

## ONLINE FIRST

# Use of Acetazolamide in Sulfonamide-Allergic Patients With Neurologic Channelopathies

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**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 had

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.

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**N**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

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-nose testing, and an

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risk of severe reaction with other sulfa-containing 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 pa-

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ataxic gait. He was unable to tandem walk or stand with his feet together. He used a walker and needed support to sit. Magnetic resonance imaging findings were normal.

An initial neurologist prescribed acetazolamide for episodic ataxia, but a pharmacist declined to fill the prescription because the patient had had a previous severe skin rash after taking sulfonamide. After reviewing recent pharmacology literature, we concluded that acetazolamide could be given. When the patient received acetazolamide at a dosage of 125 mg/d, his gait improved within 1 week but the effect lasted for only 3 to 4 hours. When the dosage was changed to 250 mg twice a day, he further improved; he could stand unsupported and tandem walk. His nystagmus persisted. The patient had paresthesias in the fingers but no allergic signs or symptoms; he is continuing treatment with acetazolamide.

### CASE 2

An 83-year-old woman with genetically confirmed Andersen-Tawil syndrome type 1 (KCNJ2, R67W) first noticed symptoms at age 14 years, when she experienced frequent palpitations lasting 10 to 30 seconds and occasionally associated with syncopal episodes. She also had 6 episodes/year of whole-body paralysis lasting 1 to 2 hours and triggered by illness, stress, or hot weather. She gradually developed persistent interepisode weakness. She had distinctive physical features, including hypertelorism, a small mandible, and clinodactyly of the fingers and toes. A cardiac pacemaker was placed in 2005 and a defibrillator was placed in 2008. She also had osteoporosis and slight dementia. She reported having had a severe skin rash with sulfonamide.

On examination, she had proximal muscle weakness (4/4 hip flexors and extensors). The patient was entered into an outgoing trial on the effect of potassium and acetazolamide in Andersen-Tawil syndrome and began treatment with acetazolamide at a dosage of 250 mg twice a day. No adverse effects were noted during treatment in an 18-week period.

### CASE 3

A 21-year-old woman with global developmental delay presented with 1 or 2 severe headaches per week associated with vertigo, ataxia, and emesis. Testing revealed a mutation in the *CACNA1A* gene consistent with episodic ataxia type 2. The patient reported severe facial edema and generalized hives after administration of a sulfa antibiotic at age 6 years. Neurologic examination showed dysarthric speech, inability to tandem walk, right-beating nystagmus, and tremor on finger-to-nose testing. The patient began treatment with acetazolamide at a dosage of 125 mg/d. The episodes of headaches, vertigo, and ataxia ceased. No adverse events were noted during treatment.

### COMMENT

Acetazolamide has been used for the treatment of episodic ataxia type 2, with benefit in 50% to 75% of patients.<sup>1,2</sup> In episodic ataxia type 1, acetazolamide was also

effective in decreasing attack frequency.<sup>3</sup> Acetazolamide is also effective in the periodic paralyses.<sup>4</sup> 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.<sup>5,6</sup>

Acetazolamide is a nonbacteriostatic sulfonamide that contains a sulfonamide functional group but lacks antibiotic activity. The sulfonamides include the following: (1) the sulfonylarylamines, which have a sulfonamide moiety attached to a benzene ring with an unsubstituted amine at the N4 position (antibiotics, notably sulfanilamide and sulfamethoxazole); (2) the nonsulfonylarylamines, which have a sulfonamide group attached to a cyclic structure without the amine moiety at the N4 position (carbonic anhydrase inhibitors, sulfonylureas, loop diuretics, thiazides, cyclo-oxygenase 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).<sup>7</sup> Patients with an allergy to sulfonamide antibiotics have been considered at risk for cross-reactivity.<sup>8</sup>

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.<sup>9,10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> For sulfonamide antibiotics, the binding of drug metabolites to self-proteins creates new

epitopes that stimulate T cells to attack native tissues.<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup>

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.<sup>17,18</sup>

Although case reports have described anaphylactic reactions to acetazolamide and postulated a cross-reaction with sulfonamide antibiotics, testing for a sulfonamide allergy was not done.<sup>8,19</sup>

In another article,<sup>20</sup> 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 sulfonamide allergy rather than a cross-reaction to acetazolamide, which does not possess the chemical structure necessary to elicit a type 1 sulfonamide reaction.<sup>9,10,15</sup>

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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