

## Sulfa Allergy: Cross-Reactivity Versus Multiple Concurrent Allergies

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Received 2012-10-13, Revised 2013-05-01; Accepted 2013-12-02

### ABSTRACT

As a medical resident we have always been taught that there is some sort of cross reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. Even the manufacturer's package inserts contain a precautionary statement about possible Cross-reactivity. The most common approach to this problem is avoidance of all sulfa containing drugs. However, there are few data supporting this contraindication. Thus we may be withholding appropriate therapies from patients unnecessarily. To provide a critical and comprehensive review of literature to explore either cross reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides is a fact or fiction and to present an approach to use nonantibiotic sulfonamides in sulfa allergic patients. A PubMed and general medline search was conducted using the individual names of nonantibiotic sulfonamides. We reviewed all of the available case reports and studies regarding sulfonamide antibiotic cross-reactivity with nonantibiotic sulfonamides. Also reviewed the manufacturer's package insert for each nonantibiotic sulfonamide drug for information concerning possible cross-reactivity with sulfonamide antibiotics. Sulfa drug allergy is one word holding the whole cross-reactivity theory in it. It should be obsolete from the medical dictionary. This one word is complicating the medical decision-making. Allergies should not be attributed to classes or groups of drugs unless proven. After reviewing all the available literature we can conclude that assumptions about cross-reactivity are a FICTION.

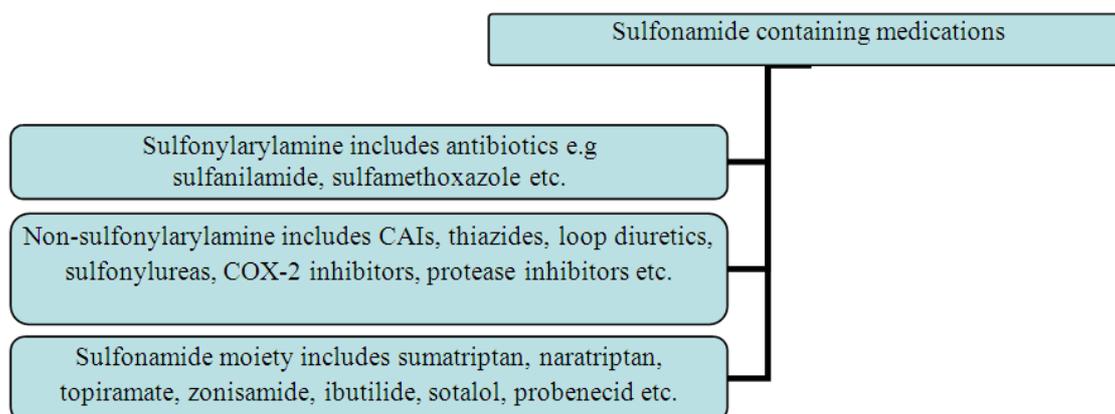
**Keywords:** Non-Antibiotic, Cross-reactivity, Contraindication, Sulfonamides, Sulfonamide Antibiotics

### 1. INTRODUCTION

Sulfonamides are commonly used drugs in primary care practice. Reactions to Sulfonamide Antibiotics (SA) are relatively common as compared to other antimicrobials. They occur in approximately 3% of the treatment courses; however, only 3% of these are true hypersensitivity reactions. Two types of allergic reactions have been described in relation to these compounds. One being an IgE mediated maculopapular or urticarial rash developing 1-3 days after medication initiation and the other being a hypersensitivity reaction. The hypersensitivity reaction, consisting of fever and non-urticarial rash, usually develops 7-14 days after the

medication initiation (Johnson *et al.*, 2005). The term "sulfa" refers to a derivative of an antimicrobial agent, sulfanilamide. The term has been applied to a diverse group of drugs, all of which contain the sulfonamide chemical structure; -SO<sub>2</sub>NH<sub>2</sub> moiety which is also a part of many common medications, such as thiazide and loop diuretics (Johnson *et al.*, 2005). We can classify sulfa drugs in two ways, one is based on the chemical structure i.e., sulfonarylamine, non sulfonarylamine and sulfonamide moiety containing drugs (**Fig. 1**) (Johnson *et al.*, 2005) and the other is based on cross reactivity theory i.e., Sulfonamides Antibiotics (SA) and Sulfonamides Non-Antibiotics (SNA) (**Table 1A**) (Strom *et al.*, 2003).

