CURRENT OPINION

Drug Safety 2001; 24 (4): 239-247
0114-5916/01/0004-0239/$22.00/0

Should Celecoxib Be Contraindicated in Patients Who Are Allergic to Sulfonamides?

Revisiting the Meaning of 'Sulfa' Allergy

Sandra Knowles,[1,2,3] *Lori Shapiro*[1,2,3,4] and *Neil H. Shear*[1,2,3,4]

1 Clinical Pharmacology, Department of Medicine, Sunnybrook & Women's Health Sciences Centre, Toronto, Canada
2 Drug Safety Clinic, Sunnybrook & Women's Health Sciences Centre, Toronto, Canada
3 University of Toronto, Toronto, Canada
4 Dermatology, Department of Medicine, Sunnybrook & Women's Health Sciences Centre, Toronto, Canada

Abstract

Celecoxib, a selective cyclo-oxygenase-2 inhibitor, is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent. Because of this structural component, celecoxib is contraindicated for use in patients who have demonstrated allergic reactions to sulfonamides. However, there is a lack of data demonstrating cross-reactivity among sulfonamide medications.

A sulfonamide is any compound with an SO_2NH_2 moiety. The major difference between sulfonamide antimicrobials and other sulfonamide-containing medications such as furosemide, thiazide diuretics and celecoxib, is that sulfonamide antimicrobials contain an aromatic amine group at the N4 position. This allows for division of the sulfonamides into 2 groups: aromatic amines (i.e., sulfonamide antimicrobials) and nonaromatic amines. In addition, sulfonamide antimicrobials contain a substituted ring at the N1-position; this group is not found with nonaromatic amine-containing sulfonamides.

Adverse reactions to sulfonamide antimicrobials include type I, or immunoglobulin (Ig) E-mediated reactions, hypersensitivity syndrome reactions, and severe skin reactions such as toxic epidermal necrolysis. The aromatic amine portion of the sulfonamide antimicrobial is considered to be critical in the development of latter 2 reactions. In susceptible individuals, the hydroxylamine metabolite is unable to be detoxified leading to a cascade of cytotoxic and immunological events that eventually results in the adverse reaction. Since celecoxib does not contain the aromatic amine, adverse reactions such as hypersensitivity syndrome reactions and toxic epidermal necrolysis would not be expected to occur at the same frequency as they do with sulfonamide antimicrobials. Similarly, for IgE-mediated reactions, the N1-substituent and not the sulphonamide moiety is important in determining specificity to antibodies. Celecoxib and other nonaromatic amine-containing sulfonamide medications do not contain the N1-substituent.

Cross-reactivity among the various sulfonamide-containing medications has

also not been substantiated by published case reports. In fact, conflicting information exists in the literature. Reports showing lack of cross-reactivity balance the few case reports suggesting cross-reactivity.

Cross-reactivity between sulfonamide medications should be based on scientific data, including chemistry, metabolism, immune responses and clinical data. Based on the current information, there is no documentation for cross-reactivity between sulfonamide antimicrobials and other sulfonamide medications, such as celecoxib.

A drug product label encompasses information on efficacy, administration, adverse drug reactions (ADRs) and contraindications. Although the information contained in the efficacy and administration sections is often based on clinical trial data, contraindications or warnings may be based on individual case reports or extrapolated from previous experience with similar agents. Because the available scientific data may be disparate from the information contained within the product label, confusion arises because of potential legal implications.

As an example, celecoxib is a selective cyclooxygenase-2 inhibitor that is indicated for the treatment of rheumatoid arthritis and osteoarthritis. It is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent. Because of this structural component, celecoxib is contraindicated for use in patients who have demonstrated allergic reactions to sulfonamides.[1]

Although many references suggest that there is cross-reactivity between various sulfonamide medications, this has not been substantiated in the literature either from a structural framework (e.g. metabolism, chemical structure) or from a clinical standpoint. This review will discuss the similarity and differences in structure between the various sulfonamide medications. As well, differences in metabolism will be highlighted between sulfonamide antimicrobials and other sulfonamide-containing compounds such as celecoxib. Finally, clinical safety data for celecoxib will be reviewed.

