The authors reply:

We thank Dr Wiholm for his comments regarding our review of cross-reactivity between sulfonamide antimicrobials and non-aromatic sulfonamides, such as hydrochlorothiazide, glibenclamide (glyburide) and celecoxib. Although our approach to sulfonamide cross-reactivity is novel, it is based on logic and good science.

A sulfonamide drug is any compound that contains the SO_2NH_2 moiety. This is a very broad definition, much like assigning a race or nationality to an individual. Similarly, the term sulfonamide does not confer specific properties to all drugs with the SO_2NH_2 moiety, anymore than one can generalize characteristics to a population based on one feature. More to the point under discussion, sulfonamide antimicrobials are more than just SO_2NH_2; they contain an aromatic amine with an amino (NH_2) at the N4 position of an aromatic ring. It is this aromatic amine that is oxidized to a hydroxylamine, which then can be auto-oxidised to a more reactive nitroso metabolite.[1] In susceptible individuals, this reactive metabolite, and *not* the sulfonamide moiety, has been shown to be associated with serious drug reactions such as drug hypersensitivity syndrome reaction and toxic epidermal necrolysis. Therefore both of these severe systemic reactions are associated with sulfonamide antimicrobials; these are the sulfonamides with the aromatic amine.

Although the aromatic amine is thought to be responsible for serious sulfonamide drug reactions, Dr Wiholm correctly states that an aromatic amine is not necessary for eliciting serious idiosyncratic reactions for other medications. There are many compounds that cause serious reactions but do not contain an aromatic amine. In many cases, the reactive or toxic metabolite has not been identified. For a small number of medications, including sulfonamide antimicrobials and possibly aromatic anticonvulsants, the toxic metabolite has been identified. The anticonvulsants phenytoin, carbamazepine and phenobarbital (phenobarbitone) have in common an aromatic benzene ring that is metabolized to toxic arene oxides,[2] which may play a pivotal role in the development of drug hypersensitivity syndrome reaction and other serious idiosyncratic drug reactions. It should be noted that the anticonvulsants do *not* contain an aromatic amine ring. Overall it is thought that a number of factors acting in concert contribute to severe idiosyncratic drug reactions. These include genetic variables, the underlying health status of the patient, and danger signals that together with drug haptens can result in serious adverse events.[3]

In a study authored by Dr Wiholm and published subsequent to our analysis, celecoxib was shown to have an increased risk of developing cutaneous adverse reactions, such as Stevens-Johnson syndrome, urticaria, photosensitivity and rash, as compared to rofecoxib.[4] We agree that these reactions can occur with celecoxib; however, we are unaware of the mechanism for these reactions. Since celecoxib does not contain an aromatic amine, no cross-reactions between it and sulfonamide antimicrobials would be expected. This is substantiated by case reports that support lack of cross-reactivity between sulfonamide antimicrobials and other sulfonamide containing drugs.[5]

Dr Wiholm suggests that a previous sulfonamide allergy may be a marker for a hapten-allergy prone individual, and that these patients should be warned against the use of celecoxib due to a predisposition to develop immunologic reactions. This concept was explored in an early study that showed a history of prior drug reactions was more common in patients reacting to penicillin than in those who did not react, suggesting the possibility that patients who experienced reactions to penicillin were more likely to do so to multiple drugs.[6] What causes patients to develop adverse drug reactions to multiple drugs is not known, but may involve non-immunologic mechanisms.

We are concerned that scientists, clinicians and patients are potentially confusing the issues. Each drug should be evaluated on its own merits, both chemical and clinical. Labelling a drug 'sulfonamide' is misleading based on the information that is now available; further sub-classification (e.g. sulfonamide antimicrobials) is helpful and relevant.

Labelling adverse drug reactions, 'sulfonamide-like adverse drug reactions' is illogical by extension. Withholding medication from individuals who have been labeled 'sulfonamide allergic', a meaningless statement, does not help. We are concerned that therapeutic choices based on concerns about possible cross-reactivity may result in suboptimal treatment at best and inappropriate treatment at worst.

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