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Safety of Celecoxib in Individuals Allergic to Sulfonamide
A Pilot Study

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Abstract

Objective: To evaluate cross reactivity between sulfonamide antimicrobials and celecoxib in patients with histories of allergies to sulfonamide antimicrobials.

Methods: Immunocompetent patients with a history of sulfonamide antimicrobial allergy who were being considered for therapy with celecoxib were prospectively enrolled. Sulfamethoxazole and trimethoprim skin prick and intradermal testing and/or an *in vitro* lymphocyte toxicity assay were performed. If skin testing was negative, an oral challenge with sulfamethoxazole and trimethoprim was performed. Oral challenges with celecoxib were administered to all patients.

Results: Twenty-eight immunocompetent patients (26 female; mean age 60 years) were evaluated. History of sulfonamide antimicrobial allergy included urticaria (n = 7), cutaneous eruptions (n = 9), and other (n = 12). Four of the 28 patients who were skin prick tested were positive to sulfamethoxazole and two of the ten patients who underwent *in vitro* testing were positive to sulfamethoxazole. All 28 patients were administered celecoxib and tolerated the medication. Phone call follow up in 25 patients disclosed that 15 patients continued to take celecoxib, while five patients did not take celecoxib following the oral challenge, and five discontinued celecoxib due to adverse effects, lack of drug efficacy or physician preference.

Conclusions: Confusion exists regarding the potential for cross reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds. The six sulfonamide-allergic patients tolerated celecoxib uneventfully. This pilot study supports the hypothesis that the potential for cross-reactivity between celecoxib and sulfonamide antimicrobials appears to be low. However, further investigations are required to confirm this.

Celecoxib was the first of two selective cyclooxygenase-2 (COX-2) inhibitors to be marketed in North America. It is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent (figure 1).[1] The celecoxib product monograph states that this drug is contraindicated for use in patients who are allergic to sulfonamides.

Sulfonamide is a generic term that refers to drugs with a sulphur dioxide and nitrogen moiety (SO_2NH_2) that directly links to a benzene ring. Although many agents contain a sulfonamide moiety, several structural differences exist among the sulfonamides. One major difference between sulfonamide antimicrobials and other sulfonamide-containing medications such as furosemide and thiazide diuretics is the presence of an aromatic amine group at the N^4 position (figure 1). Only sulfonamide antimicrobials, such as sulfadiazine, sulfamethoxazole and sulfapyridine, contain this group; this may explain the higher incidence of severe adverse reactions associated with this group of drugs compared with drugs containing a sulfonamide substituent.

Adverse reactions to sulfamethoxazole and combination products with trimethoprim occur in 4–6% of patients, with allergic reactions occurring in <3% of all recipients.[2] Differences in structure and metabolism and site-specificity requirements suggest a low propensity for cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds such as celecoxib (table I).[3,4]

We describe a pilot study in which patients with a history of allergy to sulfonamide antimicrobials were evaluated for treatment with celecoxib.

Methods

Assessment of Sulfonamide Allergy

Patients who reported a possible sulfonamide antimicrobial allergy and who were being consid-