1. Sulfonamides

Sulfonamides, or sulfonamide antimicrobials, are derivatives of sulfanilamide (see fig. 1).[2] However, the term sulfonamide is also used to describe any compound with an SO_2NH_2 moiety, regardless of whether it directly links to a benzene ring. The major difference between sulfonamide antimicrobials and other sulfonamide-containing medications such as furosemide, thiazide diuretics and celecoxib, is that sulfonamide antimicrobials contain an aromatic amine group at the N4 position. This structural difference is the basis for the division of the sulfonamides into 2 groups: aromatic amines and nonaromatic amines (see table I). Sulfonamide antimicrobials also contain a 5- or 6-member aromatic heterocyclic ring with ≥1 nitrogen at the sulfonamido-N1 position; this substituted ring is not found with other nonaromatic amine containing sulfonamides. 'Sulfa' allergy is a generic term used to describe patients with allergies to sulfonamide antimicrobials. However, it does not imply allergy to compounds containing sulfur, inorganic sulfate or sulfites.[3]

2. Adverse Drug Reactions (ADRs)

An ADR is defined as an unintended adverse response that occurs at dosages used for treatment, prophylaxis or diagnosis.[4] A classification system for adverse reactions has been described, which groups adverse events into predictable (also known as pharmacological) and unpredictable (or intrinsic reactions.[5] Predictable ADRs occur as a result of exaggerated or undesirable pharmacological effects of a drug, not necessarily related to the therapeutic effects of the drug. These ADRs are considered dose-dependent but host independent. Approximately 80% of all ADRs are classified as predictable reactions.[5] In contrast, unpredictable ADRs are generally independent of dose or pharmacological action of the drug. Examples include

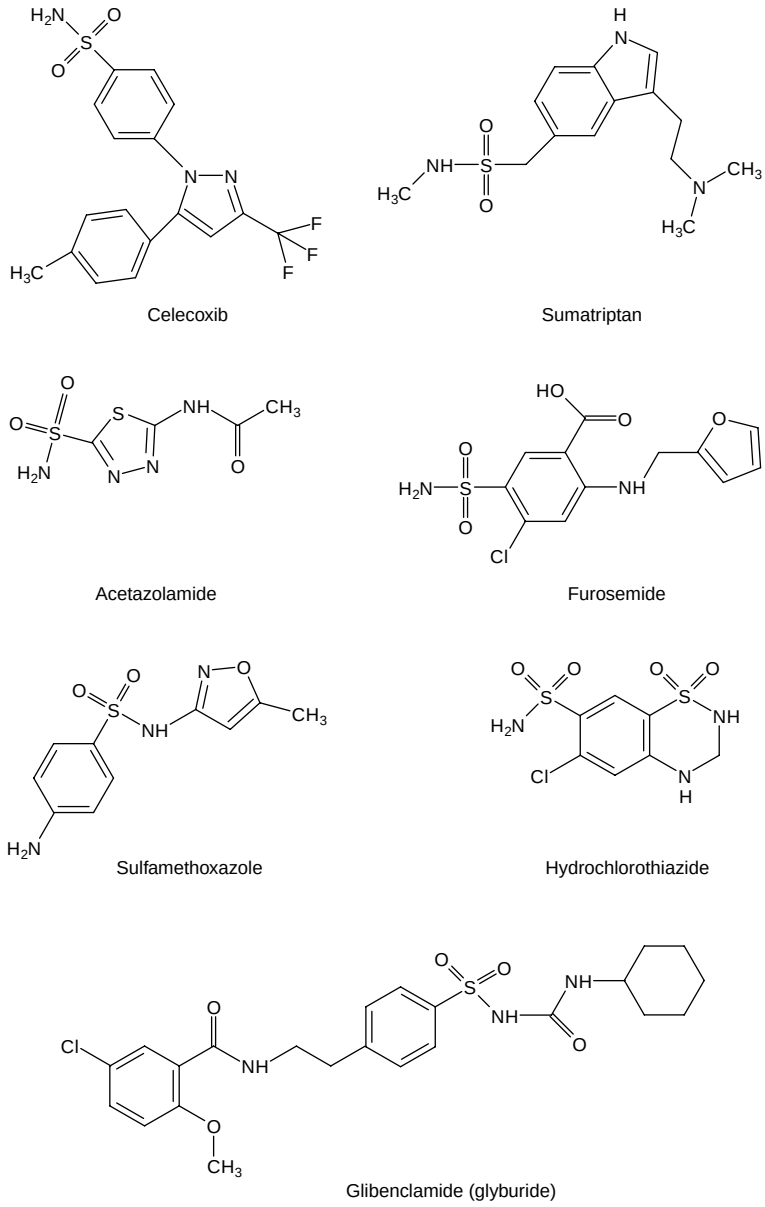

Fig. 1. Structures of sulfonamide-containing medications.