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**Fig. 1.** Classification of sulfonamides, CAI = carbonic anhydrase inhibitors; COX-2 = cyclooxygenase-2; thiazides = thiazide diuretics and related compounds

**Table 1A.** Sulfa drugs

		Drugs
Antibiotic sulfonamide	Subgroups	Sulfadiazine, sulfisoxazole sulfamethoxazole, sulfapyridine
Non antibiotic sulfonamide	Carbonic anhydrase inhibitors	Acetazolamide, Brinzolamide, Dichlorphenamide, Dorzolamide, Methazolamide, Sulthiame
	Loop diuretics	Bumetanide, Furosemide, Piretanide, Torsemide
	Thiazides and related compounds	Bendroflumethiazide, Benzthiazide, Chlorothiazide, Chlorthalidone, Clopamide, Diazoxide, hydrochlorothiazide, Hydroflumethiazide, Indapamide, methyclothiazide, metolazone, Polythiazide, Xipamide
	Sulfonyleureas	Acetohexamide, Chlorpropamide Gliclazide, Glibornuride, Glipizide, Glimepiride, Gliquidone, Glyburide, Glymidine, Tolazamide, Tolbutamide
	Cyclooxygenase 2 (COX-2) inhibitors	Celecoxib, rofecoxib, valdecoxib
	protease inhibitors	Amprenavir, Fosamprenavir
	Triptans	Naratriptan, Sumatriptan
	Other agents	Amprenavir, Dapsone, Fosamprenavir, Ibutilide, Probenecid, Sotalol, Sulfasalazine, Topiramate, Zonisamide

As a medical resident we have always been taught that there is some sort of cross-reactivity between SA and SNA. Even the manufacturer’s package insert contains a precautionary statement about possible cross-reactivity (**Table 1B**). The most common approach to

this problem is avoidance of all sulfa containing drugs. However, there is handful data supporting this contraindication, thus we may be withholding appropriate therapies from patient unnecessarily (Ditto, 2002; Knowles *et al.*, 2001; SDISCPN, 2003).

**Table 1B.** Manufacturer’s package insert information for sulfonamide-containing medications

Drug Class	Manufacturer’s package insert statement		Brand
	Presence	Recommendation	
<b>Carbonic anhydrase inhibitors</b>			
acetazolamide	Yes	Warnings	Avkare
brinzolamide	yes	Warnings	Azopt
Dichlorphenamide	no		Daranide
dorzolamide	yes	Warnings	Cosopt
methazolamide	yes	Warnings	Methazolamide
Sulthiame	yes	Contraindications	Ospolot
<b>Loop diuretics</b>			
bumetanide	yes	Warnings	Bumetanide
furosemide	yes	Precautions	Furosemide
Piretanide	yes	Contraindications	Tauliz
torseamide	no		Demadex
<b>Thiazide diuretics and related compounds</b>			
Bendroflumethiazide	yes	Contraindications	Corzide
Benzthiazide	yes	Contraindications	Aquatag
Chlorothiazide	yes	Contraindications	Diuril
chlorthalidone	yes	Contraindications	Thalitone
Clopamide	yes	Contraindications	Brinaldix
diazoxide	yes	Contraindications	Hyperstat
hydrochlorothiazide	yes	Contraindications	Hydrochlorothiazide
Hydroflumethiazide	yes	Contraindications	Saluron
indapamide	yes	Contraindications	Indapamide
methyclothiazide	yes	Contraindications	Enduronyl
metolazone	yes	Warnings	Mykrox
Polythiazide	yes	Contraindications	Renese
Xipamide	yes	Contraindications	Aquatag
<b>Sulfonylureas</b>			
Acetohexamide	no		Dymelor
chlorpropamide	no		Diabinese
Glibornurinde	no		Glutril
Gliclazide	no		Diamicon
Glipizide	no		Glipizide
Glimepiride	no		Amaryl
Gliquidone	no		Glurenorm
Glyburide	no		Diabeta
Glymidine	no		Redul
Tolazamide	no		Tolinase
Tolbutamide	no		Orinase
<b>5-HT3 receptor antagonists</b>			
Naratriptan	no		Amerge
Sumatriptan	no		Imitrex
<b>COX-2 inhibitors</b>			
Celecoxib	yes	Contraindications	Celebrex
Rofecoxib	no		Vioxx
Valdecoxib	yes	Contraindications	Bextra
<b>Other compounds</b>			
Amprenavir	yes	Precautions	Agenerase
Dapsone	no		Aczone
Fosamprenavir	yes	Precautions	Lexival
Ibutilide	no		Corvert
Probenecid	no		Probenicid
Sotalol	no		Sorine
Sulfasalazine	yes	Contraindications	Azulfidine
Topiramate	no		Topamax
Zonisamide	yes	Contraindications	Zonegran

