Objective: To report the safe and successful use of the carbonic anhydrase inhibitor acetazolamide for treatment of patients with episodic ataxia and periodic paralysis who had been denied treatment because of a history of severe allergic reactions to antibiotic sulfonamides.

Design: Case reports.

Setting: University of Rochester Medical Center, Rochester, New York.

Patients: A 61-year-old man with late-onset episodic ataxia, an 83-year-old woman with mutation-positive Andersen-Tawil syndrome, and a 21-year-old woman with mutation-positive episodic ataxia 2, all of whom had a history of severe skin rash with the use of sulfonamides for treatment of infection.

Results: The 3 patients had been considered for carbonic anhydrase inhibitor treatment but a pharmacist refused to fill a prescription for acetazolamide for 1 patient and the other 2 patients were denied treatment because of the allergy history. All 3 patients were prescribed acetazolamide and had no adverse reaction. Two patients improved substantially and are continuing treatment. A review of the pharmacology literature suggests that cross-reactivity between antibiotic and nonantibiotic carbonic anhydrase inhibitors is unlikely. Moreover, a review of case reports does not suggest cross-reactivity. Previous reports in the ophthalmology literature also indicate that acetazolamide can be administered to patients with a history of antibiotic sulfonamide allergic reaction.

Conclusions: These 3 cases confirm that the carbonic anhydrase inhibitor acetazolamide can be given to patients with a history of allergic skin rash with antibiotic sulfonamide.


ONANTIBIOTIC SULFONAMIDES are used for treatment of diseases such as type 2 diabetes mellitus, hypertension, and ion channelopathies. However, patients who might benefit from these medications have often been prohibited from taking them owing to fear of cross-reactivity between antibiotic and nonantibiotic sulfonamides. In patients with severe allergic responses to sulfonamide antibiotics, the risk of severe reaction with other sulfacetamidic drugs such as acetazolamide was thought to outweigh potential benefits. However, recent studies of the chemical structure and mechanisms of immune response to these drugs suggest that cross-reactivity is unlikely. Furthermore, there is little clinical evidence supporting allergic cross-reactivity, and several case studies have found them safe in patients allergic to sulfonamide antibiotics. Herein, we report successful treatment of 3 patients with a reported sulfonamide allergy who had channelopathies meriting treatment with acetazolamide.

REPORT OF CASES

CASE 1

A 61-year-old man had difficulty walking, double vision, and slurred speech once or twice per week beginning at age 57 years. Episodes progressively worsened in frequency and duration, and he developed interepisode incoordination. The episodes were triggered by exertion, stress, caffeine, and alcohol. His medical history included hypertension, hypercholesterolemia, and glucose intolerance. The patient reported that while in the military, prophylactic treatment for meningitis caused throat and facial swelling and itchy eyes. On examination, he had downbeat gaze-evoked nystagmus on horizontal gaze, tremor on finger-to-toe testing, and an
Acetazolamide has been used for the treatment of episodic ataxia type 2, with benefit in 50% to 75% of patients. In episodic ataxia type 1, acetazolamide was also effective in decreasing attack frequency. Acetazolamide is also effective in the periodic paralyses. Carbonic anhydrase inhibitors have been used to prevent altitude sickness, to lower intraocular pressure in open-angle glaucoma, and to treat refractory absence, myoclonic, and catamenial epilepsy as part of multidrug regimens. Acetazolamide has recently been used for hemiplegic migraine and idiopathic intracranial hypertension.

Acetazolamide is a nonbacteriostatic sulfonamide that contains a sulfonamide functional group but lacks antibiotic activity. The sulfonamides include the following: (1) the sulfonarylamines, which have a sulfonamide moiety attached to a benzene ring with an unsubstituted amine at the N4 position (antibiotics, notably sulfaflanilamide and sulfamethoxazole); (2) the nonsulfonarylamines, which have a sulfonamide group attached to a cyclic structure without the amine moiety at the N4 position (carbonic anhydrase inhibitors, sulfonfylureas, loop diuretics, thiazides, cyclo-oxgenase 2 inhibitors, and protease inhibitors); and (3) the simple sulfonamides, which have a sulfonamide moiety not directly connected to a ring structure (triptans, topiramate, probenecid, etc.). Patients with an allergy to sulfonamide antibiotics have been considered at risk for cross-reactivity.

