CME

Approach to managing patients with sulfa allergy

Use of antibiotic and nonantibiotic sulfonamides

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ABSTRACT

OBJECTIVE To present an approach to use of sulfonamide-based (sulfa) medications for patients with sulfa allergy and to explore whether sulfa medications are contraindicated for patients who require them but are allergic to them.

SOURCES OF INFORMATION A search of current pharmacology textbooks and of MEDLINE from 1966 to the present using the MeSH key words "sulfonamide" and "drug sensitivity" revealed review articles, case reports, one observational study (level II evidence), and reports of consensus opinion (level III evidence).

MAIN MESSAGE Cross-reactivity between sulfa antibiotics and nonantibiotics is rare, but on occasion it can affect the pharmacologic and clinical management of patients with sulfa allergy.

CONCLUSION How a physician approaches using sulfa medications for patients with sulfa allergy depends on the certainty and severity of the initial allergy, on whether alternatives are available, and on whether the contemplated agent belongs to the same category of sulfa medications (ie, antibiotic or nonantibiotic) as the initial offending agent.

RÉSUMÉ

OBJECTIF Proposer une façon d'utiliser les médicaments à base de sulfamides (sulfas) chez les patients allergiques aux sulfas et vérifier si ces médicaments sont contre-indiqués pour ces patients.

SOURCES DE L'INFORMATION Une consultation des récents ouvrages de pharmacologie et de MEDLINE entre 1966 et aujourd'hui à l'aide des mots clés MeSH «*sulfonamide*» et «*drug sensitivity*» a permis de repérer plusieurs articles de revue et études de cas, une étude d'observation et des rapports d'opinion consensuelles (preuves de niveau III).

PRINCIPAL MESSAGE Les réactions croisées entre sulfas antibiotiques et non antibiotiques sont rares, mais elles peuvent à l'occasion affecter le traitement pharmacologique et clinique des patients allergiques aux sulfas.

CONCLUSION La façon d'utiliser les médicaments à base de sulfas chez les patients allergiques aux sulfas dépend du degré de certitude quant à l'allergie initiale, de la sévérité de cette condition, de la disponibilité de médications alternatives et du fait que l'agent envisagé appartient ou non à la même catégorie de médicament sulfamide (i.e., antibiotique ou non antibiotique) que l'agent initialement responsable.

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Case description

Mrs MacDonald, a 70-year-old woman, is relatively new to my practice. She recently helped me review my understanding of what we mean by "sulfa allergy." (Patient's name and age have been changed to protect her privacy.) On her initial visit, she had a medical history of hypertension, obstructive sleep apnea, osteoarthritis, and multiple allergies, including to "sulfa" drugs, hydrochlorothiazide, and various environmental elements for which she received allergy shots. Her medications included 240 mg of verapamil, 8 mg of perindopril, and 150 mg of sulindac (a nonsteroidal anti-inflammatory drug), all taken by mouth twice daily, and 81 mg of acetylsalicylic acid taken once daily.

Her sleep apnea was well controlled with nightly use of a continuous positive airway pressure machine set at a pressure of 5 cm of H_2O. She had never had signs of left- or right-sided heart failure. She complained of increasing dyspnea on exertion, orthopnea, and peripheral edema. Clinical examination, and later radiographic and echocardiographic findings, confirmed biventricular congestive heart failure.

After explaining the diagnosis and her predisposition to it, I prescribed 40 mg of oral furosemide to be taken once daily and asked her to stop taking sulindac, thinking it was contributing to fluid retention. I also switched her nondihydropyridine calcium channel blocker to amlodipine (initially 5 mg by mouth once daily), a dihydropyridine medication that contributes less to fluid retention. I received a telephone call from the pharmacist later that day, however, warning me that she should not take furosemide because of her history of allergy to sulfonamide medications. Although furosemide indeed carries a sulfa moiety, I have not in the past hesitated to prescribe it to patients who are allergic to sulfa antibiotics because I thought cross-reactivity was very unlikely. The pharmacist pointed out that Mrs MacDonald had reported a previous "serious" reaction to hydrochlorothiazide (another sulfonamide nonantibiotic), so I refrained from prescribing furosemide.