idiosyncratic reactions and various immunological (or allergic) reactions. Immunological reactions are often categorised according to the Gell and Coomb's classification scheme[6] (see table II). Unfortunately, various terms to describe unpredictable reactions have been used throughout the literature with different connotations. For example, although patients and many clinicians may refer to an adverse event as an 'allergy', the mechanism of many of these adverse events does not involve the

Table I. Classification of sulfonamide-containing medications

Aromatic amines
Antimicrobials: sulfamethoxazole, sulfadiazine, sulfafurazole (sulfisoxazole)
Nonaromatic amines
Diuretics: thiazides, furosemide, metolazone, bumetanide
Oral hypoglycaemics: glibenclamide (glyburide), chlorpropamide
Carbonic anhydrase inhibitors: acetazolamide, dorzolamide
Other: celecoxib, sumatriptan

immune system. In this review the term 'drug allergy' will, therefore, refer to reactions with an immunological basis. 'Hypersensitivity reaction' is a nonspecific term that encompasses both allergic and idiosyncratic reactions. This is in contrast to 'hypersensitivity syndrome reaction', which is a specific entity that relates to the development of fever, rash and internal organ involvement.

Idiosyncratic reactions, although rare, can affect a large number of organ systems, either in isolation or in conjunction with other symptoms. Single organ dysfunction includes hepatitis, nephritis and various cytopenias as well as serious dermatological eruptions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Multiple-organ dysfunction can result in the drug hypersensitivity syndrome, drug-induced lupus, serum sickness–like reaction and SJS/TEN. Most idiosyncratic reactions are believed to be initiated via the effects of a reactive metabolite – hence the term 'reactive metabolite syndromes'. These metabolites, if not detoxified, can directly bind to cellular and circulating proteins leading to toxicity. Alternatively, initiation of an immune response can occur resulting in an ADR.

3. Sulfonamide ADRs

Sulfonamide ADRs can be manifested in a wide variety of clinical presentations. Some examples of predictable reactions include nausea and vomiting and headache and other neurological disturbances.[7]

3.1. Immunological Reactions

Immunological reactions associated with sulfonamide antimicrobials encompass the entire Gell-Coombs spectrum: type I, or immunoglobulin (Ig) E-mediated, reactions (i.e. development of urticaria, angioedema, hypotension and/or anaphylaxis) to immune thrombocytopenia (type II reaction), sulfonamide-induced vasculitis (type III reaction) and fixed drug eruptions and morbilliform exanthem (type IV reaction).[7]

For type I reactions, the N1-substituent and not the sulfonamide group has been found to direct specificity to IgE antibodies.[8] Two allergenic components have been identified: (i) 5- to 6-member aromatic heterocyclic ring with ≥1 nitrogen at the sulfonamido-N1 position; and (ii) the presence of a single methyl group on the carbon atom beta to the sulfonamido substitution. Although haptenation is thought to occur at the N4 position on the benzene ring,[9,10] this group was not an important determinant of IgE antibody recognition.[8] In contrast to sulfonamide antimicrobials, celecoxib (and other nonaromatic amine sulfonamides) does not contain a heterocyclic ring with a methyl group attachment at the N1 position, nor does it contain an N4 aromatic amine group. Although nonaromatic amine–containing sulfonamides may produce a variety of haematological toxicities, dermatological eruptions and anaphylaxis,[11,12] there is lack of evidence for cross-reactivity between any sulfonamide-containing drug.

3.2 Idiosyncratic Reactions

3.2.1 Serum Sickness-Like Reaction

Other unpredictable reactions, including various idiosyncratic reactions, have also been well described with sulfonamide antimicrobials. For example, serum sickness-like reactions have been rarely observed with sulfonamide antimicrobials and are characterised by the presence of fever, a skin eruption, often urticarial, arthralgia and/or lymphadenopathy.[13] The average onset in 10 days after initiation of therapy. Immune complexes have not been identified. Internal organ (i.e. renal) involvement is unusual. The incidence in a retrospective study in a paediatric population was <1/1000.[13]

Table II. Four classic allergic reactions as proposed by Gell and Coombs[6]

Type of reaction	Description	Primary effect or mechanism	Clinical reaction
I	Anaphylactic	IgE antibodies	Urticaria, hypotension, angioedema, bronchospasm, anaphylaxis
II	Cytotoxic	IgG or IgM	Haemolytic anaemia
III	Immune complex reaction	Soluble immune complexes	Leucocytoclastic vasculitis
IV	Delayed or cell-mediated hypersensitivity	Sensitised T-lymphocytes	Contact dermatitis, fixed drug eruptions, exanthematous eruptions

Ig = immunoglobulin.