Sulfonamide antibiotic reactions encompass the entire Gell-Combs spectrum of hypersensitivity (types 1-4). Type 1 responses are IgE-mediated and include urticaria, angioedema, and anaphylaxis with cardiovascular collapse. In the case of the sulfonamide antibiotics, interaction of IgE is highly stereospecific and is directed against the unmetabolized parent drug at the N1 heterocyclic ring but not at the sulfonamide group of the antibiotic. Thus, a type 1 hypersensitivity cross-reaction between a sulfa antibiotic and a nonantibiotic such as acetazolamide, which lacks the N1 ring, is unlikely.

Type 2 responses involve IgM- or IgG-mediated cytotoxic attack on cells, leading to hemolytic anemias, neutropenias, thrombocytopenias, and vasculitides. For the sulfonamide antibiotics, these humoral hypersensitivity reactions are not directed against the parent drug but instead result from antibody association with drug metabolites. Drug metabolites also play a role in type 3 hypersensitivity reactions, which involve formation of antigen-antibody immune complexes in serum and deposition of those complexes in tissues and organs throughout the body (glomerulonephritis, arthritis, serum sickness, Arthus reaction) and in the sulfonamide hypersensitivity syndrome are characterized by serum sickness, fever, rash, and organ dysfunction that can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. The sulfonamide antibiotics form multiple metabolites, but most hypersensitivity reactions result from hydroxylation at the N4 position by CYP2C9. Because nonantibiotic sulfonamides do not contain an N4 amine group, they do not produce these reactive metabolites or cause type 2 or 3 hypersensitivity reactions, or sulfonamide hypersensitivity syndrome.

Type 4 reactions are delayed-type hypersensitivity mediated by sensitized T cells. These reactions cause maculopapular rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis. For sulfonamide antibiotics, the binding of drug metabolites to self-proteins creates new
epitopes that stimulate T cells to attack native tissues.\textsuperscript{14} The formation of the reactive metabolites is stereospecific: generation of cross-reactive metabolites by the non-antibiotic sulfonamides (including acetazolamide) is mechanistically improbable and does not occur in vitro.\textsuperscript{15} Recently, it was shown that antibiotic-induced epidermal necrolysis might result from direct, drug-specific cytotoxic effects against keratinocytes rather than from metabolite formation; cross-reaction was found to be extremely stereospecific, such that only a few very closely related sulfonamide antibiotics, and no sulfonamide non-antibiotics, could reproduce the T-cell activation.\textsuperscript{16}

In addition to the arguments based on chemical and immunological analysis, reviews have also found little clinical or pharmacological evidence to suggest cross-reactivity between sulfonamide antibiotics and acetazolamide.\textsuperscript{17,18}

Although case reports have described anaphylactic reactions to acetazolamide and postulated a cross-reaction with sulfonamide antibiotics, testing for a sulfonarylamine allergy was not done.\textsuperscript{8,19}

In another article,\textsuperscript{20} skin testing of a patient with an allergic reaction to acetazolamide was positive to a sulfonamide solution. However, anaphylaxis to a drug without prior exposure is unlikely because type 1 IgE responses depend on preformed antibody. The patient had never received acetazolamide. Thus, the positive skin test could represent a concurrent IgE-mediated sulfonarylamine allergy rather than a cross-reaction to acetazolamide, which does not possess the chemical structure necessary to elicit a type 1 sulfonarylamine reaction.\textsuperscript{9,10,15}

The lack of available clinical or pharmacological evidence to support cross-reactivity between sulfonamide antibiotics and acetazolamide lends support to the use of acetazolamide to treat patients with episodic ataxia and periodic paralysis. Of our 3 sulfonamide-allergic patients, 2 improved in symptoms after treatment with acetazolamide and none of the 3 had a hypersensitivity reaction. We conclude that a sulfonamide allergy should not be a contraindication to treatment with acetazolamide in patients with neurologic channelopathies.

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