Examining the evidence

Before proceeding further, and having the luxury of time as the patient was not in any acute distress, I decided to examine the evidence for and against prescribing sulfa nonantibiotics to patients with a history of sulfa allergy. This and similar questions arise commonly in primary care, especially with the re-emergence of sulfamethoxazole compounds as important first-line antibiotics in this age of increasing resistance to them. Such compounds are also used for *Pneumocystis carinii* prophylaxis for patients with HIV and AIDS. It is surprising, therefore, that an approach to this problem is not more often discussed.

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Sources of information

I first read the relevant chapters of authoritative texts on pharmacology and the manufacturer's package insert for Lasix (furosemide). Although the textbooks were not useful in answering my question, they did provide a good review of classes of sulfa medications. The manufacturer's package insert simply stated that patients might be allergic to Lasix if they are allergic to "sulfonamides" without further discussion or differentiation among various kinds of sulfonamides.

I then searched MEDLINE using the MeSH keywords "sulfonamide" and "drug sensitivity" from 1966 to the present, looking for the best available evidence to guide my decision. Although a randomized controlled trial (level I evidence) would have been most useful, no such evidence was found. The search did reveal many review articles and reports of consensus opinion (level III evidence), but surprisingly, these all referred to only a few primary studies that dealt with my question. Most of these studies were case reports, but one was an observational study (level II evidence).

Main message

Sulfonamides are commonly used in primary care. Although trimethoprim-sulfamethoxazole and other sulfa-antibiotic combinations are especially widely used (sulfonamides were the first antibiotics ever introduced in 1936), this class of medication also includes many nonantibiotic agents. **Table 1** lists the most common drugs containing a sulfa (SO_2NH_2) moiety in Canada. Several of these drugs are rarely thought of as sulfonamides.

Adverse reactions to sulfa antibiotics are relatively common compared with such reactions to other antimicrobial agents. Adverse reactions have been estimated to occur in 3% of courses,[1] but only 3% of these actually are true hypersensitivity.[2] Unfortunately, hypersensitivity reactions to sulfonamides can be severe and even life-threatening. They include immediate, immunoglobulin E–mediated anaphylactic reactions and florid dermatologic reactions, such as Stevens-Johnson syndrome. Hypersensitivity reactions are more commonly characterized by fever or a maculopapular rash that develops 7 to 14 days after initiating the offending agent.[2] There is no reliable skin test to rule out or confirm sulfa allergy.

There are important chemical differences between sulfa antibiotics and nonantibiotics. Most authors agree that nonantibiotics are less likely to cause severe reactions, and that the chemical differences between sulfa

Table 1. Commonly used sulfonamide nonantibiotic medications available in Canada

DIURETICS
Carbonic anhydraze inhibitors (Acetazolamide)
Loop diuretics • Furosemide • Bumetanide Note that ethacrynic acid is not a sulfonamide
Thiazide and related diuretics • Hydrochlorothiazide • Chlorothiazide • Chlorthalidone • Indapamide • Metolazone
SULFONYLUREAS
Glyburide Chlorpropamide Gliclazide Glimepiride Tolbutamide
RHEUMATOLOGIC AGENTS
Sulfasalazine Probenecid (also commonly used to prolong the half-life of certain antibiotics) Celecoxib Valdecoxib Note that rofecoxib, currently unavailable in Canada, is not a sulfonamide
OTHER AGENTS
Sumatriptan Naratriptan Topiramate Ibutilide Sotalol Dapsone

antibiotics and nonantibiotics make true cross-reactivity extremely unlikely.[1-3] There is only one case report in the literature of anaphylaxis caused by furosemide[4]; the authors were unable to prove conclusively that the allergen was in fact chemically related to the sulfa moiety.[5]