### 1.1. Data Sources

A PubMed and general medline search was conducted using the individual names of non-antibiotic sulfonamides (48 non-antibiotic sulfonamides were identified). Terms like hypersensitivity, adverse effects and cross- reactions were used. We reviewed all the available case reports and studies about sulfonamide antibiotic cross-reactivity with non-antibiotic sulfonamides. A critical review of the methodology, results and conclusion for each available study was conducted. Review of the manufacturer's package insert for each nonantibiotic sulfonamide drug was performed to obtain information concerning possible cross-reactivity with sulfonamide antibiotics (**Table 1B**).

### 1.2. Literature Review

The cross reactivity hypothesis was tested in a large retrospective cohort study by Strom *et al.* (2003) Authors identified 20,226 patients seen from 1987 through March 1999 who were prescribed a systemic SA and then at least 60 days later received a SNA. Researchers reviewed records to determine whether patients described as having an allergic reaction to SA were at increased risk of having a subsequent allergic reaction to SNA of 969 patients with an allergic reaction after a SA, 96 (9.9%) had an allergic reaction after receiving a SNA. For comparison, out of 19,257 patients who had no allergic reaction after a SA, 315 (1.6%) had an allergic reaction after receiving a SNA (adjusted odds ratio, 2.8; 95% confidence interval, 2.1 to 3.7).

However, risk of an allergic reaction was greater after receiving penicillins, in patients with a prior hypersensitivity reaction to SA, as compared to patients with no such history (adjusted odds ratio, 3.9; 95% confidence interval, 3.5 to 4.3). Furthermore, among patients who had prior hypersensitivity reaction to a SA, risk of an allergic reaction after the subsequent receipt of a SNA was lower than the risk of an allergic reaction after the subsequent receipt of a penicillin (adjusted odds ratio, 0.7; 95% confidence interval, 0.5 to 0.9). Similarly, it was seen that in patients with a history of hypersensitivity to penicillins, risk of an allergic reaction after the receipt of a SNA was lower than the SA (adjusted odds ratio, 0.6; 95% confidence interval, 0.5 to 0.8).

Hence, the data shows that among SA-allergic patients, the incidence of concurrent penicillin allergy was greater than the incidence of reactivity to SNA. This observation seems to imply an element of cross-reactivity between SA and penicillins, which is biochemically a distinct group. The incidence of allergic reactions to SNA drugs was higher among penicillin allergic individuals than among SA

allergic patients. As it is not possible to suggest crossover sensitivity between penicillins and SNA, the authors conclude that simultaneous allergy to SA and SNA is common and likely exclusive of cross-reactivity.

In a small retrospective study Lee and co-researchers revealed small risk of cross-reaction. Researchers reviewed 363 hospital charts examined 34 patients with a self-reported history of sulfa allergy who were subsequently given acetazolamide, furosemide, or both (Lee *et al.*, 2004). The nature of the self-reported sulfa allergic reaction was documented in 79% of the 34 patients. Of these, 329 patients (91%) were excluded of the remaining 34 cases that did report so-called sulfa allergy, 13 (38%) received acetazolamide alone, 7 (21%) received furosemide alone and 14 (41%) received both acetazolamide and furosemide of the 27 patients who received acetazolamide, 10 (37%) had no documented allergic cross-reaction to sulfa and 2 (7%) cases had urticaria. None of the patients experienced severe allergic cross-reaction to sulfa of 21 patients who received furosemide, no unpredictable adverse reactions or allergic cross-reactions to sulfa was noted. They concluded that there is little clinical or pharmacological evidence to suggest that a self-reported sulfa allergy is likely to produce a life-threatening cross-reaction with acetazolamide or furosemide. They also concluded that these medications should be considered if the risk-to-benefit ratio warrants their use.

