sulfamoxole	Hydrochlorothiazide, chlorthalidone
Sulfamerizine	Sumatriptan
Sulfamethazine	Celecoxib
Sulfoxazole	Glyburide
Sulfamylon	Sulfasalazine

a systematic approach can be used to determine whether the use of acetazolamide is a safe option.

Chemistry and Cross-Reactivity

Two distinct categories of drugs contain the sulfonamide component: antibiotics and nonantibiotics. They differ in both their chemical structure and clinical use. The antimicrobial sulfonamide group includes sulfamethoxazole, a component of Bactrim® and Septra®. These antibiotic sulfonamides contain an arylamine moiety (an amine linked to a benzene ring) (Tilles, 2001). This arylamine is attached to the sulfonamide structure and is believed to be central to the pathogenesis of hypersensitivity reactions. Interestingly, only the antibiotic sulfonamides contain this arylamine. The nonantibiotic sulfonamides do not contain an arylamine group or a substituted aromatic ring (Fig. 1).

Whether cross-reactivity exists between the two groups is controversial. Available information about cross-reactivity between these two groups is limited to observational studies; there are no validated skin tests or serologic tests to diagnose or confirm a sulfonamide allergy. In the case of sulfonamides, the reactant antigen is not the intact drug itself, but rather the metabolites, which differ structurally from the parent drug and bind to serum or cell-surface carrier proteins, thereby creating the immunologic stimulus. Simple skin testing with the original (unmetabolized) sulfonamide medication is thus useless, because this testing does not induce a positive wheal-and-flare response, even in the most convincing cases of sulfonamide anaphylaxis (Montanaro, 2010).

In addition, cross-reactivity studies among medications are often complicated since a clinical history of drug allergy by itself identifies a subset of patients who are at increased risk of reactions to medications in general, even in the absence of actual cross-reactivity among the implicated drugs (Slatore and Tilles, 2004). Multiple drug allergy syndrome is a diagnosis given to patients who mount an immunologic reaction to two or more chemically distinct medications. A large medical database review revealed that individuals with documented allergic reaction to a sulfonamide antibiotic in the past did indeed react more commonly to a sulfonamide nonantibiotic (10%) compared with those who tolerated sulfonamide antibiotics (1.6%). However, the same individuals with documented sulfonamide antibiotic reactions reacted to penicillins even more often (14%). Likewise, there was a higher risk of reaction to sulfonamide nonantibiotics in those with a history of reactions to penicillins than in those with a history of reactions to sulfonamide antibiotics (Strom et al,. 2003; Brackett et al., 2004). These data imply that some individuals have a propensity to drug hypersensitivity reactions and that this better predicts possible allergy than previous reaction to a different type of sulfonamide.

Supporting the lack of cross-reactivity between antibiotic and nonantibiotic sulfonamides, multiple other studies have concluded that the vast majority of patients with a history of reacting to an antibiotic sulfonamide will tolerate nonantibiotic sulfonamides (Cribb et al., 1996; Lee et al., 2004; Hemstreet and Page, 2006). Other authors have concluded that, when subjected to closer examination, the data did not establish a reasonable probability of immunologic or hypersensitivity syndrome cross-reactivity between the two sulfonamide groups (Montanaro, 2010). Overall, the existence of cross-reactivity between the two groups of sulfonamides is not supported by the evidence.

Despite this lack of evidence, the United States Food & Drug Administration (FDA) has approved product information for many nonantibiotic sulfonamide drugs that contains

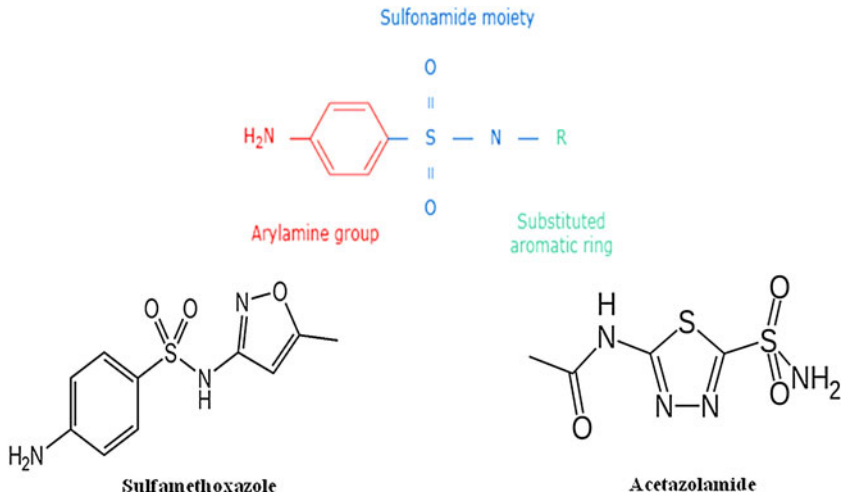

FIG. 1. Sulfa allergy flow chart.

warnings of possible cross-reactions. The FDA product information for 17 of 33 nonantimicrobial sulfonamide drugs (including acetazolamide) includes varying warnings, or actual contraindication statements, against their use in patients with sulfonamide allergy (Johnson et al., 2005).