Perhaps the most reassuring evidence comes from Strom et al,[1] who elegantly turned the United Kingdom General Practice Research Database into a retrospective cohort study (level II evidence) to show that giving sulfa nonantibiotics to patients with a history of sulfa (antibiotic) allergy carries little risk of cross-reactivity. The authors reviewed the charts of 969 patients who had had allergic reactions to sulfonamide antibiotics and of 19 257 patients who had not. All these patients subsequently received sulfonamide nonantibiotics. For this study, "allergy" was defined very broadly and included development of eczema and various unspecified adverse effects within a full month of receiving the medication in question, making underreporting bias unlikely. Although Strom and colleagues found that patients allergic to sulfonamide antibiotics were more likely than nonallergic patients to react to sulfonamide nonantibiotics (9.9% vs 1.1%), they also found that the rate of reaction was even greater among patients allergic to penicillin who received sulfonamide nonantibiotics (14.2%). Penicillins do not have a sulfonamide moiety, so the researchers argued that any sulfonamide cross-reactivity appears predominantly related to a greater predisposition to allergic reactions in general among patients allergic to sulfonamide antibiotics, rather than to a specific sulfa hypersensitivity.

In our case, our patient's previous reactions to "sulfa" drugs and hydrochlorothiazide were not well documented, and neither she nor the pharmacist could recall the specific nature of the reactions. Since the patient thought that her reactions were serious, and because her allergy extended to both antibiotic and nonantibiotic sulfonamides, I was compelled to find an alternative to furosemide.

A look at **Table 1** shows that most diuretic agents are sulfonamide derivatives. The only diuretics that are not are the potassium-sparing diuretics (triamterene, spironolactone, and amiloride) and ethacrynic acid.[6] At the time, the pharmacist informed me that they did not have any ethacrynic acid in stock, so I chose amiloride. I realized that it did not have the same natriuretic effect as ethacrynic acid, the agent of choice in this case, and that she needed close follow-up as she was also taking an angiotensin-converting enzyme inhibitor. Some might argue that spironolactone, a potassium-sparing agent with strong anti-aldosterone activity, would be preferable based on the landmark Randomized Aldactone Evaluation Study[7] that showed improved survival among patients with severe (class III or IV) congestive heart failure using it. My patient, however, did not have this degree of illness. Several weeks after starting amiloride (10 mg by mouth daily), Mrs MacDonald developed hyperkalemia (K+=6.3 mmol/L). By this time, however, the pharmacy had received ethacrynic acid tablets, and my patient is now doing well on this medication at a dose of 50 mg daily and is no longer complaining of dyspnea or edema.

Conclusion

This case and the literature review I did for it illustrate that, although cross-reactivity between sulfa antibiotics and nonantibiotics is rare, certain situations warrant prudence. A difficult decision would await her physician should Mrs MacDonald's condition deteriorate. Would furosemide continue to be contraindicated if she developed acute pulmonary edema? After some reflection and discussion with my patient, I believe that, considering her history of serious reaction to hydrochlorothiazide, all possible alternatives should be explored before using another sulfonamide diuretic, such as furosemide. Alternatives would include using parenteral ethacrynic acid and a bilevel positive airway pressure mask.

For most patients with sulfa allergy who have no history of life-threatening reactions and are not allergic to more than one class of sulfonamides, however, available evidence suggests that furosemide can be used safely in an emergency. Further research that would help clinicians with this decision should include level I evidence from a randomized controlled trial or at least a prospective study.

When prescribing furosemide or other sulfonamide nonantibiotics to patients with sulfa allergy, it would be prudent to administer a test dose, orally if possible and in a monitored environment. Specialist consultation might also be helpful, as several desensitization protocols for sulfonamides are described in the literature.[2,8] A comprehensive approach to difficult cases involving sulfa allergies is shown in **Figure 1**.

