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Volume 20, Issue No. 2 **April - May, 2003**

SULFONAMIDE CROSS-REACTIONS EXPLAINED

A frequent question received by SDIS is "What drug can be used by a patient with a sulfa allergy"? The most common approach to this problem is avoidance of all sulfonamides. Analysis of the literature, however, indicates that cross-reaction among different classes of sulfonamide drugs is unlikely to occur; thus we may be withholding appropriate therapies from patients unnecessarily.

SULFONAMIDES DEFINED

Sulfonamides are compounds than contain sulfur in a SO_2NH_2 moiety directly attached to a benzene ring.[1] Many medications contain sulfur but are not sulfonamides, e.g., amoxicillin, captopril, omeprazole, spironolactone, sulfates and sulfites.[2] There is no risk of cross-reactivity between these substances and sulfonamides.[2]

Sulfonamides can be divided into two groups; the antibiotics (eg, sulfamethoxazole, sulfisoxazole, sulfacetamide) and the non-antibiotic sulfonamides (e.g., thiazides, furosemide, glyburide, sumatriptan, celecoxib). Certain chemical structures unique to the antibiotic group are implicated in the production of hypersensitivity reactions - an arylamine moiety at the N4 position and substitutions at the N1 position of the benzene ring.[1]

HYPERSENSITIVITY ADVERSE EFFECTS

The term "sulfa allergy" is often incorrectly applied to all adverse reactions that occur with sulfonamide-containing medications and not just to those due to hypersensitivity mechanisms. Patients who experience side effects such as nausea and vomiting may interpret this as an allergy and subsequently report that they are allergic to sulfas.[1]

Approximately 3 % of patients who receive sulfonamide antibiotics experience true hypersensitivity reactions.[3] These include the entire range of immunologic reactions as well as idiosyncratic reactions (Table 1).[4] Mild maculopapular or urticarial rashes are the most common symptoms.[5] These generally occur within one week of drug therapy and disappear 7 to 14 days after the drug is discontinued.[6] Less frequently, more serious dematologic reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis develop.[5] Non-dermatological reactions such as drug fever, serum sickness syndrome, vasculitis, nephritis, hepatitis and hemolytic anemia have also been reported.[5]

Type 1 (immediate) anaphylactic reactions are rare.[5] These reactions have been linked to the N-1 substituents in the antibiotic structure. As mentioned above, non-antibiotic sulfonamides do not contain these substituents.[1,4]

Idiosyncratic reactions to antibiotic sulfonamides are thought to be caused by a reactive metabolite produced by oxidation of the arylamine structure.[1,4] If not detoxified, this

metabolite acts as a hapten (partial antigen) and binds to endogenous proteins to form a compound that triggers an immune reaction.[2] Haptenated compounds may also be directly toxic to cells.[4] The arylamine structure is not found in non-antibiotic sulfonamides.

Table 1: Hypersensitivity Reactions to Sulfonamide Antibiotics[1,4]

Reaction type	Mechanism	Clinical reaction
Immunological reactions		
Gell-Coombs type I	IgE antibodies (anaphylactic)	urticaria, hypotension, angioedema, bronchospasm, anaphylaxis
Gell-Coombs type II	IgG or IgM (cytotoxic)	thrombocytopenia
Gell-Coombs type III	Soluble immune complexes	vasculitis
Gell-Coombs type IV	Sensitized T-lymphocytes	contact dermatitis, fixed drug eruptions, photoallergic reactions
Idiosyncratic reactions		
Serum sickness-like reaction	Reactive metabolites	fever, arthralgia, urticaria, morbilliform rash
Hypersensitivity syndrome reaction		fever, malaise, rash, Stevens Johnson syndrome, toxic epidermal necrolysis, hepatitis, nephritis, pneumonitis

CROSS-REACTIVITY AMONG SULFONAMIDES

Cross-reactivity is the likelihood that a person who has had a hypersensitivity reaction to one drug will have the same reaction to a structurally similar drug. In theory, therefore, cross-reactivity would be expected to occur among different members of the antibiotic sulfonamides but not between different classes of sulfonamides.[1,4] In fact, reports in the literature documenting the safe use of sulfonamide medications in patients with a previous history of allergy to a sulfonamide outnumber reports of adverse reactions to two or more sulfonamides.[1]

A possible explanation for reports of sulfonamide cross-sensitivity may be the tendency of certain patients to be more susceptible to hypersensitivity reactions. Patients allergic to one antimicrobial drug are reported to be 10 times more likely to react to another non-structurally related drug than patients without a history of allergy.[7] Thus, reactions to more than one sulfonamide may actually represent multiple allergies rather than a specific allergy to sulfonamides.[7]

RISK FACTORS FOR HYPERSENSITIVITY REACTIONS

Patients with a history of previous reactions to other drugs, including non-sulfonamides, are at the highest risk of adverse reactions.[1] Other risk factors include concurrent infection (appears to

increase susceptibility to the effects of haptenation products)[1], genetic predisposition (patients with the slow acetylator phenotype shunt more drug into the CYP oxidative pathway that forms the reactive metabolite) [8], and glutathione deficiency (glutathione plays an important role in detoxifying reactive metabolites) [9].

MANAGEMENT STRATEGIES

1. History of severe life-threatening reaction to a sulfonamide (e.g., Stevens Johnson syndrone, toxic epidermal necrolysis, hepatotoxicity, anaphylaxis) is an absolute contraindication to the use of sulfonamides.[6]

2. A mild to moderate reaction is not necessarily a contraindication to the use of another class of sulfonamide but when available, a non-sulfonamide alternative of equivalent efficacy and safety is the preferred option.[6] (Table 2)

3. If there is not an appropriate alternative, the patient should be started on a low dose of the sulfonamide and closely monitored.[7] Patient counselling should include a discussion of the risks and benefits of the therapy.[6]

4. For patients with a demonstrated allergy to a necessary drug, e.g., loop diuretics in congestive heart failure, co-trimoxazole for *Pneumocystis carinii* pneumonia, desensitization can be tried.[1,6] Desensitization involves starting with a very small amount of the drug and gradually increasing to the therapeutic dose. Sucessful protocols for co-trimoxazole, furosemide and sulfasalazine have been reported.[1,6]

Table 2: Commonly used sulfonamides and non-sulfonamide alternatives [2,6]

Drug class	Sulfonamide drugs *	Alternative drugs *
Antibiotics	silver sulfadiazine, sulfacetamide, sulfadiazine, sulfadoxine, sulfamethoxazole, sulfapyridine, sulfisoxazole	aminoglycosides, cephalosporins, clindamycin macrolides, nitrofurantoin, penicillins, fluoroquinolones, tetracyclines, trimethoprim
Anti-inflammatory agents	celecoxib, valdecoxib	rofecoxib, non-selective NSAIDs
Anti-glaucoma agents	acetazolamide, brinzolamide, dorzolamide, methazolamide	ophthalmic beta-blockers, prostaglandin analogues, apraclonidine, brimonidine, dipivefrin
Diuretics	bumetanide, chlorthalidone, chlorothiazide, diazoxide, furosemide, hydrochlorothiazide, indapamide, metolazone, torsemide	amiloride, spironolactone, triamterene
Hypoglycemics	chlorpropamide, tolbutamide, glyburide, gliclazide, glimepiride	acarbose, metformin, thiazolidinediones, nateglinide, repaglinide

Inflammatory bowel disease therapy	sulfasalazine	5-ASA products

* Please note these lists do not include all sulfonamides or all possible alternatives. Suggested alternatives may not be appropriate or effective in all clinical circumstances.

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