

Severe Allergic Reaction to Hydrochlorothiazide Mimicking Septic Shock

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Hydrochlorothiazide (HCTZ) is a sulfonamide-containing drug with commonly reported adverse effects that include electrolyte abnormalities, orthostatic hypotension, hyperglycemia, and photosensitivity. A few reports have described rare but serious drug complications such as interstitial pneumonitis, angioedema, and aplastic anemia. We describe a patient who experienced a serious HCTZ-induced adverse event that, to our knowledge, has not yet been reported in the literature. A 78-year-old woman came to the emergency department with dyspnea and severe fatigue; her signs and symptoms were suggestive of septic shock from pneumonia. She was treated accordingly, her condition improved, and she was discharged home. During the next 2 months, the patient returned to the emergency department 2 more times and was hospitalized each time with the same diagnosis. During her third admission, it was discovered that the patient's primary care physician had restarted her HCTZ for hypertension after it had been discontinued during each of the first two hospitalizations. The patient's symptoms began within hours of the first and second hospitalizations and almost immediately after taking a dose of HCTZ on the day of the third hospitalization. Her medical history revealed documented allergic reactions to sulfonamide drugs and penicillin; thus a hypersensitivity reaction to HCTZ was suspected. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship between the patient's hypersensitivity reactions and HCTZ therapy. Because of a lack of evidence showing cross-reactivity among the different classes of sulfonamides, the mechanism of the allergic reaction to HCTZ was unlikely to be cross-sensitivity between sulfonamide antibiotics and sulfonamide nonantibiotic drugs. Although the mechanism is not clear, evidence shows that the allergy to the HCTZ (sulfonamide nonantibiotic) may be due to a predisposition to drug allergies rather than sulfonamide cross-sensitivity. Clinicians should be aware of the potential for these types of allergic reactions.

Key Words: hydrochlorothiazide, HCTZ, sulfonamide, adverse drug reaction, drug allergy, critical care, hypersensitivity, cross-reactivity.

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The United States Food and Drug Administration approved hydrochlorothiazide (HCTZ) for clinical use in 1959. Based on information from the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood

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Pressure, HCTZ is commonly the first drug used to treat mild hypertension.¹ The report recommends thiazide-type diuretics as treatment for most patients with uncomplicated hypertension.

Adverse effects from HCTZ include hypovolemia, electrolyte abnormalities, hyperglycemia, abdominal pain, constipation, diarrhea, and headache. These effects are usually mild and relatively easy to treat, or they resolve rapidly without sequelae when the drug is discontinued.

More severe reactions, such as Stevens-Johnson syndrome, interstitial pneumonitis, angioedema, and aplastic anemia, may occur, but much less frequently than the other effects.²⁻⁴

Serious adverse drug reactions, such as hypersensitivity reactions, are implicated in 7.5% of admissions to critical care units.⁵ Therefore, clinicians are extremely cautious when prescribing drugs that have the potential of cross-sensitivity with drugs documented on a patient's allergy profile. Because of the theoretical possibility of drug cross-sensitivity, patients with allergies to sulfonamide antibiotics may be excluded from receiving nonantibiotics that contain sulfonamide groups, such as diuretics and hypoglycemic drugs. It is unclear whether cross-reactivity exists among the sulfonamide classes, and current data suggest that it may be unlikely.⁶

We describe a patient with allergies to sulfonamide antibiotics and penicillin who developed a hypersensitivity reaction to HCTZ that resulted in presumed septic shock and repeated admissions to the intensive care unit.

Case Report

A 78-year-old woman came to the emergency department after a rapid onset of dyspnea and severe fatigue. Her body temperature was 103.4°F, heart rate 20 beats/minute, and systolic blood pressure 70 mm Hg. Initial diagnostic tests showed a white blood cell count of $23 \times 10^3/\text{mm}^3$ (normal range $3.5\text{--}12.5 \times 10^3/\text{mm}^3$), with a differential blood count of 61% neutrophils (50–70%), 32% bands (0–5%), and 2% lymphocytes (20–50%). Her lactate concentration was 40.4 mg/dl (6.3–18.9 mg/dl). Arterial blood gases measured while she was receiving 100% oxygen by nonrebreather mask revealed a partial pressure of carbon dioxide of 38 mm Hg (normal range 35–45 mm Hg), partial pressure of oxygen 72 mm Hg (80–95 mm Hg), and pH 7.34 (7.35–7.45). Chest radiography showed diffuse bilateral infiltrates, and electrocardiographic findings were within normal limits except for tachycardia.

The patient and her family stated that she was in her usual state of health and had just been seen by her primary care provider for a routine examination. Her medical history included hypertension, hyperlipidemia, glaucoma, asthma, depression, and below-the-knee amputation of her left leg because of melanoma. The patient's drug therapy consisted of HCTZ 25 mg/day (first

taken within hours of this admission), simvastatin 80 mg/day, trazodone 25 mg at bedtime, albuterol inhaler as needed, and brimonidine and levobunolol eye drops. She had documented allergies to penicillins and sulfamethoxazole. Her penicillin allergy manifested as a skin rash; no specific reaction was known for sulfamethoxazole.