Clinical Presentations of Allergic Reactions to Sulfonamides

Sulfonamide-containing antibiotics are the second most frequent cause of allergic drug reactions, after the β-lactams (penicillins and cephalosporins). In one large study, the incidence of reactions to trimethoprim–sulfamethoxazole (TMP-SMX) was 3% of patients exposed, compared with 5% for amoxicillin (Bigby et al., 1986). The incidence of reactions to nonantibiotic sulfonamides is not well established; it is clearly less than with antibiotics.

The clinical presentation and severity of hypersensitivity reactions to sulfonamides vary widely. Isolated dermatologic reactions are by far the most common and may include erythema, maculopapular or morbilliform rash, urticaria, and pruritis. Most of these reactions appear within days of initiation of therapy, are self-limited, and resolve promptly after drug discontinuation (Jick, 1982).

In escalating severity, but significantly less common, is a reaction characterized by a pruritic, maculopapular, or morbilliform rash accompanied by systemic complications. Typically, a fever precedes the rash. Symptoms generally develop 1 to 2 weeks after the first dose. Organ involvement can include elevation of serum transaminases, interstitial nephritis, pulmonary infiltrates, leukemoid reaction, and cytopenia (Gordin et al., 1984). The reaction and its sequelae generally resolve 1 to 2 weeks after discontinuation of the offending agent. Reexposure can precipitate a return of symptoms within 1 to 2 days. These reactions are much more common with the antibiotic (usually TMP-SMX) than with the nonantibiotic sulfonamide (Orfan and Stocker, 1994; Cribb et al., 1996; Slatore and Tilles, 2004).

Although uncommon, anaphylaxis or type I, IgE-mediated hypersensitivity reactions have been attributed to antibiotic sulfonamides (Hemstreet and Page, 2006). Type I reactions are mediated primarily by specific IgE antibodies, which trigger sensitized mast cells and basophils to degranulate, releasing histamine and other vasoactive mediators and resulting in urticaria, angioedema, bronchospasm, laryngeal edema, gastrointestinal disturbance, and hypotension. Non antibiotic sulfonamides have also been implicated in these reactions, but the evidence is not always convincing (Chichmanian et al., 1991). Anaphylaxis has been reported rarely with acetazolamide, both in patients with and without antibiotic sulfonamide hypersensitivity (Peralta et al., 1992; Tzanakis, 1998; Gallerani et al., 2002). Anaphylaxis has also been observed with other nonantibiotic sulfonamides, such as furosemide and celecoxib, and in patients with and without previous reactions to sulfonamide antibiotics. In summary, nearly any drug can produce rare episodes of anaphylaxis, and such is the case for the sulfonamides, with the antibiotic group much more commonly than with the nonantibiotic group. Evidence for cross-reactivity between the groups with regard to anaphylaxis is not compelling.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening hypersensitivity conditions affecting the skin in which cell death causes the epidermis to separate from the dermis. Most experts consider SJS and TEN to be different manifestations of the same process. Antibiotic sulfonamides are strongly associated with SJS/TEN; in contrast, the nonantibiotic sulfonamides are not (Roujeau et al., 1995).

Hemolytic anemia secondary to glucose-6-phosphate dehydrogenase (G6PD) deficiency is a known complication of some sulfonamide-containing drugs and is usually considered a contraindication to their use. This is a genetic, metabolic adverse drug reaction and not the result of an immunologic or hypersensitivity response. Sulfonamides vary in their risk of causing hemolysis in patients with G6PD deficiency. Several of the antimicrobials are considered high risk, whereas few of the nonantimicrobials are associated with increased risk. Our research has not found a link between acetazolamide and complications in patients with G6PD deficiency.

Management

There are several approaches to the use of sulfonamide drugs (specifically acetazolamide) in patients with past reactions to this class of medications. The choice of strategy depends on the type and severity of the previous reaction, as well as the class of drug (antibiotic versus non antibiotic) and the risk–benefit profile for the patient. However, regardless of the approach, the risks of subsequent reactions cannot be completely eliminated, and a thorough discussion between the medical provider and the patient should include this point so that an informed decision regarding the use of acetazolamide can be made.

The safest approach for the patient with any prior reaction to a sulfa drug, multiple drug allergies, or penicillin allergy would be to avoid all drugs in the sulfonamide group, including acetazolamide. Other therapeutic options for treating altitude-related issues include staged ascent to facilitate acclimatization to altitude, supplemental oxygen, dexamethasone for prevention of acute mountain sickness (AMS), and dexamethasone and symptomatic medications for treatment of AMS or high alltitude cerebral edema (HACE) (Luks et al, 2010).

Avoidance of the entire sulfonamide drug group is warranted for individuals whose previous reaction included a serious and/or life-threatening condition such as anaphylaxis, SJS, and TEN. Any form of reexposure to the precipitating drug or a sulfonamide in the same group is strictly contraindicated. Published evidence has shown that SJS/TEN can recur with even minor reexposures and may be more severe in the second episode (Revuz et al., 1987). Even though SJS/TEN reactions are so far not associated with nonantibiotic sulfonamides, because of the severity and life-threatening nature of these reactions, a safe practice is to avoid *all* sulfonamides in patients with past SJS or TEN from sulfonamide-containing medications.