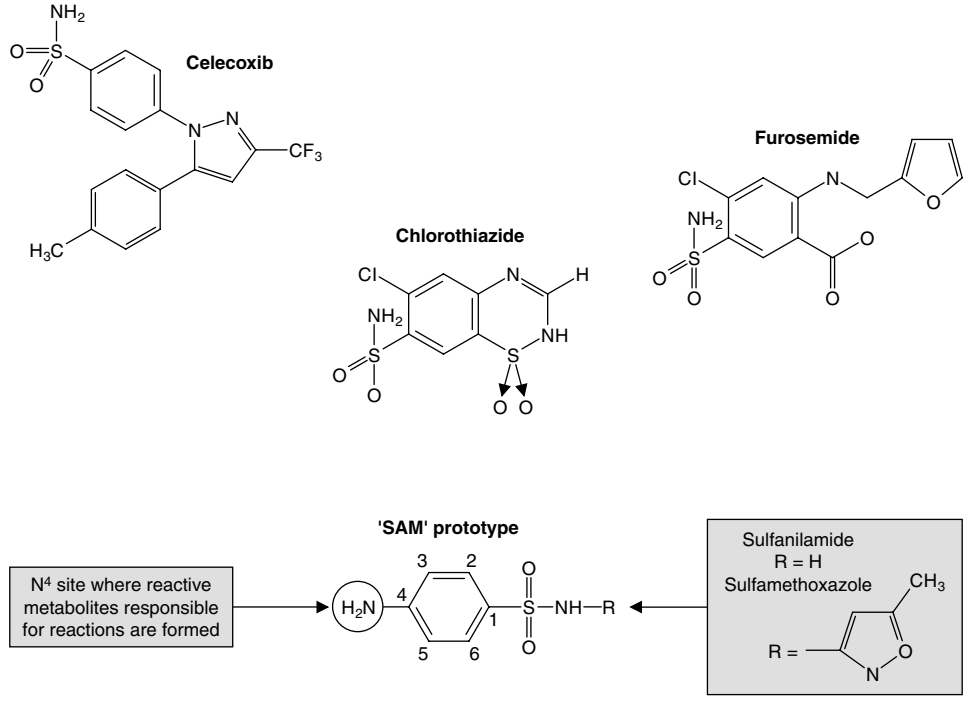

Fig. 1. The structure of sulfonamide antimicrobials (SAM) and non-aromatic amine sulfonamides.

Table I. Summary of literature discussing sulfonamide cross reactivity

Reaction	Testing	Interpretation
Anaphylaxis after IV furosemide[5]	Positive intradermal skin test with chlorothiazide, sulfamethoxazole/trimethoprim and furosemide. No oral challenges were administered	The differences in structures/metabolism of these drugs suggest that immunological cross reactivity would be rare[6]
33 patients with urticaria/angioedema or fixed drug eruption[7]	Prick/intradermal skin tests, oral challenges and/or patch tests to procaine, furosemide and a sulfonamide antimicrobial	No cross reactivity between sulfonamide antimicrobials and furosemide or procaine was observed
Development of oedema, respiratory distress and haemoglobinuria following acetazolamide administration (for the treatment of CHF) in a patient with a previous history of a 'sulfa' allergy[8]	None	Cross reactivity between acetazolamide and sulfonamide antimicrobials is not confirmed. Symptoms could have been secondary to worsening of CHF[9,10]
16 patients who developed a skin reaction following indapamide therapy[11]	11 patients subsequently took chlorthalidone, hydrochlorothiazide, furosemide, epitizide or clopamide without a relapse	Cross reactivity between thiazides is rare
Fixed drug eruption after indapamide therapy for hypertension[12]	Positive oral challenge to indapamide, sulfamethoxazole, sulfadiazine and negative oral challenge to furosemide	Cross-reactivity m ay be directed against metabolite of drug
82 patients on sulfonylurea; 8 patients had previous history of hypersensitivity reaction to sulfonamide[13]	All patients tolerating sulfonylurea	Cross-reaction between sulfonamide antibiotics and sulfonylurea unlikely
Thrombocytopenia after using tolbutamide for 2 years developed in a woman[14]	Exposed to hydrochlorothiazide 2 years later and within 2 days developed thrombocytopenia	Does not confirm drug-induced thrombocytopenia
7 of 34 patients taking oral sulfonylurea had history or reaction to sulfonamide[15]	One of these 7 patients had mild rash with sulfonylurea. The other 6 patients all tolerated the oral antidiabetic agent	Supports the hypothesis that cross reactivity between sulfonamide antimicrobials and sulfonamides is low
Fever and pustular eruption developed in a patient after celecoxib[16]	PBMCs from a sulfamethoxazole allergic patient and PBMCs from this patient did not cross react	Suggests that the sulfonamide structure does not account for the reaction

CHF = congestive heart failure; **IV** = intravenous; **PBMC** = peripheral blood mononuclear cell.

ered for therapy with celecoxib were prospectively enrolled in this study conducted at the Drug Safety Clinic. This is a multidisciplinary clinic in a large university-based teaching hospital that evaluates patients with complex histories suggestive of adverse drug reactions. All patients signed an informed consent that was approved by the institutional review board. Depending on the nature of the reaction, patients were subsequently assessed by skin prick and intradermal testing to sulfamethoxazole-trimethoprim (cotrimoxazole), and/or blood sampling for *in vitro* lymphocyte toxicity assay to sulfamethoxazole-trimethoprim as previously published.[17] If skin testing was negative, the individual would then receive oral challenges with the combination of sulfamethoxazole-trimethoprim (400/80mg). If there were no adverse reactions, a separate oral challenge to celecoxib was administered with a washout period of at least 2 days after oral sulfamethoxazole-trimethoprim challenge. Oral exposure to celecoxib initiated with a dose of 10mg and, if no adverse reaction occurred, 100mg was administered 1 hour later. Patients were observed for a minimum of 3 hours following oral challenges. Phone call follow up to all evaluated patients was done to assess tolerance to celecoxib during subsequent continuous and prolonged therapy.