3.2.2 Hypersensitivity Syndrome Reaction

Clinical Features

Hypersensitivity syndrome reaction has been well described for sulfonamides, with an incidence of approximately 1 : 1000 to 1 : 10000 per treatment course.[14] These reactions are a cause of major morbidity and can result in fatalities. The triad of fever, rash and internal organ involvement usually occurs 2 to 8 weeks after the initiation of therapy. Fever is often the first clinical sign and the patient may have concomitant malaise and pharyngitis. This is followed by a rash, ranging from an exanthem to more serious eruptions such as SJS/TEN. Initial examination of the peripheral blood smear reveals an atypical lymphocytosis with a subsequent eosinophilia. Internal organ involvement usually involves the liver, although pulmonary, haematological or renal impairment may occur. Hypothyroidism may be a complication in the patients following resolution of symptoms.[15]

Pathogenesis

Using sulfamethoxazole as a representative sulfonamide antimicrobial, the metabolic pathway of sulfonamide antimicrobials has been elucidated. In normal hosts, 45 to 70% of sulfamethoxazole is acetylated at the N4 position to form N4-acetyl sulfamethoxazole, which is renally excreted as a nontoxic metabolite. An alternative pathway, quantitatively more important in slow acetylators, involves the cytochrome P450 (CYP) mixed-function oxidase system. Sulfamethoxazole is oxidised to sulfamethoxazole hydroxylamine by the CYP2C9 system.[16] Although sulfamethoxazole-hydroxylamine is relatively unreactive, it can auto-oxidise to a more reactive nitroso metabolite.[17] This metabolite is subsequently detoxified in most individuals. However, in susceptible individuals, a combination of cytotoxic and immunological events are likely to be involved in the development of the drug hypersensitivity syndrome reaction and other reactive metabolite syndromes.[18] For example, the hydroxylamine metabolites of sulfamethoxazole inhibit the ability of natural killer cells to act, suppress the production of the cytokine tumour necrosis factor and inhibit the ability of T lymphocytes to respond to mitogenic stimulation.[19,20] Reactive N4-metabolites bind to proteins and cause apoptosis leading to severe drug reactions.[21]

An *in vitro* cytotoxicity assay has been developed which compares peripheral blood lymphocytes of patients with a history of sulfonamide hypersensitivity syndrome reactions to controls.[22,23] Studies have shown that patients with a past idiosyncratic reaction have a significant increase in cytotoxicity caused by the hydroxylamine metabolite of sulfamethoxazole suggesting that patients and controls have inherent differences in detoxification of the hydroxylamine metabolite.[24]

4. Cross-Reactivity

Cross-reactivity has been described, or hypothesised, for a large number of compounds including beta-lactam antibacterials, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants (table III). Immunological cross-reactions may occur among penicillins and cefalosporins by virtue of the beta-lactam group that is found in all beta-lactam antibacterials. Although initial evidence suggested a cross-reactivity rate of approximately 15 to 20%,[6] more recent data indicate that the cross-reaction rate is less than 2%.[25] However, cross-

Table III. Cross-reactivity

Class of drugs	Type of reaction	Proposed mechanism
Beta-lactam antibacterials	IgE-mediated reactions	Beta-lactam group similarity
Aromatic anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital)	Hypersensitivity syndrome reaction	Accumulation of toxic metabolite
Nonsteroidal anti-inflammatory drugs	Asthma ± rhinoconjunctivitis	Inhibition of cyclo-oxygenase enzyme
ACE inhibitors	Cough or angioedema	Increased bradykinin levels
Sulfonamide antimicrobials	Hypersensitivity syndrome reaction	Accumulation of toxic metabolite

Ig = immunoglobulin.