I asked Mrs MacDonald to obtain a MedicAlert bracelet and will refer her to an allergist for advice regarding future use of diuretics in emergencies. Family physicians need to be especially attentive to the relatively common scenario in which a patient with a history of allergy to a sulfonamide antibiotic presents with congestive heart failure. The presence of allergies to other sulfonamides and the seriousness of these allergies, as well as the acuity of the patient's presentation, should all be taken into account when deciding on clinical management. Finally, the most important lesson from this case might be that family physicians can have a critical role

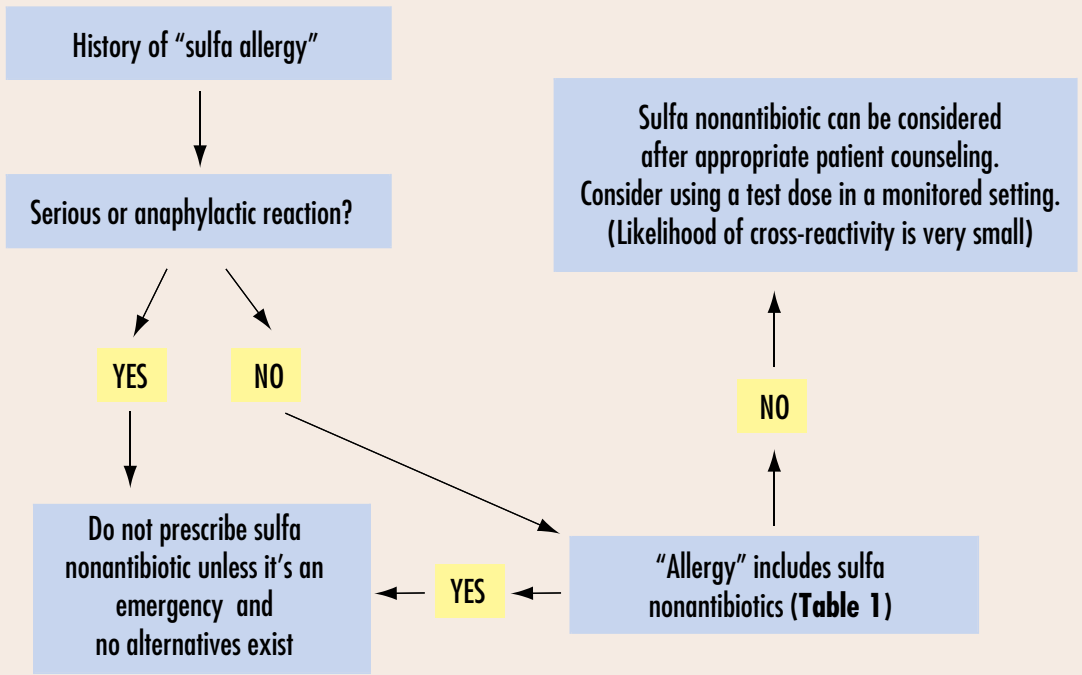
EDITOR'S KEY POINTS

- This article examines the evidence for and against prescribing sulfa nonantibiotics to patients with a history of sulfa allergy.
- The literature search revealed many review articles and reports of consensus opinion (level III evidence), but surprisingly, these all referred to only a few primary studies (case reports and one observational study).
- Cross-reactivity between sulfa antibiotics and nonantibiotics is rare, but on occasion it can affect the management of patients with sulfa allergy.

POINTS DE REPÈRE DU RÉDACTEUR

- Cet article fait le point sur les données favorables et défavorables quant à la prescription de sulfas non antibiotiques aux patients qui ont une histoire d'allergie aux sulfas.
- Une recherche dans la littérature a repéré plusieurs rapports de synthèse et rapports d'opinion consensuelle (preuves de niveau III), mais étonnamment, ils se référaient tous à un petit nombre d'études primaires (des études de cas et une étude d'observation).
- Les réactions croisées entre sulfas antibiotiques et non antibiotiques sont rares mais elles peuvent occasionnellement nuire au traitement des patients allergiques aux sulfas.

Figure 1. Approach to prescribing sulfa nonantibiotics for patients with sulfa allergy



in documenting and reporting allergic reactions properly and in anticipating possible clinical dilemmas in patients with multiple drug allergies.

Competing interests

None declared

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