Skin Testing

Skin Prick and Intradermal Testing

Skin prick and intradermal testing was performed with trimethoprim and sulfamethoxazoyl-poly-L-tyrosine, considered to be the major sulfamethoxazole determinant.[18,19] Non-irritating

concentrations for trimethoprim and sulfamethoxazole of up to 0.1 mg/mL were used for skin prick and intradermal testing. Normal saline (negative control) and histamine 1 mg/mL (positive control) were performed in each testing session. Reactions were considered positive in prick testing when a wheal greater than 3mm in diameter was positive 15–20 minutes after testing. Results were considered positive for intradermal testing when wheals greater than 5mm were present after 15–20 minutes. Delayed positive intradermal skin tests were defined by a wheal appearing 24 hours or more after cutaneous testing.

In Vitro Lymphocyte Toxicity Assay

The methodology used patient lymphocytes prepared from whole blood. Murine hepatic microsomes were prepared from Swiss Mice (National Institute of Health) pretreated with phenobarbital (10 mg/kg of bodyweight), given intraperitoneally for 3 days. Untreated lymphocytes (those with no drug exposure) were considered as controls.[20] The lymphocytes treated with different drugs without microsomes were the second set of controls and the lymphocytes resuspended with drugs and microsomes were considered as the test lymphocytes. Lymphocytes treated with different drugs without microsomes were used as controls to assess the drug's ability to cause cytotoxicity in the absence of its oxidative metabolism by the murine microsomal system. After 24 hours in microtrays, formazan [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) – 100μL] was added for 1 hour and the toxicity assay was performed using an ELISA reader. The percentage of cells displaying cytotoxicity compared with controls (cells treated only with drug) was calculated.[17]

Statistical Analysis

Descriptive statistics were applied. For the lymphocyte toxicity assay, each experimental condition was studied in triplicate sample and the mean percent of dead lymphocytes was determined. The change from baseline values (calculated as percent dead cells in the presence of drug and murine hepatic microsomes minus the percent dead cells in the absence of drug) was used as the measure of toxicity. Toxicity values from patients that were above the upper limit for normal were considered positive.

Results

Patient Characteristics

Patient characteristics are outlined in table II. A patient algorithm is shown in figure 2. Twenty-eight patients completed testing; 26 were female (93%). The mean age of patients was 60 years. The reactions to sulfonamide antimicrobials had occurred 1–60 years prior to their present consultation. Details of sulfonamide allergy in these subjects included a history of urticaria (n = 7), cutaneous eruption (n = 9), or other (n = 12). Interestingly, ten of the patients described adverse events to penicillin-type drugs.

Of the 24 patients in whom skin prick and intradermal testing to sulfamethoxazole was performed, four tests were positive to the sulfamethoxazole component, two were immediate to intradermal testing and two had delayed intradermal responses. In the former patients, one had a history of diarrhoea and dizziness and the other had a history of sulfonamide allergy that was unknown. In the latter two patients, one had a history of cutaneous eruption and the other patient could not recall the details. Trimethoprim skin prick and intradermal testing was negative in all patients. In addition, two of ten patients had a positive result in the *in vitro* lymphocyte toxicity assay (figure 3). One patient had a history of fever, cutaneous eruption and arthralgia after exposure to sulfamethoxazole-trimethoprim and the other had a history of urticaria after sulfonamide antimicrobials.

Oral challenge to sulfamethoxazole-trimethoprim in all skin test negative patients was not associated with any adverse reactions.