reactivity between cefalosporins and penicillins may lead to life-threatening anaphylaxis in rare cases.[26] In contrast, cross-reactions among NSAIDs are not based on structural resemblance, nor immunological mechanisms, but rather are attributable to NSAID-induced inhibition of cyclo-oxygenase. This results in accumulation of 5-lipoxygenase and increased production of leukotrienes,[27] resulting in respiratory reactions with or without rhinoconjunctivitis. Another potential mechanism for cross-reactivity is development of toxic metabolites. For example, patients who develop a hypersensitivity syndrome reaction from 1 aromatic anticonvulsant (i.e. phenytoin, phenobarbital, carbamazepine) will have a 75% likelihood of developing a similar reaction with another aromatic anticonvulsant.[28] The aromatic anticonvulsants are metabolised to similar toxic metabolites that accumulate in susceptible individuals.[29]

For sulfonamide antibacterials, the sulfonamide moiety (i.e. SO_2NH_2) itself does not trigger serious drug reactions such as hypersensitivity syndrome reaction, but rather the aromatic amine moiety is critical in the pathogenesis of these reactions, as well as severe cutaneous reactions (e.g. SJS/TEN) and single organ dysfunction such as hepatitis or cytopenias. Nonaromatic amine sulfonamides, such as celecoxib, furosemide and acetazolamide, would not be expected to clinically cross-react with sulfonamide antimicrobials for these serious drug reactions. However, for patients who experience a serious drug reaction with 1 sulfonamide antimicrobial, cross-reactivity would be expected for sulfonamide antimicrobials as a class. For patients who develop sulfonamide-induced hypersensitivity syndrome reaction, it is reasonable to avoid other aryl amines, such as procainamide, dapsone and acebutolol because they form similar reactive metabolites; however, there is little clinical data to confirm that this is necessary.[30]

For IgE-mediated reactions with sulfonamide antimicrobials, the N1-substituent and not the sulfonamide group is important in determining specificity to antibodies.[8] Nonaromatic amine containing sulfonamides, such as celecoxib, do not contain this essential chemical substituent and therefore, would not be expected to cross-react with aromatic amine containing sulfonamides.

5. Literature Review

Cross-reactivity among the various sulfonamide-containing medications has not been substantiated by reports in the literature. There are only a small number of cases in which cross-reactivity between 2 or more sulfonamide medications has been documented.[31-35]

A 54-year-old woman developed thrombocytopenia after using tolbutamide for 2 years; the thrombocytopenia resolved upon drug discontinuation. Upon exposure to hydrochlorothiazide 2 years later, she once again developed thrombocytopenia after 48 hours of therapy.[31] Another patient developed urticaria, angioedema and hypotension within 5 minutes after the intravenous administration of furosemide. The patient was positive on skin testing with furosemide, cotrimoxazole (sulfamethoxazole-trimethoprim) and chlorothiazide, but negative on ethacrynic acid. The patient was not challenged with any of these medications, although he had previously tolerated hydrochlorothiazide.[32] A 55-year-old patient developed several

episodes of serum sickness (fever, arthralgias and angioedema of the hands) following treatment with glisoxepide, glibenclamide (glyburide), furosemide and probenecid.[33] A 56-year-old patient developed angioedema and an exanthematous eruption on 3 separate occasions after treatment with sulfadimethoxin, chloramidobenzol and acetazolamide, respectively.[35] Concurrent, noncross-reactive antibody responses in a hapten allergy-prone individual may be a more likely explanation for patients who react to 2 or more sulfonamides.[36]

There have been several reports of potentially cross-reacting sulfonamides being used safely in patients with a history of allergy to sulfonamides. A 68-year-old woman developed several episodes of fixed drug eruption following indapamide therapy. Oral challenges with indapamide, sulfamethoxazole and sulfadiazine produced positive results, whereas furosemide did not cause recurrence of the skin eruptions.[37] In a report of 16 patients who developed a skin reaction (erythematous eruption, urticaria) following indapamide therapy, 11 patients later took chlorthalidone, hydrochlorothiazide, furosemide, epitizide or clopamide without a relapse.[38] A study of 33 patients with urticaria or fixed drug eruption attributable to a sulfa-containing drug demonstrated cross-reactivity between sulfonamide-containing antimicrobials but not between the sulfonamide-containing antimicrobials and furosemide or procaine.[39]

