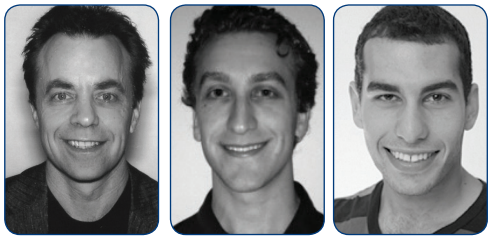
REVISITING RISK

It is time to take a fresh look at carbonic anhydrase inhibitors and sulfonamide allergy.

BY JEFF MARTOW, MDCM, FRCSC; EVAN MARTOW, BMSc, MDCM; AND MATTAN LUSTGARTEN, BSc



As the average age of the general population increases, the incidence of glaucoma follows. As a result, ophthalmologists are seeing more patients for whom eye drops and laser therapy may be insufficient and for whom surgery may be impractical, making it crucial to consider additional medical options such as oral carbonic anhydrase inhibitors (CAIs).

Although patients' intolerance limits the use of this medication class, a subset of patients both tolerates and derives significant clinical benefit from drugs like oral acetazolamide, the most commonly used CAI. Even so, there is widespread concern about cross-reactivity and sulphonamide allergy, which affects approximately 3% of the general population[1] and up to 8% of hospitalized patients.[2] The package inserts for all CAIs state that "fatalities have occurred due to adverse reactions to sulphonamides."[3] A fresh look at the research, however, leads us to question current assumptions about this risk.

EVIDENCE IN THE LITERATURE

The first report of a reaction to acetazolamide was published in 1955, when Moseley and Baroody discussed a patient with congestive heart failure and a history of sulfa allergy who experienced gait abnormality, vertigo, paresthesias, and facial numbness 20 minutes after receiving oral Diamox (acetazolamide; Wyeth Pharmaceuticals).[4] Mosely and Baroody postulated that the response to sulfa-based acetazolamide could have been related to a previous reaction to another sulfa medication.[4] This case introduced the concept of sulfa cross-reactivity to the medical community.

A literature search uncovered five other case reports of acetazolamide reactions, but they were all limited by a history lacking in sulfa allergy and/or poor evidence for cross-reactivity.[5-9] With a paucity of historical evidence, we must then examine the theoretical basis for cross-reactivity between sulfonamides.

THEORY OF CROSS-REACTIVITY

The term *sulfonamide* refers to molecules that contain the SO_2NH_2 functional group (Figure 1), and it refers to two subsets: antibiotic and nonantibiotic sulfonamides. It should not be confused with sulfates, sulphites, or sulfurs, which are all chemically distinct from sulfonamides and demonstrate no cross-reactivity.[10]

The basic sulfonamide functional group structure has not been shown to incite an immune response. The two structures responsible for the immune reactions induced by sulphonamides, the arylamine group at the N4 position and a five- or six-membered nitrogen-containing ring attached to the N1 nitrogen of the sulfonamide group (Figure 2), are only present on sulphonamide antibiotics (Figure 3). Because nonantibiotic sulfonamides such as acetazolamide (Figure 4) do not possess the immune-inducing structures found in antibiotic sulfonamides, cross-reactivity between these two types of sulfonamides is not supported theoretically.

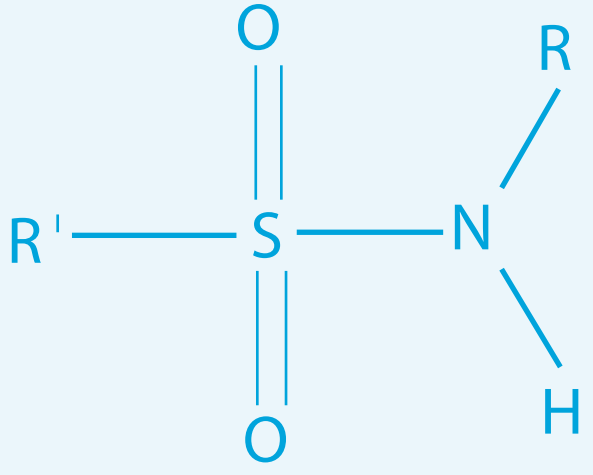


Figure 1. Chemical structure of the sulfonamide functional group.

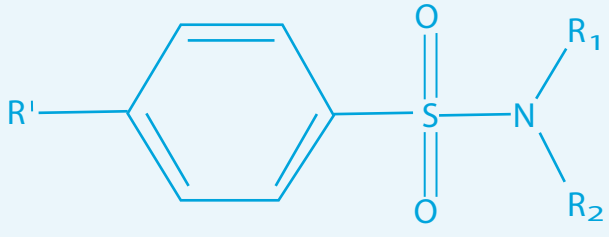


Figure 2. Basic chemical structure of all sulfonamide antibiotics.

