'Sulfur allergy' label is misleading

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Summary

The term 'sulfur allergy' is misleading and dangerous and should not be used. An allergy to a sulfonamide antibiotic may imply cross-reactivity with other sulfonamide antibiotics, but does not imply cross-reactivity with non-antibiotic sulfonamides or other drugs containing sulfhydryl or sulfate groups. Patients who suffer from an allergic reaction to the combination of sulfamethoxazole and trimethoprim should be considered potentially allergic to trimethoprim and/or sulfamethoxazole until proven otherwise, and not recorded simply as 'sulfur allergic'. Allergy to sulfonamides also does not imply cross-reactivity with sulfite preservatives, sulfates or elemental sulfur.

Key words: cross-reactivity, sulfonamide allergy.

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Introduction

Sulfonamides were the first class of antibiotics to be introduced in the 1930s. They remain important because they are effective, relatively safe and inexpensive, but adverse effects are relatively common.

Up to 8% of hospitalised patients and 1–2% of those in the community are reported to suffer adverse effects from the combination of sulfamethoxazole with trimethoprim, although only about 3% of these are thought to represent hypersensitivity. The situation is markedly different in patients with HIV as up to 60% experience allergic adverse reactions.

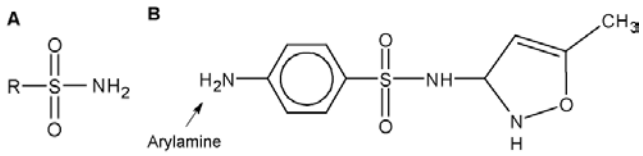
While most hypersensitivity reactions are relatively mild, sulfonamides account for a disproportionate number of cases of life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis.

Allergic mechanisms

The mechanisms of hypersensitivity to sulfonamides are not completely understood, but some principles are apparent.[1] The term sulfonamide applies to a sulfone group connected to an amine group (Fig. 1). All antibiotic sulfonamides are arylamines (Table 1).

Fig. 1

Sulfonamide structure



A Basic sulfonamide structure – present in many drugs.

B Sulfamethoxazole. The arylamine moiety, and also probably the 5-member ring containing a nitrogen atom, is thought to be important for hypersensitivity reactions.

Like most small chemical allergens, sulfonamides probably require metabolism or haptenation for immunogenicity. Hepatic oxidation of the arylamine group by the cytochrome P450 system results in the formation of a hydroxylamine intermediate metabolite which can be reduced by glutathione and excreted. However, the capacity for glutathione conjugation may be exceeded. The reactive hydroxylamine is capable of haptenating endogenous proteins and has been shown to be associated with hypersensitivity. Other reactive metabolites have also been identified. These may act by forming immunogenic structures (epitopes) for antibodies or T cells and also by direct cytotoxicity to lymphocytes and other immune cells.

Cross-reactivity

Many commonly used drugs, such as thiazide diuretics, gliclazide, frusemide and celecoxib, contain a sulfonamide moiety, but none contain the arylamine group. While it has long been considered that allergic cross-reactivity may exist between sulfonamide antibiotics and other sulfonamide drugs, this is actually unlikely because of the structural differences. Reports of cross-reactivity are based on single cases or small series.[2] The co-existence of hypersensitivity reactions to several drugs does not prove cross-reactivity between them. A review of all available relevant studies concluded that the dogma of cross-reactivity between sulfonylarylamines and other sulfonamide drugs cannot be supported by the evidence.[3] In patients who have had an allergic reaction to one drug, allergic reactions to other drugs, even if entirely unrelated, occur more commonly. In support of this concept, a very large cohort study showed

Table 1

Common examples of arylamine and non-arylamine sulfonamides

Drug groups	Cross-reactivity
Sulfonamide antibiotics (sulfonylarylamines) sulfamethoxazole sulfadiazine sulfadoxine sulfacetamide sulfasalazine (contains sulfapyridine)	Allergic cross-reactivity within this group is possible
Sulfonamide antiretrovirals (sulfonylarylamines) amprenavir fosamprenavir	Allergic cross-reactivity with sulfonamide antibiotics is likely on structural grounds but has not been established
Non-antibiotic sulfonamide drugs (non-sulfonylarylamines) frusemide hydrochlorothiazide gliclazide celecoxib	Current evidence suggests that allergy to sulfonamide antibiotics is not associated with increased risk of allergy to these drugs
Sulfhydryl drugs penicillin piroxicam captopril	No relationship to sulfonamide allergy
Sulfate drugs morphine sulfate heparin sulfate hydroxychloroquine sulfate glucosamine sulfate	No relationship to sulfonamide allergy

that the association between allergy to sulfonylarylamines and other sulfonamide drugs was no stronger than that between sulfonylarylamines and the completely unrelated penicillins.[4] The evidence therefore suggests that non-antibiotic (non-arylamine) sulfonamide drugs need not be considered as contraindicated in those with a history of hypersensitivity to antibiotic (sulfonylarylamine) sulfonamides. This conflicts with the product information of many drugs.

