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## Which diuretics are safe and effective for patients with a sulfa allergy?

### Evidence-based answer

Diuretics that do not contain a sulfonamide group (eg, amiloride hydrochloride, eplerenone, ethacrynic acid, spironolactone, and triamterene) are safe for patients with an allergy to sulfa. The evidence is contradictory as to whether a history of allergy to sulfonamide antibiotics increases the risk of

subsequent allergic reactions to commonly used sulfonamide-containing diuretics (eg, carbonic anhydrase inhibitors, loop diuretics, and thiazides) (strength of recommendation: **C**, based on case series and poor quality case-control and cohort studies).

### Clinical commentary

#### Are all sulfa drugs created equal?

Historical bromides commonly fall by the wayside as better evidence becomes available. Who would have thought 15 years ago that we would be promoting beta-blockers for patients with congestive heart failure?

Likewise, with closer inspection, we have learned that not all sulfa drugs are created equal. The stereospecificity due to the absence of aromatic amines in common diuretics means they are safe for patients with known sulfa antibiotic allergies. Given that diuretics are older

agents and off-patent, with no company to take up their cause, no one has been willing to challenge outdated package insert warnings.

As clinicians who regularly work without a net, we are accustomed to prescribing medications in less than ideal circumstances. Thankfully, reasonable evidence is available to support what many of us are already doing—using cheap thiazides for patients despite a history of sulfa allergy.

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### FAST TRACK

**Reasonable evidence supports what many of us are doing: Using cheap thiazides for patients with a history of sulfa allergy**

### Evidence summary

Little research has been performed on sulfonamide antibiotic and sulfonamide diuretic allergic cross-reactivity. What we do know is that there are 2 classes of sulfonamides—those with an aromatic amine (the antimicrobial sulfonamides) and those without (eg, the diuretics acetazolamide, furosemide,

hydrochlorothiazide, and indapamide). Hypersensitivity reactions occur when the aromatic amine group is oxidized into hydroxylamine metabolites by the liver. Sulfonamides that do not contain this aromatic amine group undergo different metabolic pathways, suggesting that allergic reactions that do occur in this group are not due to cross-reactivity

in sulfa-allergic patients. But that point is far from settled by the research.

### **On one side, a large cohort study shows some cross-reactivity**

A large retrospective cohort study using Britain's General Practice Research Database identified 20,226 patients seen from 1987 through March 1999 who were prescribed a systemic sulfonamide antibiotic, and then at least 60 days later received a nonantibiotic sulfonamide (eg, thiazide diuretic, furosemide, oral hypoglycemic).<sup>1</sup> Researchers reviewed records to determine whether patients described as having an allergic reaction to a sulfonamide antibiotic were at increased risk of having a subsequent allergic reaction to a sulfonamide nonantibiotic.

Patients were identified as being allergic using both narrow definitions (anaphylaxis, bronchospasm, urticaria, laryngospasm, or angioedema) and broad ones. As only 18 patients out of the 20,226 patients were reported as having an allergic reaction using the narrow definition, analysis was based on the broad definition. Added to the broad category were asthma, eczema, and other "adverse" drug effects that were not specified by the author.

Using this broad definition, researchers identified allergies to sulfonamide antibiotics in 969 patients. Of this group, 96 patients (9.9%) had a subsequent reaction to a sulfonamide nonantibiotic, which included drugs from the loop and thiazide diuretic classes (including bumetanide, chlorothiazide, furosemide, hydrochlorothiazide, indapamide, and torsemide). It was unclear if any patients taking a carbonic anhydrase inhibitor experienced an allergic reaction. For comparison purposes, of the 19,257 patients who were not identified as having an allergy to a sulfonamide antibiotic, again using the broad definition, 315 (1.6%), had a subsequent allergic reaction to a sulfonamide nonantibiotic, for an unadjusted odds ratio of 6.6 (95% confidence interval [CI], 5.2–8.4).