Only 1 case report of possible cross-reactivity between sulfonamides and acetazolamide exists. A patient with mitral stenosis and 'sulfa' allergy developed symptoms (oedema, respiratory distress, haemoglobinuria) following acetazolamide use for treatment of congestive heart failure.[40] Although these symptoms were attributed to a cross-reactivity between acetazolamide and sulfonamides, they could have been attributable to a worsening of the patient's congestive heart failure.[41]

Sumatriptan is a nonaromatic amine containing sulfonamide. A retrospective chart review of 15 patients was done to evaluate the safety of sumatriptan in patients with known sulfonamide allergy.[42] Prior sulfonamide reactions included angioedema, rash, urticaria, fever, photosensitivity and severe headache. No patients reported adverse effects from sumatriptan therapy. The authors suggested that sumatriptan can be safely used in patients allergic to sulfonamides, although study limitations included a small sample size and a retrospective study design.

6. Clinical Safety Data with Celecoxib

A recent study evaluated the data for 11 008 patients who had participated in 14 double-blind trials of celecoxib in arthritis.[43] Although a history of sulfonamide hypersensitivity reactions was among the exclusion criteria for celecoxib clinical trials, 135 patients deviated from the study protocols. The majority of these patients had a history of reactions to sulfonamide antimicrobials. Of these patients, 73 (54%) received celecoxib, 30 (22%) received active comparators (NSAIDs) and 32 (24%) received placebo. There were no statistically significant differences between the groups with regards to allergic reactions. No patient receiving celecoxib reported severe cutaneous adverse reactions such as SJS/TEN. Use of celecoxib with other sulfonamide-containing diuretics (e.g. bumetanide, chlorothiazide, furosemide) and sulfonylureas (e.g. chlorpropamide, glyburide) did not increase the risk of allergic-type reactions.

Approximately 7 million prescriptions for celecoxib were written from January 1999 until June 1999.[44] During this time, 2 possible cases of SJS or TEN were reported to the manufacturer via their postmarketing surveillance programme. There were no reports of a hypersensitivity syndrome reaction. If this were sulfamethoxazole, 7 million exposures would result in 30 to 70 cases of SJS or TEN and 1500 to 2000 cases of hypersensitivity syndrome reaction.[45] 20 to 30 deaths would occur from just these reactions alone. Based on these figures, SJS/TEN may occur extremely rarely with celecoxib; however, the pathogenesis appears to be different from the pathogenesis with sulfonamide antimicrobials.

The Therapeutic Products Programme of Health Canada received 220 reports of adverse reactions

Table IV. Sulfonamide-containing medications – product labelling for the use of medications in patients with a history of a sulfonamide hypersensitivity[47]

Drug	PDR listing
Celecoxib	Contraindication
Sulfasalazine	Contraindication
Hydrochlorothiazide	Contraindication
Dorzolamide	Warning
Furosemide	Precaution
Glibenclamide (glyburide)	No warning/precaution
Dapsone	No warning/precaution
Sumatriptan	No warning/precaution
Chlorpropamide	No warning/precaution

PDR = Physician's Desk Reference.

to celecoxib with 562 possible adverse events.[46] There were 74 reports (34%) that described a dermatological reaction; no serious cutaneous adverse reactions (e.g. SJS/TEN) were reported. As well, allergic-type reactions were documented in 74 reports. 16 reports indicated that the patient had a previous adverse reaction to sulfonamides although no further details were provided.

7. Product Labelling

One of the key sources of information regarding product use is the product monograph. However, rather than clarifying the confusion that exists regarding cross-reactivity among the various sulfonamide medications, product labelling actually creates more confusion. Product labelling for cross-reactivity among sulfonamides is not based on scientific evidence (i.e. chemical structures or metabolism of drugs) nor is it based on clinical data. In fact, there is inconsistent labelling of sulfonamide-containing medications for use in patients with a history of a sulfonamide allergy.[43] For example, hydrochlorothiazide contains a contraindication for use in patients with a sulfonamide allergy, whereas a precaution is listed in the furosemide monograph and no warning/precaution contraindication is listed for chlorpropamide (table IV).

Based on the scientific evidence and clinical data presented, the information in the celecoxib product monograph should be the same and in the same section as other nonaromatic amine sulfonamides.