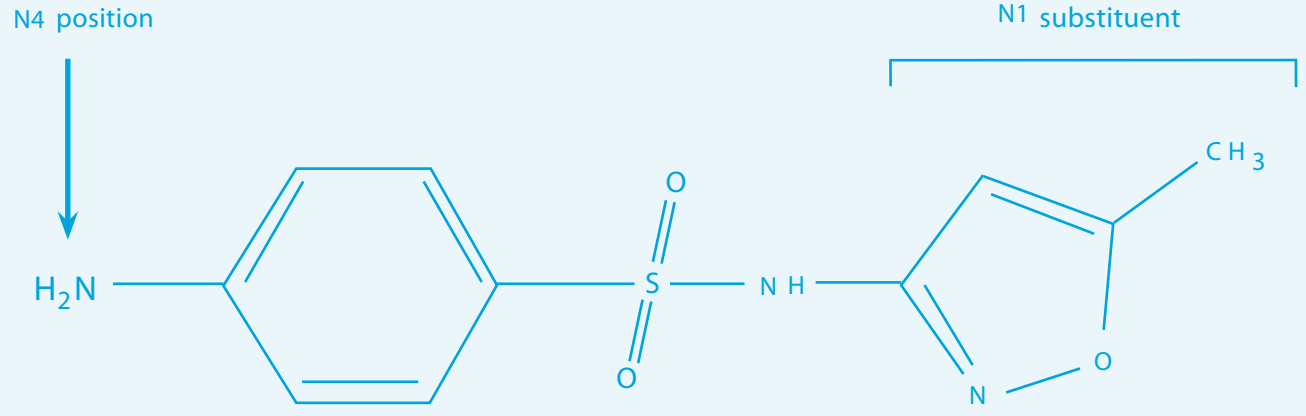


Figure 3. Chemical structure of sulfamethoxazole.

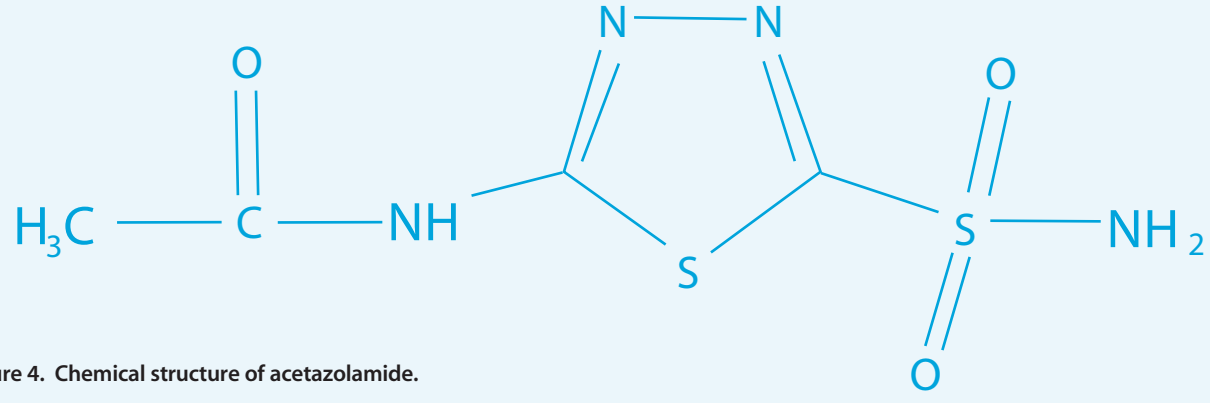


Figure 4. Chemical structure of acetazolamide.

CLINICAL TRIALS

Although there is neither theoretical nor historical support for sulphonamide cross-reactivity, it is important to assess any relevant and methodologically credible trials. The largest study on this subject was published in 2003 in *The New England Journal of Medicine*.[11] This UK-based, retrospective cohort study assessed more than 20,000 patients for the risk of allergic reactions within 30 days after receiving a nonantibiotic sulfonamide. Patients with a history of antibiotic sulfa allergy developed an allergic reaction after subsequent administration of a nonantibiotic sulfonamide 9.9% of the time. Patients with no history of sulfa allergy developed an allergic reaction 1.6% of the time.[11] These findings suggest that having a history of sulfonamide allergy increases the risk of an allergic reaction when the individual is subsequently exposed to nonantibiotic sulfonamides.