Oral challenge to sulfamethoxazole was tolerated in the 20 patients with negative skin testing. Oral challenge with celecoxib was administered in the 28 patients including those who had shown pos-

Table II. Summary of patient characteristics

Patient	Sex	Age (y)	Details of 'allergy'	Skin testing to SMX and TMP	LTA
1	F	44	Oral and nasal discharge	Negative	ND
2	F	76	Diarrhoea	Negative	ND
3	F	71	Urticaria	Negative	ND
4	F	61	Arthralgia/arthritis	Negative	ND
5	F	74	Urticaria	Negative	ND
6	F	51	Fever, malaise, headache	ND	Negative
7	F	70	Unknown	Negative	Negative
8	F	58	Pruritus, cutaneous eruption	ND	Negative
9	F	39	Unknown	Positive delayed to SMX	Negative
10	F	75	Pruritus	Negative	ND
11	F	53	Unknown	Positive immediate to SMX	Negative
12	F	56	Cutaneous eruption	Negative	ND
13	F	51	Malaise, cutaneous eruption	Negative	Negative
14	F	77	Cutaneous eruption	Positive delayed to SMX	Negative
15	F	54	Urticaria, shortness of breath	Negative	ND
16	F	63	Urticaria	Negative	ND
17	F	60	Seizure	Negative	ND
18	F	66	Facial swelling	ND	ND
19	M	61	Rash	Negative	Negative
20	F	63	Urticaria	Negative	ND
21	F	77	Urticaria	Negative	Positive
22	M	60	Urticaria	Negative	ND
23	F	72	Malaise	Negative	ND
24	F	41	Fever, rash, arthralgia	ND	Positive to SMX
25	F	66	Swelling, chest tightness	Negative	ND
26	F	46	Emesis	Negative	ND
27	F	29	Dyspepsia	Negative	ND
28	F	57	Diarrhoea, dizziness	Positive immediate to SMX	ND

F = female; **LTA** = lymphocyte toxicity assay; **M** = male; **ND** = no data/not done; **SMX** = sulfamethoxazole; **TMP** = trimethoprim.

itive sulfamethoxazole skin prick tests and in the one patient with a positive *in vitro* test. All patients tolerated the medication without any adverse reaction. Phone call follow up in 25 of these patients revealed that 15 continued to tolerate celecoxib therapy, five patients did not take the drug following the oral challenge, and five discontinued therapy due to adverse effects, lack of drug efficacy or their physician's preference. In this latter group, gastrointestinal adverse effects were experienced in a single patient who discontinued therapy. Specific follow up in five of the six patients with documented sulfonamide allergy who tolerated the celecoxib oral challenge revealed that four patients continued to take the drug long-term uneventfully and the other patient discontinued the drug after 12 days due to gastrointestinal adverse effects. The sixth patient, who was the one patient with a history of sulfonamide hypersensitivity syndrome reaction and positive *in vitro* test did not take celecoxib after completion of the oral challenge as her physician perceived there to be a risk of continued therapy.

Discussion

Our data support the concept that patients who are validated to have sulfonamide antimicrobial allergy can tolerate oral celecoxib. This suggests that the allergic determinant for these reactions is specific to the sulfonamide antimicrobial and may

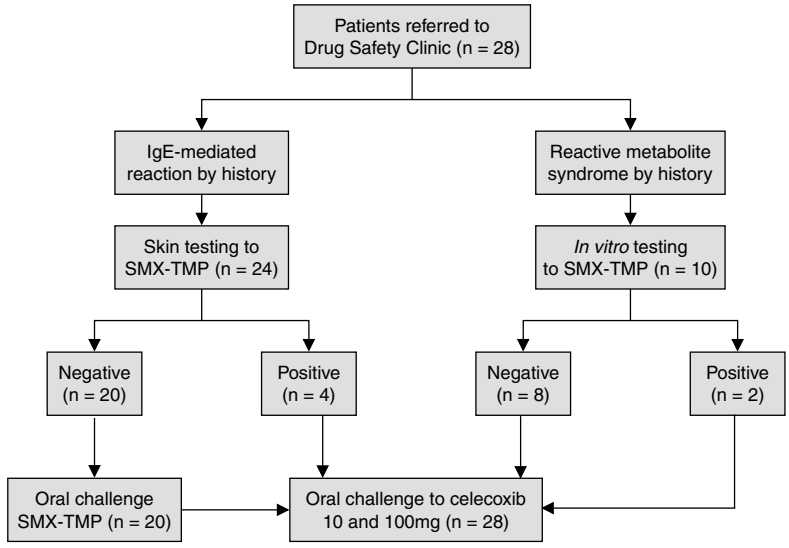

Fig. 2. Patient algorithm. **IgE** = immunoglobulin E; **SMX-TMP** = sulfamethoxazole-trimethoprim (cotrimoxazole).

explain why these patients went on to tolerate celecoxib despite the fact that both drugs contain a sulfonamide substituent as part of their chemical structure.