When the results were adjusted for age, sex, history of asthma, use of medications for asthma or corticosteroids, the adjusted odds ratio for individuals experiencing an allergy to a nonantibiotic sulfonamide in those persons with a history of allergy to a sulfonamide antibiotic was 2.8 (95% CI, 2.1–3.7). Of note, the adjusted odds ratio for the occurrence of a penicillin allergy in a patient with a history of sulfonamide antibiotic allergy was significantly higher at 3.9 (95% CI, 3.5–4.3).

Some limitations of the study included uncertainty of cause and effect of prescribed medications and subsequent reactions, possible inconsistency of physician diagnosis and coding, and lack of precision in the diagnosis of allergic reactions. There is also the possibility of "suspicion bias," where patients with a history of allergies may be more closely monitored for subsequent reactions than nonallergic patients.

### **On the other side, small studies reveal little risk of cross-reaction**

Researchers involved in a retrospective study of 363 hospital charts examined 34 patients with a self-reported history of sulfa allergy who were subsequently given acetazolamide (a carbonic anhydrase inhibitor), furosemide (a loop diuretic), or both.<sup>2</sup> The nature of the self-reported sulfa allergic reaction was documented in 79% of the 34 patients. These reported reactions included urticarial rash, nonspecified rash, dyspnea, swelling, nausea or vomiting, throat swelling, red eyes, and bullae. Two patients who were given acetazolamide developed urticaria. No allergic reactions occurred for those patients given furosemide.

The researchers concluded that there was little clinical or pharmacological evidence to suggest that a self-reported sulfa allergy was likely to produce a life-threatening cross-reaction with acetazolamide or furosemide. Small numbers and the lack of a standard definition for an allergic reaction limited the strength of their conclusion.

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### **FAST TRACK**

**The odds of an allergy to a nonantibiotic sulfonamide more than doubled if the patient had a history of allergy to a sulfonamide antibiotic**

A small single-blind study of 28 patients with a history of fixed drug eruption to sulfonamide antibiotics examined the usefulness of patch testing as an alternative to controlled oral challenge testing.<sup>3</sup> Before patch testing, a sulfonamide antibiotic allergy was confirmed by each patient with an oral challenge of sulfamethoxazole, sulfadiazine, or sulfamethazole. Potential cross-reactivity to several nonantibiotic sulfonamides (including furosemide) was also investigated using controlled oral challenge testing of these agents. Every patient tolerated a subsequent oral challenge with furosemide.

#### **Literature reviews limited by small numbers**

Two literature reviews examined the small number of case series, case reports, and “other articles” and concluded little evidence supports the presence of cross-reactivity between sulfonamide antibiotics and non-sulfonamide antibiotics.<sup>4,5</sup> These reviews were limited by their search criteria and lack of explicit critical appraisal.

A literature review of Medline from 1966 to early 2004 revealed 21 case series, case reports, and “other articles” that evaluated the presence of cross-reactivity.<sup>4</sup> When the authors of this literature reviewed drilled down to diuretics, they found 5 case reports for cross-reactivity to acetazolamide, 2 case reports for furosemide, 1 case series, and 2 case reports for indapamide (a thiazide diuretic). After reviewing the studies, the authors concluded that little evidence suggested a problem with cross-reactivity either with acetazolamide or furosemide and that there may be an association of cross-reactivity between sulfonamide antibiotics and indapamide. This study was limited by its small numbers and lack of explicit critical appraisal.

In another literature review—in which the main focus was cross-reactivity between sulfonamide antibiotics and celecoxib—the authors concluded that little evidence supported definitive cross-reactivity between sulfonamide antibiotics and diuretics.<sup>5</sup> The limitations of this study were similar to those of the previous study.

#### **Recommendations from others**

The manufacturer insert for furosemide states, under the heading “General Precautions,” that “patients allergic to sulfonamides may also be allergic to furosemide.”<sup>6</sup> A similar warning occurs for hydrochlorothiazide under the heading “Contraindications.”<sup>7</sup> ■

#### **References**

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