SULFA AND PENICILLIN

Interestingly, the aforementioned study also found that patients with a history of sulfa allergy were at greater risk of a subsequent reaction to penicillin than individuals without a sulfa allergy and that the former were more likely to react to penicillin than to a nonantibiotic sulphonamide.[11] Additionally, the risk of an allergic reaction to a sulfonamide nonantibiotic was lower among patients with a history of hypersensitivity to sulfonamide antibiotics than among those with a history of hypersensitivity to penicillin.[11] If the shared sulfonamide structure was the inciting agent, patients should have reacted to nonantibiotic sulphonamides more often than penicillin, but the opposite was also true. These findings strongly suggest that, in patients with a history of sulfonamide allergy, cross-reactivity is not involved in subsequent hypersensitivity reactions to nonantibiotic sulfonamides.

(Continued on page 20)

AT A GLANCE

- Carbonic anhydrase inhibitors can be beneficial, but their use among sulfa-allergic patients has been limited by cross-reactivity concerns.
- A patient with a sulfa allergy has a higher risk of a subsequent reaction to carbonic anhydrase inhibitors than someone without a history of sulfa allergy, but the risk is not as great as might be expected of a cross-reactivity mechanism.
- In patients with a history of previous antibiotic sulfonamide allergy, the risk of an allergic reaction to penicillin is greater than that for a nonantibiotic sulfonamide.

(Continued from page 18)

CONCLUSION

The concept of sulfonamide cross-reactivity may have seemed plausible in 1955, but newer information suggests it likely is not true. The immune mechanisms producing hypersensitivity reactions are limited to antibiotic sulfonamides and are not present in nonantibiotic sulfonamides.

A patient with a history of sulfonamide allergy has a higher risk of a subsequent reaction to CAIs than someone without a history of sulfa allergy, likely because of generally increased immune sensitivity, but the risk is not as great as might be expected of a cross-reactivity mechanism. In fact, in patients with a history of previous antibiotic sulfonamide allergy, the risk of an allergic reaction to penicillin is greater than that for a non-antibiotic sulfonamide.

It is the duty of clinicians to remain apprised of treatment options and to provide an accurate assessment of risk. It is to be hoped that FDA recommendations will be modified to reflect better understanding. As a community, eye care providers must remain vigilant and question traditional practice patterns based on misconceptions so that they may progress towards more robust, evidence-based best practices. ■

1. Allen J. Which medications to avoid in patients with sulfa allergy. *Pharmacist's Letter/Prescriber's Letter*. 2000;16(7):160708.
2. Jick H. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis*. 1982;4(2):426-428.
3. Canadian Pharmacists Association. Compendium of Pharmaceuticals and Specialties. Ottawa, ON: Canadian Pharmacists Association; 2003:495.
4. Moseley V, Baroody N. Some observations on the use of acetazolamide as an oral diuretic in various edematous states and in uremia with hyperkalemia. *Am Pract Digest Treat*. 1955;6(4):558-566.
5. Kristinsson A. Fatal reaction to acetazolamide. *Br J Ophthalmol*. 1967;51(5):348-349.
6. Gerhards LJ, Van Arnhem AC, Holman ND, Nossent GD. Fatale anafylactische reactie na inname van acetazolamide (Diamox) wegens glaucoom. *Ned Tijdschr Geneeskd*. 2000;144(25):1228-1230.
7. Tzanakis N, Metzidaki G, Thermos K, et al. Anaphylactic shock after a single oral intake of acetazolamide. *Br J Ophthalmol*. 1998;82(5):588.
8. Thien T, Braam RL, Russel FG. Fatal anaphylactic reaction after oral (Diamox) for glaucoma [in Dutch]. *Ned Tijdschr Geneeskd*. 2000;144(45):2173-2174.
9. Peralta J, Abelairas J, Fernández-Guardiola J. Anaphylactic shock and death after oral intake of acetazolamide. *Am J Ophthalmol*. 1992;114(3):367.
10. Dwenger C. 'Sulfa' hypersensitivity [letter]. *Anesthesia*. 2000;55(2):200-201.
11. Strom BL, Schinnar R, Apter A, et al. Absence of cross-reactivity between sulfonamide antibiotic and sulfonamide nonantibiotics. *N Engl J Med*. 2003;349(17);1628-1635.

Mattan Lustgarten, BSc
- medical student CC-2, faculty of medicine, University of Toronto, Ontario, Canada
- mattan.lustgarten@mail.utoronto.ca
- financial interest: none acknowledged

Evan Martow, BMSc, MDCM
- post-graduate year 3, internal medicine, University of Alberta, Edmonton, Alberta, Canada
- martow@ualberta.ca
- financial interest: none acknowledged

Jeff Martow, MDCM, FRCSC
- ophthalmology division head, Markham-Stouffville Hospital, Markham, Ontario, Canada
- jeff.martow@rogers.com
- financial interest: none acknowledged