Sulfonamide allergy can manifest in a variety of clinical presentations including immunological (or allergic) or idiosyncratic reactions, such as the sulfonamide drug hypersensitivity syndrome.

In type I reactions involving sulfamethoxazole, immunoglobulin (Ig) E antibodies to the drug have been demonstrated in sulfamethoxazole allergic patients by an *in vitro* solid phase assay and by *in vivo* skin testing with multivalent sulfamethoxazole-poly-L-tyrosine.[19] Two allergenic components have been identified: the attachment of a five- or sic-member aromatic heterocyclic ring with at least one nitrogen at the sulfonamide-N1 position, and the presence of a single methyl group on the carbon atom beta to the sulfonamido substitution of sulfonamide antimicrobials, and not the sulfonamide group.[21] The N^4 arylamine group was not an important determinant of IgE antibody recognition.[21] Celecoxib does not contain the epitope to which IgE antibodies have been demonstrated to sulfonamide antimicrobials.

The triad of fever, rash and single or multiple internal organ involvement that starts within 12 weeks after initiation of therapy characterises the

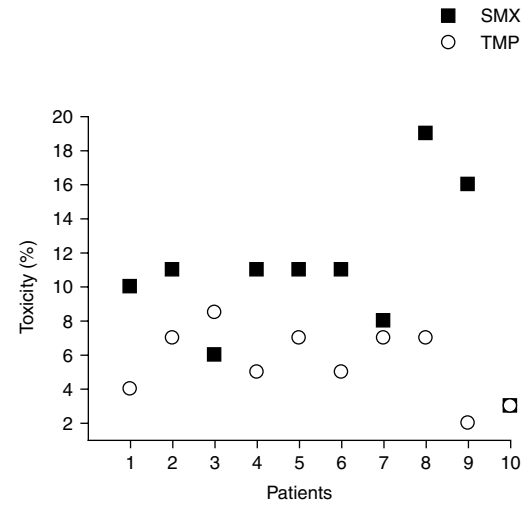

Fig. 3. Results of lymphocyte toxicity assay. **SMX** = sulfamethoxazole; **TMP** = trimethoprim.

drug hypersensitivity syndrome.[22-24] The pathogenesis of this drug reaction pattern is based on the development of reactive metabolites in the host's handling of the drug and may be mediated by both metabolic and immunological factors (figure 4).[25] In normal hosts, 45–70% of SMX is acetylated while only a small fraction of the parent compound undergoes oxidation to form a reactive hydroxylamine intermediary.[26-28] The sulfamethoxazole hydroxylamine (SMX-HA) is further metabolised to the more reactive nitrososulfamethoxazole that covalently links to host proteins leading to 'hapten-protein' conjugates.[29] For sulfonamide antimicrobials, haptenation occurs at the N^4 position, the site of the arylamine group, on the benzene ring. Reactive N^4-metabolites bind to proteins and can cause apoptosis leading to severe cutaneous adverse reactions and drug-induced hypersensitivity syndrome reactions.[30,31] The sulfonamide substituent itself does not trigger these reactions.[32] Diagnosing drug hypersensitivity syndromes relies on clinical acumen in recognising a reaction pattern consisting of fever, cutaneous eruption and internal organ involvement. We have validated the MTT-based lymphocyte toxicity assay and found that in the setting of sulfonamide hypersensitivity syndrome reactions the test has a specificity and positive predictive value each of 90%.[33-35]

Although many references suggest that patients who are 'sulfa allergic' should avoid other 'sulfonamide-type' drugs, cross-reactivity between these drugs has not been substantiated by clinical reports in the literature (table I).[36]