8. Conclusion

It has taken over 60 years to begin to understand the pathogenesis of sulfonamide antimicrobial-induced reactions. However, why some people experience reactions and why some organs are involved more than others, are important questions that still need to be answered. Reactions to nonantimicrobial sulfonamides, such as celecoxib or hydrochorothiazide, are a separate issue. The simple question is, why do some people have reactions to these drugs. The answer may not be dependent upon the sulfonamide moiety at all. Once that myth is destroyed, we are no longer left with the inappropriate 'allergic to sulfa' label. We will need to examine the chemistry, metabolism and immune responses more thoughtfully. Prospective clinical studies in patients with well documented allergic reactions to sulfonamide antimicrobials should be done that specifically address the issues of cross-reactivity. In the meantime we need to rationally examine the warnings that we give patients, to ensure that they are based on science and rational reasoning. For the present, the contraindication is based on myth at best.

References

1. Welbanks L, editor. CPS: compendium of pharmaceuticals and specialties, 35th ed. Ottawa: Canadian Pharmacists Association, 2000: 289
2. Hardman J, Limbird L, editors. Goodman & Gilman's: the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill, 1996: 1057
3. Dwenger C. 'Sulpha' hypersensitivity [letter]. Anaesthesia 2000; 55: 200
4. Venulet J, Ten Ham M. Methods for monitoring and documenting adverse drug reactions. Int J Clin Pharmacol Ther 1996; 34: 112-29
5. Pirmohamed M, Park B. The adverse effects of drugs. Hosp Med 1999; 60: 348-52
6. Management of drug hypersensitivity: a practice parameter. Ann Allergy Asthma Immunol 1999; 83 (Pt 3): 665-700
7. Cribb A, Lee B, Trepanier L, et al. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. Adverse Drug React Toxicol Rev 1996; 15: 9-50
8. Harle D, Baldo B, Wells J. Drugs as allergens: detection and combing site specificities of IgE antibodies to sulfamethoxazole. Mol Immunol 1988; 25: 1347-54