The patient's presentation was suggestive of septic shock from pneumonia. Therefore, early goal-directed therapy was started with aggressive fluid resuscitation and norepinephrine guided by central venous pressure and continuous monitoring of central venous oxygen saturation. Empiric broad-spectrum antibiotic therapy with ceftriaxone and azithromycin was started. The patient's condition rapidly improved, and she was weaned off norepinephrine within 8 hours. Her elevated lactate level and central venous oxygen saturation levels returned to normal within 24 hours after the start of therapy. No infectious microorganism was identified.

The patient was discharged from the hospital 1 week after admission, and a follow-up appointment was scheduled with her primary care physician. Her drug therapy at time of discharge consisted of azithromycin 500 mg/day (for 3 more days), beclomethasone 80 µg two puffs twice/day, lisinopril 20 mg/day, furosemide 20 mg/day, simvastatin 80 mg at bedtime, and brimonidine and levobunolol eye drops.

Two weeks later, the patient returned to the emergency department with flu-like symptoms, nausea, and vomiting associated with watery stools. Her initial diagnostic results were similar to those observed on her first admission except that her white blood cell count was $2.4 \times 10^3/\text{mm}^3$ with 54% neutrophils, 17% bands, and 29% lymphocytes. The patient's family stated that she had seen her primary care physician earlier that day for her follow-up visit and had felt well at that time. When questioned about the patient's drug therapy, both the patient and her family stated that no new drugs had been prescribed; however, they reported that her drug therapy consisted of furosemide 20 mg/day, HCTZ 25 mg/day, beclomethasone inhaler, and brimonidine and levobunolol eye drops.

Pneumonia with septic shock was again suspected. The patient's therapy and hospital course were similar to those of her first admission. During her second hospitalization, she received aztreonam, metronidazole, moxifloxacin, lisinopril, and furosemide. Because of nonspecific QT changes on her

electrocardiogram during this admission and because of a slightly elevated cardiac troponin I level, echocardiography and adenosine thallium stress testing were done before discharge. Neither test showed any abnormalities.

At the time of discharge, the patient's drug therapy consisted of lisinopril 20 mg twice/day, simvastatin 80 mg at bedtime, aspirin 81 mg/day, furosemide 20 mg/day, potassium chloride 10 mEq/day, moxifloxacin for 5 more days, prednisone 10 mg/day for 7 days, beclomethasone inhaler, and brimonidine and levobunolol eye drops.

Approximately 2 weeks after discharge from her second hospitalization, and within hours after a routine visit with her primary care physician, the patient again came to the emergency department with severe dyspnea and fatigue. This time, her drug therapy was listed as alprazolam 0.25 mg/day, aspirin 81 mg/day, furosemide 20 mg/day, potassium chloride 10 mEq/day, lisinopril 20 mg/day, HCTZ 25 mg/day, simvastatin 80 mg/day, trazodone 25 mg at bedtime, beclomethasone, albuterol, and brimonidine and levobunolol eye drops.

Because of the frequent recurrences of shock, other mitigating factors were suspected. The family was questioned about the patient's clinic visit, but they were not aware of any clinically significant findings or changes in her care. Her primary care physician was contacted and it was discovered that during the past two follow-up visits, she had been instructed to resume HCTZ therapy. Given this information, an anaphylactic reaction to HCTZ was suspected, rather than septic shock, as the cause of her emergency presentation.

The patient's condition improved with fluid administration, norepinephrine infusion, and oxygen supplementation. She was then questioned about her HCTZ prescriptions. According to pharmacy records, the patient had filled her prescription for HCTZ 3 days before her first admission. The patient stated she had taken a dose of HCTZ within hours before her previous two admissions. With the latest presentation, her symptoms started almost immediately after she took a dose of HCTZ.

Discussion

Septic shock can appear similar to anaphylaxis, with symptoms that include hypotension, fever, increased heart rate, and respiratory distress. Our patient's clinical presentation in the

emergency department did not seem consistent with a possible drug reaction to any of the drugs that she reported she was taking. Therefore, with no other reason to explain her signs and symptoms, and given her advanced age and the infiltrates seen on her chest radiograph, the presumptive diagnosis was septic shock secondary to pneumonia. However, by the patient's third admission, it seemed unusual for septic shock to occur repeatedly within a short period.

On review of our hospital records, we found that the patient had been exposed to HCTZ on three occasions and that her symptoms began within hours after she took each dose. The dates of her second and third admissions coincided with the days on which she visited her primary care physician, when she was hypertensive and was instructed to restart HCTZ. We discovered that the cause was actually an unrecognized drug hypersensitivity reaction secondary to HCTZ. Use of the Naranjo adverse drug reaction probability scale⁷ yielded a score of 5, indicating a probable relationship between the hypersensitivity reactions in our patient and HCTZ.