Epidemiological data also substantiate the absence of cross reactivity between sulfonamide antimicrobials and celecoxib. A recent study looked at the allergic adverse events in the North American celecoxib studies with over 11 000 individuals.[37] Although sulfonamide 'allergy' was among the exclusion criteria for all celecoxib clinical trials, 135 patients deviated from protocols in this regard. There were no statistically significant differences between the groups with regards to incidence of allergic reactions. No patient receiving celecoxib reported severe cutaneous adverse reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

A recent paper identified serious adverse drug reactions to celecoxib.[38] These reactions included reports of toxic epidermal necrolysis and Stevens Johnson syndrome. Therefore it is clear that cele-

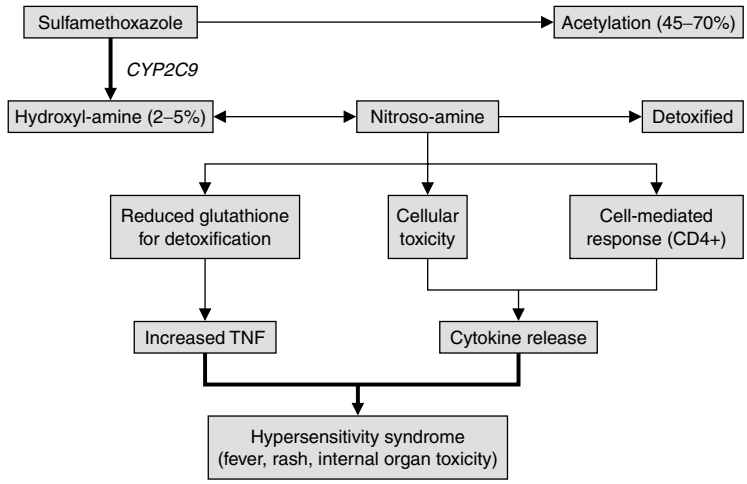

Fig. 4. Pathogenesis of sulfonamide hypersensitivity syndrome. The reactive metabolite theory. **TNF** = tissue necrosis factor.

coxib, like other non-aromatic sulfonamide compounds, is capable of causing serious reactions; however, cross reactions between these compounds and sulfonamide antimicrobials are unlikely to occur.

While our study results are reassuring, one limitation of the study is the small sample size. In the 28 patients with a history of sulfonamide antimicrobial allergy, only 6 patients (21%) had validated sulfonamide antimicrobial allergy by intradermal or *in vitro* testing. As in other studies, patient history was not predictive of positive skin or *in vitro* testing.[39] It can be difficult to diagnose drug reactions by history and that is why testing is done, to add to the likelihood of an accurate assessment. However, the patient history may lead to different interpretations of the type of reaction and the type of testing that should be done. Therefore, it is only in these patients that the safety of celecoxib was proven. In the one patient in whom celecoxib therapy was discontinued due to gastrointestinal upset, it is clear that this adverse effect does not represent a sulfonamide reaction. Three of the four patients with positive sulfonamide skin testing tolerated more prolonged exposure to celecoxib. Data in the literature suggests that IgE antibodies are specific for individual sulfonamides and there is no data to suggest that continued administration of a second sulfonamide medication will eventually lead to the development of an IgE response. Although the patient with a history of a sulfonamide drug hypersensitivity syndrome and positive *in vitro* test did not go on to have more prolonged exposure to celecoxib, it is reassuring that there was no reaction after the two dose oral challenge as brief exposures to the inciting medication in these patients can trigger a prompt recrudescence of the drug symptom complex.

Nevertheless, both the direct challenge of sulfonamide allergic patients with a sulfonamide help clear safety concerns for larger studies and help to change the current paradigm of sulfonamide allergy.

Our pilot study is the only trial to date to provide long-term follow up in patients with a history of sulfonamide allergies who were able to tolerate celecoxib. It is also interesting to note that in several patients who completed testing, physician reluctance prevented continued therapy with celecoxib.

Conclusion

Generally, patients who state that they have a sulfa allergy are referring to sulfonamide antimicrobials. Much confusion exists regarding the potential for cross reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds. This pilot study supports the hypothesis that the potential for cross-reactivity between celecoxib and sulfonamide antimicrobials appears to be low. Another worthy goal would be to revise the current product monograph of celecoxib to more accurately address the issue of sulfonamide sensitivity and to revise the paradigm of what sulfonamide allergy really means. Perhaps other non-aromatic sulfonamides such as furosemide should also be prospectively studied to show the lack of cross-reactivity.

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