Similarly, because of the severity of symptoms and potential for harm, patients with past reactions consistent with type I, IgE-mediated allergy or anaphylaxis (i.e., angioedema, bronchospasm, laryngeal edema, and/or hypotension) should probably avoid all sulfonamides within both groups. Patients who have experienced a morbilliform rash with systemic or multiorgan system involvement *and* who have other drug allergies should generally avoid acetazolamide (Montanaro, 2010). These cautions are warranted not because of cross-reactivity between sulfonamide groups, but because

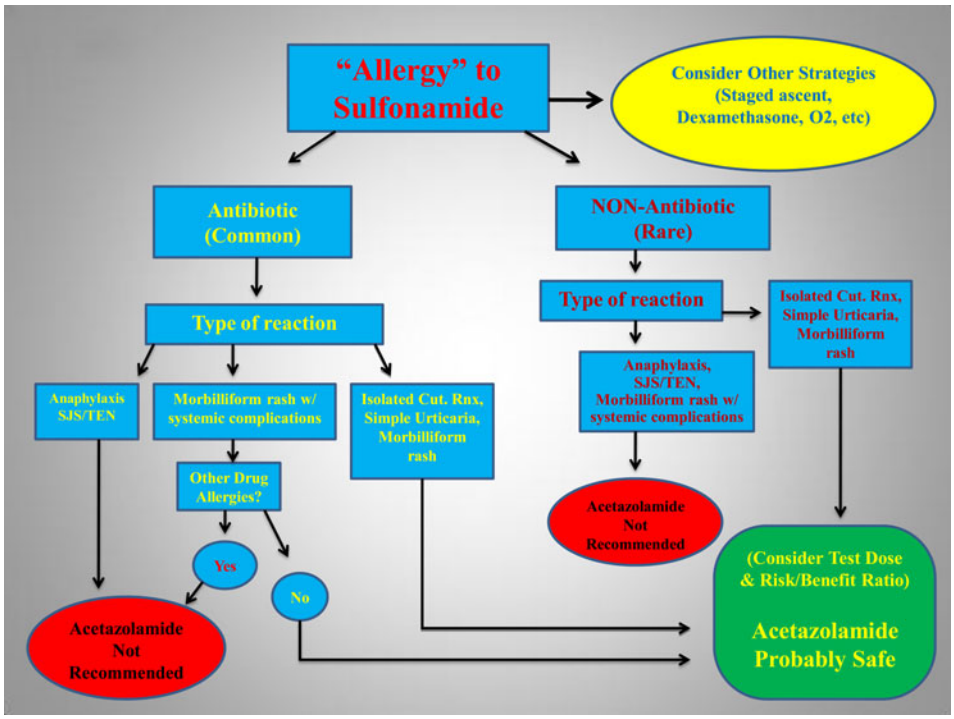

FIG. 2. Sulfonamide allergy flow chart.

of the general tendency to allergy in these patients, as described previously.

Individuals with the far more common minor reactions to antibiotic sulfonamides, including isolated cutaneous reactions, simple urticaria, and morbilliform rash with or without systemic complications can usually be safely treated with nonantibiotic sulfonamides such as acetazolamide. Although cross-reactivity is doubtful, the history of allergy does increase the chance of an allergic reaction to any medication, including acetazolamide. Therefore, one recommended approach is to administer a single, low, test dose, perhaps 62.5 or 125 mg, under controlled circumstances or medical observation in advance of the journey to altitude to rule out anaphylaxis. This single-test-dose approach is a proven and reliable tool in managing certain patients with a history of adverse reactions to drugs (Passalacqua et al., 2002). Although a negative test does not reduce to zero the risk of a subsequent reaction, it does offer some reassurance that a serious adverse event is unlikely. Clinicians should also be aware that in the study cited above 22% of patients with a history of anaphylactic-like reactions to medications also developed similar symptoms to the administration of a placebo.

When considering acetazolamide for patients with isolated cutaneous reactions to medications in the nonantibiotic sulfonamide group other than acetazolamide, there is little evidence to support any particular approach. Intragroup cross-reactivity within the nonantimicrobial sulfonamide class appears rare. For these patients, it may also be prudent to administer a low-dose test of acetazolamide as described previously. If no adverse reaction is observed, proceed with appropriate acetazolamide therapy. However, if past reaction to the nonantimicrobial group involves systemic complications, avoiding intragroup sulfonamides and incorporating alterative measures would be prudent. (Fig. 2).

Patients with allergy to sulfonamide medications do not necessarily have to forego the use of acetazolamide. A history of sulfa allergy remains a vague term and does not provide the information needed to make clinical-based decisions. When the offending agent and the specifics of the adverse reaction are known, reasonable and sound therapeutic decisions can be made regarding the use of acetazolamide for high altitude issues.

Disclosures

The authors have no conflicts of interest or financial ties to disclose.

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