9. Gruchalla R, Sullivan T. Detection of human IgE to sulfamethoxazole by skin testing with sulfamethoxazoyl-poly-L-tyrosine. J Allergy Clin Immunol 1991; 88: 784-92
10. Meekins C, Sullivan T, Gruchalla R. Immunochemical analysis of sulfonamide drug allergy: identification of sulfamethoxazole-substituted human serum proteins. J Allergy Clin Immunol 1994; 94: 1017-24
11. Machtey I. Sudden death after intramuscular furosemide [letter]. Lancet 1968; II: 1301
12. Gould L, Reddy C, Zen B, et al. Life-threatening reaction to thiazides. NY State J Med 1980; 80: 1975-6
13. Heckbert S, Stryker W, Coltin K, et al. Serum sickness in children after antibiotic exposure: estimates of occurrence and morbidity in a Health Maintenance Organization population. Am J Epidemiol 1990; 132: 336-42
14. Roujeau JC, Stern R. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994; 331 (19): 1272-85
15. Gupta A, Eggo M, Uetrecht J, et al. Drug-induced hypothyroidism: The thyroid as a target organ in hypersensitivity reactions to anticonvulsants and sulfonamides. Clin Pharmacol Ther 1992; 51: 56-67
16. Cribb A, Spielberg S, Griffen G. N4-hydroxyation of sulfamethoxazole by cytochrome P450 of the CYP2C subfamily and microsomal reduction of its hydroxylamine metabolite in human and rat hepatic microsomes. Drug Metab Disp 1995; 23: 406-14
17. Cribb A, Miller M, Leeder J, et al. Reactions of the nitroso and hydroxylamine metabolites of sulfamethoxazole with reduced glutathione. Drug Metab Disp 1991; 19: 900-6
18. Spielberg S, Leeder J, Cribb A, et al. Is sulfamethoxazole hydroxylamine the proximal toxin for sulfamethoxazole toxicity? Eur J Clin Pharmacol 1989; 36 Suppl.: A146
19. Rieder M, M Mask, Bird I. Production of tumour necrosis factor by cells exposed to sulphonamide reactive metabolites. Can J Physiol Pharmacol 1992; 70: 719-22
20. Rieder M, Sisson F, Bird I. Suppression of T lymphocyte proliferation by sulphonamide hydroxylamine. Int J Immunopharmacol 1992; 14: 1175-80
21. Naibitt D, Hough S, Gill H, et al. Cellular disposition of sulphamethoxazole and its metabolites: implications for hypersensitivity. Br J Pharmacol 1999; 126: 1393-407
22. Shear N, Spielberg S, Grant D, et al. Differences in Metabolism of Sulfonamides Predisposing to Idiosyncratic Toxicity. Ann Intern Med 1986; 105: 179-84
23. Shear N, Spielberg S. In vitro evaluation of a toxic metabolite of sulfadiazine. Can J Physiol Pharmacol 1985; 63: 1370-2
24. Rieder M, Uetrecht J, Shear N, et al. Diagnosis of sulfonamide hypersensitivity reactions by in-vitro 'rechallenge' with hydroxylamine metabolites. Ann Intern Med 1989; 110: 286-9
25. Shepherd G, Burton D. Administration of cephalosporin antibiotics to patients with a history to penicillin [abstract]. J Allergy Clin Immunol 1993; 91 (1 Pt 2): 262
26. Pumphrey R, Davis S. Under-reporting of antibiotic anaphylaxis may put patients at risk. Lancet 1999; 353: 1157-8
27. Szezeklik A, Stevenson D. Aspirin-induced asthma: advances in pathogenesis and management. J Allergy Clin Immunol 1999; 104: 5-13
28. Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome, in vitro assessment of risk. J Clin Invest 1988; 82: 1826-32
29. Knowles S, Shapiro L, Shear N. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. Drug Saf 1999; 21: 489-501
30. Knowles S, Uetrecht J, Shear N. Idiosyncratic drug reactions: the reactive metabolite syndromes. Lancet 2000; 356: 1587-91
31. Bretza J. Thrombocytopenia due to sulfonamide cross-sensitivity. Wiscon Med J 1982; 81: 21-3
32. Hansbrough J, Wedner JH, Chaplin D. Anaphylaxis to intravenous furosemide. J Allergy Clin Immunol 1987; 80: 538-41
33. Ummenhofer B, Jawari D. Kreuzallergie zwischen Sulfonamid-Diuretika, Probenecid, Sulfamethoxazol und Sulfonylharnstoffen. Dtsch Med Wschr 1979; 104: 514-7
34. Conner C. Cross-sensitivity of sulfonamide antibacterials and antihypertensives. Drug Ther 1975; 5: 63-64
35. Goerz V, Ippen H, Meiers H. Sulfonamid-Uberempfindlichkeit: gekreuzte Reaktionen zwischen antibakteriellen Sulfonamiden und Diuretika. Dtsch Med Wschr 1964; 89: 1301-3
36. Sullivan T. Cross-reactions among furosemide, hydrochlorothiazide and sulfonamides. JAMA 1991; 265: 120-1
37. De Barrio M, Tornero P, Zubeldia J, et al. Fixed drug eruption induced by indapamide. Cross-reactivity with sulfonamides. Invest Allergol Clin Immunol 1998; 8: 253-5
38. Stricker B, Biriell C. Skin reactions and fever with indapamide. BMJ 1987; 295: 1313-4
39. Barrio M, Tornero P, Baeza M, et al. Cross-reactivity among para-amine group in sulfonamide-induced urticaria and fixed drug eruption [abstract]. J Allergy Clin Immunol 1991; 87 (1 Pt 2): 230
40. Moseley V, Baroody N. Some observations on the use of acetazoleamide as an oral diuretic in various edmatous states and in uremia with hyperkaliemia. Am Pract Digest Treat 1955; 6: 558-66
41. Stock J. Sulfonamide hypersensitivity and acetazolamide. Arch Ophthalmol 1990; 108: 634-5
42. Newman L, Lay C, O'Connor K, Russell M. Lack of cross-reactivity to sumatriptan in patients allergic to sulfonamides: a retrospective chart review [abstract]. Headache 1999; 39: 372
43. Patterson R, Bello A, Lefkowtih J. Immunologic tolerability profile of celecoxib. Clin Ther 1999; 21: 2065-73
44. Data on file, Searle (Pharmacia), 2000
45. Roujeau J, Kelly J, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333: 1600-7
46. McMorran M, Morawiecka I. Celecoxib (Celebrex): one year later. Can Adv Drug React Newslett 2000; 10: 1-3
47. Physicians' Desk Reference, 54th ed. Montvale (NJ): Medical Economics Company, 2000

Correspondence and offprints: Dr *Neil H. Shear*, Sunnybrook & Women's College Health Sciences Centre, Division of Clinical Pharmacology, E240, 2075 Bayview Avenue, Toronto, ON, M4N 3M5, Canada.
E-mail: neil.shear@swchsc.on.ca