When a patient reports having an adverse reaction to a sulfonamide antibiotic and subsequently takes a sulfonamide nonantibiotic, a relevant clinical concern is whether an immune-mediated cross-reaction to the sulfonamide component has occurred. That is, has the patient had an allergic reaction to sulfur or an idiosyncratic reaction to the primary drug? Examples of drugs that contain sulfur but that are not sulfonamides are amoxicillin, clopidogrel, captopril, ranitidine, spironolactone, sulindac, and omeprazole. Adverse responses to these drugs can sometimes be idiosyncratic reactions and are not known to be cross-reactions to sulfonamide-containing compounds. Sulfites, which are used as antioxidants or preservatives in prepared foods and drugs, are known to cause respiratory hyperreactivity as well as immunoglobulin E-mediated immediate hypersensitivity reactions.⁸ Cross-reactivity between sulfites and sulfonamide antibiotics is highly unlikely because the mechanisms or antigenic sites that mediate the allergic response to sulfites appear to differ from those responsible for sulfonamide antibiotic sensitivity.

A number of antibiotics and nonantibiotics contain a sulfonamide functional group that includes a sulfur dioxide and nitrogen moiety directly attached to a benzene ring. Examples of sulfonamide nonantibiotic drugs are acetazolamide,

amprenavir, bendroflumethiazide, bumetanide, celecoxib, chlorpropamide, chlorothiazide, chlorthalidone, dapsone, diazoxide, furosemide, glimepiride, glipizide, glyburide, HCTZ, indapamide, metolazone, probenecid, sulfasalazine, sumatriptan, tolazamide, tolbutamide, torsemide, and zonisamide.

Immune-mediated cross-reactivity is believed to be common with sulfonamide antibiotics. However, whether cross-reactivity occurs with sulfonamide nonantibiotics is in doubt.^{9, 10} The chemical structure of sulfonamide antibiotics consists of a sulfur dioxide group, an arylamine group at the N4 position, and a five- or six-member nitrogen-containing ring attached to the N1 nitrogen of the sulfonamide group at the R1 or R2 position (Figure 1). This structural configuration is absent in sulfonamide nonantibiotics. Immunologic reactions to either the arylamine or the five- or six-member nitrogen ring or their metabolites are thought to be responsible for the hypersensitivity related to sulfonamide antibiotics.¹¹

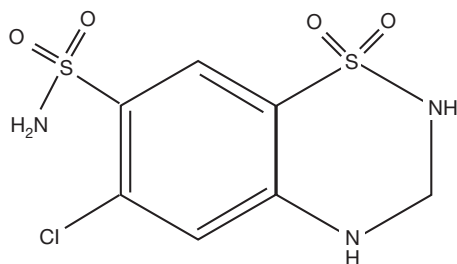
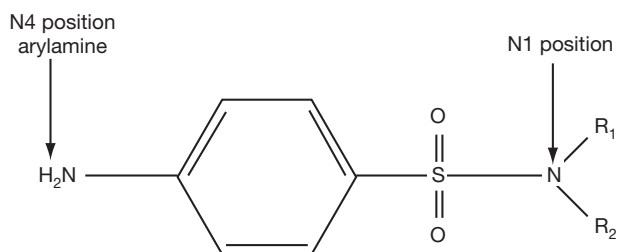
In one study, sera from patients who experienced life-threatening anaphylactic reactions to

sulfamethoxazole were tested with 13 other sulfonamide antibiotics.¹² The 5-methyl-3-isoxazolyl heterocyclic ring at the N1 position (the sulfonamide nitrogen) was the allergenic determinant since the sulfonamide antibiotics that contained this group had the strongest affinity for immunoglobulin E. In immunologic studies, serum-derived antibodies against sulfamethazine were tested against sulfonamide nonantibiotics, including HCTZ.¹³ The results showed no reactivity of the antibodies with any of the tested drugs.

In a retrospective cohort study published in 2003, investigators evaluated the potential for allergic cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotic drugs.¹⁴ The study included more than 20,000 patients who had taken both types of drugs within 60 days of each other. Of the 969 patients who reported having an allergic reaction to the sulfonamide antibiotic, 96 patients (9.9%) had an allergic reaction to the sulfonamide nonantibiotic drug (unadjusted odds ratio of 6.6, 95% confidence interval 5.2–8.4). In addition, the risk of having an allergy to sulfonamide nonantibiotics was higher among patients with a history of penicillin reactions than among patients with previous sulfonamide antibiotic allergy (adjusted odds ratio 0.6, 95% confidence interval 0.5–0.8). The authors concluded that allergies to sulfonamide nonantibiotic drugs were more strongly associated with penicillin allergies than with allergies to sulfonamide antibiotics. This association appeared to be due to a predisposition to allergic reactions rather than cross-reactivity with sulfonamide.

Conclusion

Our patient's history of allergies to several drugs may have placed her at risk for having a hypersensitivity reaction to HCTZ, which manifested as septic shock. Because of a previously described lack of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotic drugs, the potential for a hypersensitivity reaction to the sulfonamide component in HCTZ seemed unlikely. Although the exact immunologic mechanism may not be fully understood, having an allergy to sulfonamide antibiotics, along with multiple allergies, may be a risk factor for developing hypersensitivity to sulfonamide nonantibiotics. Clinicians should be aware of the potential for these types of allergic reactions.



Hydrochlorothiazide

Figure 1. Basic structures of sulfonamide antibiotics and hydrochlorothiazide.

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