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

In a recent article, Knowles et al.[1] provide a comprehensive and insightful analysis of sulfonamide adverse reactions and possible cross reactivity between sulfonamide antimicrobials and non-aromatic sulfonamides. They point out that type I allergic reactions to aromatic sulfonamide antimicrobials are linked to the N1-substituent rather than the sulfonamide structure. For serious adverse reactions like the hypersensitivity syndrome and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) they claim that the aromatic amine moiety and not the sulfonamide moiety trigger the reaction. Therefore, in theory, non-aromatic sulfonamides like acetazolamide, celecoxib and furosemide would not be expected to cross-react with aromatic sulfonamides. They also find little evidence that non-aromatic sulfonamides such as acetazolamide, celecoxib, furosemide, thiazide diuretics and the hypoglycaemic sulfonylureas cross react with sulfonamide antimicrobials.

In order to support the concept that celecoxib is not contraindicated in patients with sulfonamide allergy, they review a meta-analysis of celecoxib trials.[2] From this analysis, they emphasize that: no patient taking celecoxib in the clinical trials developed SJS or TEN; among 135 patients with a history of sulfonamide hypersensitivity there were no statistical differences in the frequency of allergic reactions between 73 patients given celecoxib, 30 patients receiving conventional nonsteroidal anti-inflammatory drugs, and 32 receiving placebo; and 'use of celecoxib with other sulfonamide diuretics and sulfonylureas did not increase the risk of allergic-type reactions'.[2]

Some of these statements need comments and corrections. Although the Patterson meta-analysis includes a large number of patients, the sample size is small when it comes to evaluating type B reactions. Seeing no case of SJS or TEN among 6376 patients treated with celecoxib only excludes a relative risk of >470 (i.e. celecoxib would have to increase the risk more than 470 times compared with the background) and if the analysis is limited to the 135 patients with a history of sulfonamide allergic reactions the relative risk would have had to be 3700 to produce one case of either SJS or TEN.

It may be true that, in theory, sulfonamide antimicrobials have little potential to cross react with celecoxib but the power for finding a statistical difference of allergic reactions between these three patient groups is very limited. Moreover, in that meta-analysis patients with a history of allergic reactions to sulfonamides had a 3- to 6-fold increase in the incidence of dermatological reactions in comparison to the whole arthritis population.[2]

In Canada, 16 of 74 patients (21%) who were reported to have developed an 'allergic-type' reaction to celecoxib also reported a previous reaction to sulfonamides.[3] This is substantially higher than the 3% of sulfonamide allergy in the general population in the US[4] and in Sweden.[5]

There is no reason for allergic reactions to be more frequent in patients taking non-aromatic sulfonamides in combination with celecoxib. On the contrary, such patients tolerate the sulfonamide they were taking, and one would rather expect the frequency of allergic reactions in this group to be less than in those who did not take concomitant sulfonamides because of depletion of patients prone to hypersensitivity reactions.

The suggestion that the aromatic ring structure is responsible for the serious allergic reactions to sulfonamide antimicrobials is not documented in the review. The authors claim that there are certain individuals who will react to the aromatic hydroxylamine moiety. This is probably true but, the publication referred to by Spielberg et al.,[6] does not seem to contain information on this issue.

In clinical practice, an aromatic amine is not necessary for eliciting serious, sulfonamide like adverse reactions such as agranulocytosis, aplastic anemia, hepatitis, phototoxicity or SJS/TEN. Acetazolamide can give rise to aplastic anemia[7] and agranulocytosis, thrombocytopenia and serious skin reactions are labelled. For furosemide anaphylaxis, urticaria, nephritis, thrombocytopenia, and vasculitis are labeled and the risk for aplastic anemia is increased.[8] Moreover, lamotrigine, a non-aromatic antiepileptic, can cause ADRs that are very similar to the so called 'anticonvulsant hypersensitivity syndrome' including SJS and TEN that is usually associated with aromatic anticonvulsants.[9] Finally, in a study based on suspected adverse reactions reported to the WHO database, celecoxib was found to have an ADR-profile similar to that of antimicrobial sulfonamides[10] and the reported incidence of sulfonamide-like ADRs was almost twice that of the non-sulfonamide comparator rofecoxib (relative risk 1.8; 95% confidence interval 1.6 to 1.9). The relative reporting rate was significantly higher for celecoxib compared with rofecoxib for rash, urticaria, SJS, and phototoxicity. The reported incidence of SJS/TEN with celecoxib was 2.5 to 5 times the background incidence of 1 to 2 cases per million inhabitants per year.[11] Thus, it seems like type 1 allergic reactions like urticaria can be elicited by sulfonamides that do not contain the N-1 substituent and hypersensitivity syndrome reactions are not dependent on the aromatic amine moiety.

It is always difficult to interpret comparisons of drug risk profiles based on spontaneous reports, especially if the drugs compared have been on the market for different lengths of time.[12] It is meaningless to compare commonly occurring reactions, especially of type A, since such reactions are haphazardly reported. Still, such comparisons are published.[13] For rare and or idiosyncratic reactions comparisons have, however, given valid results when the drugs compared have the same or similar patient populations and are used on a long-term, or defined short-term basis in relatively standardised dosages and if good sales and prescription data are available.[14,15]

When a new drug is authorised for marketing, little is known about its potential to elicit immunological/idiosyncratic reactions or cross-reactions. Therefore, it is logical for a regulatory agency to choose to be on the safe side until enough clinical data have been gathered to make a valid analysis of the situation. Since allergy to sulfonamides is relatively rare, about 3%, a possible cross reactivity between aromatic sulfonamides and celecoxib is quantitatively a small clinical problem, especially as there is an alternative cyclo-oxygenase 2 inhibitor that does not contain a sulfonamide moiety.

One interesting case history has been published[1] in which a patient developed angioedema and exanthematous eruption thrice when taking sulfadimethoxin, chloramidobenzol and acetazolamide. This case was judged by Knowles et al.[1] to be a hapten allergy-prone patient having developed three separate hypersensitivities. Thus, the contraindication for patients with previous sulfonamide allergy may not be relevant because of cross-reactivity but as a marker for a hapten-allergy prone individual. The logical thing to do would then be to warn against use of celecoxib for patients that have a disposition to develop immunological reactions or hapten forming metabolites, a much larger group than the 3% reporting previous allergy to sulfonamides. A thorough patient history of any previous ADR that could be elicited by an immunological mechanism is required before prescribing celecoxib.

The authors conclude, 'For the present, the contraindication (of celecoxib use in patients with sulfonamide allergy) is based on myth at best'. It could be that the contraindication should be there, but the reason may not be primarily because of sulfonamide cross-reactivity, but because this is a marker of a hapten allergic trait in these patients. The data in the WHO database seems to indicate that sulfonamide typical ADRS, including SJS/TEN occur more commonly than expected. This, together with the higher than expected number of patients with celecoxib allergy reporting a known

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sulfa allergy does not seem to support this conclusion, and to suggest the removal of this contraindication may have negative implications for patient safety.

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