Trimethoprim with sulfamethoxazole

The most common sulfonamide antibiotic used in Australia is sulfamethoxazole in combination with trimethoprim. This combination has synergistic antimicrobial activity, however, when hypersensitivity reactions occur, the patient might be allergic to trimethoprim or sulfamethoxazole (or possibly both). Trimethoprim, on its own, has been reported to cause type 1 allergy (anaphylaxis)[5] and even to cause fatal toxic epidermal necrolysis.[6] There are cases in which patients who had anaphylaxis after trimethoprim-sulfamethoxazole were labelled 'sulfur allergic' and subsequently had anaphylaxis after receiving trimethoprim alone, indicating that the patient was actually allergic to trimethoprim, not sulfamethoxazole.

Patients who suffer from hypersensitivity reactions to trimethoprim-sulfamethoxazole should avoid both sulfonamide antibiotics **and** trimethoprim. If the original reaction to trimethoprim-sulfamethoxazole was mild, a cautious challenge with trimethoprim under observation is reasonable, but if the original reaction was severe, trimethoprim should not be used unless proven safe by testing or a careful graded dose challenge under the supervision of a clinical immunology and allergy specialist.

Sulfur

Sulfur is a natural element and exists in many forms. There are many substances which have names stemming from 'sulfur' such as sulfites (preservatives in food and drugs) and sulfates (common compounds found in drugs, soaps and cosmetics). Some patients who have suffered from hypersensitivity reactions to sulfonamide antibiotics are unfortunately labelled 'sulfur allergic'. This term creates confusion for the patient and often for health professionals. Many patients believe that having been labelled 'sulfur allergic' they are also at risk of adverse reactions or allergies from sulfites, sulfates and even elemental sulfur and may attempt to avoid them. Sulfates are sometimes mildly irritant and sulfites can cause respiratory reactions in patients with asthma and, rarely, non-immunoglobulin E-mediated

anaphylactic reactions, but there is no relationship between these reactions and hypersensitivity to sulfonamides. Patients who have had allergic reactions to sulfonamide drugs do not need to avoid sulfites, sulfates or sulfur.

Conclusion

As a general principle, all allergic adverse reactions to medications should be recorded in the patient's file with the specific name of the drug or drugs to which the patient has reacted and the nature of the reaction. Allergies should not be attributed to classes or groups of drugs unless proven because assumptions about cross-reactivity may later be found to be incorrect. The term 'sulfur (or sulphur, sulpha, sulfa) allergy' should not be used.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 27)

3. A patient who has an allergic reaction to the combination of trimethoprim and sulfamethoxazole may have a similar reaction to trimethoprim.
4. Patients who are allergic to sulfonamides should avoid food containing sulfites.

Medicinal mishap

Neutropenia with quetiapine

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Case

An 85-year-old woman was admitted to hospital with an exacerbation of heart failure secondary to cardiac arrhythmia. Her past history included atrial fibrillation, diastolic heart failure, emphysema, gastritis, Alzheimer's disease and anxiety. She was taking quetiapine, sertraline, donepezil, omeprazole, tiotropium, salbutamol and diltiazem.

Examination revealed rapid atrial fibrillation, with no systemic or focal signs of sepsis, and she was afebrile. Haemoglobin, thyroid function, liver function and serum creatinine were normal. Her chest X-ray showed changes consistent with pulmonary oedema and bilateral pleural effusions. She was treated with frusemide and aspirin.

On the day before admission her white cell count was normal (5.5×10^9/L) with a neutrophil count of 4.1×10^9/L. However, on admission her white cell count was low (2.9×10^9/L with a neutrophil count of 1.9×10^9/L). The day after admission her white cell count fell to 2.7×10^9/L and her neutrophil count to 1.5×10^9/L.

Following a detailed review of all her drugs and in consultation with the psychiatry team, we decided to start risperidone and cease her quetiapine as it could have been the cause of the neutropenia. She had started quetiapine 200 mg twice a day four months earlier for the control of psychotic behaviour related to Alzheimer's disease. Her white cell counts were normal before she started quetiapine.

Five days after admission, the white cell count had increased to 4×10^9/L and the neutrophil count to 2.6×10^9/L (see Table 1). Given her improvement, bone marrow biopsy was not performed. Her psychotic symptoms remained controlled with the switch to risperidone, and she was discharged from hospital.

Comment

Quetiapine is an atypical antipsychotic drug with a similar chemical structure to clozapine and olanzapine. Clozapine was the first atypical antipsychotic drug, but the risk of significant agranulocytosis requires rigorous monitoring.