Patterson *et al.* (1999) evaluated literature associated with several sulfonamide drug classes including Carbonic Anhydrase Inhibitors (CAI), sulfonyleureas, loop diuretics, thiazide diuretics, 5-HT agonists and COX-2 inhibitors. Authors performed three meta-analyses and looked at data from 14 randomized controlled trials involving 11008 patients. In the first meta-analysis, patients with a reported allergy to sulfonylarylamines and non-sulfonylarylamines, such as furosemide, thiazide diuretics or sulfonyleureas, who received celecoxib (n = 73), a placebo (n = 32) or an active comparator (n = 32) were included. There was no statistically significant difference among the 3 groups in terms of potential allergic events. In the end of the three meta-analyses the incidence of allergic reactions with celecoxib was compared to the active comparators. No statistically significant findings were noted in these meta-analyses. Based on these findings authors concluded that the risk of cross-reactivity between SA and celecoxib is low. Based on this review Johnson *et al.* (2005) made the recommendation that patients with a sulfonylarylamine allergy can be administered medications from the other two groups with proper monitoring if it is not possible to use an unrelated product.

On the other hand Hamstreet and Page followed patients during their hospital stay to document prescription and adverse reactions of SA and SNA (Hemstreet, 2006). Inpatient and outpatient use of potentially cross-reactive drugs was observed in 52% of patients, 60% of those patients took furosemide. No adverse effects were reported or documented with outpatient or inpatient SNA use, even among patients with a history of life-threatening reactions to SA.

All of the above studies conclude that patients with a history of allergic reactions to drugs may be at increased risk for all drug-induced adverse events that appear to be allergic in nature. Practically this cross-reactivity theory is not valid.

Now let's see if theoretically cross-reactivity is possible. Brackett *et al.* (2004) and coworkers concluded that the difference in chemical structure between the sulfonylarylamines and other types of sulfonamides implies that cross-reactivity is unlikely. However, T-cell mediated immune response to the unmetabolized, nonhaptenated parent SA has been reported to occur occasionally, although it is not known whether T-cell recognition of antibiotic is related to the sulfonamide functional group or not. Until the mechanism of this recognition was elucidated, cross-reactivity with SNA appeared to remain theoretically possible (Slatore and Tilles, 2004). In 2007 the same first author Brackett concluded that the stereo specificity of T-cell response renders cross-reactivity between SA and SNA highly unlikely (Stock, 1999). Apparently cross-reactivity responses to sulfonamide-containing drugs likely represent multiple concurrent, rather than linked, drug hypersensitivities. Hence, most up to date researchers conclude that the cross-reactivity can neither be explained theoretically nor practically (Brackett, 2007).

Finally, in an exhaustive review of all the relevant case reports from 1955 to 2004 Johnson *et al.* (2005) concluded that, none of the drug pairs implicated during this 50-year period showed enough strength of association to establish the existence of sulfonamide cross-reactivity.

In total 48 sulfonamide non-antibiotics were identified during the search listed in **Table 1A**. We listed all the important information in the Manufacturer's Package Inserts (MPI), in **Table 1B**. When we analyzed all of these 48 MPI together, 21 MPI documented no reaction; rest of the 27 MPI documented the risk of cross-reactivity under contraindications (18), warnings (6) and precautions (3). Six Carbonic Anhydrase Inhibitors (CAIs) were identified. The MPI for all CAI contains the warning and contraindication except

dichlorphenamide, whereas they have also mentioned that fatalities have occurred, although rarely, due to severe reactions to SA. We identified four sulfonamide loop diuretics during search. Their MPI recommends some sort of reaction with SA except torsemide. Torsemide MPI lists a contraindication to sulfonylurea use, whereas none of the MPI for sulfonylureas shows any concern regarding concurrent use of torsemide. Thirteen thiazide diuretics and related compounds were identified. All of these medications list SA allergy either in contraindications or in warnings. Eleven sulfonylureas and two 5HT<sub>3</sub> receptor blocking drugs were identified and none of the MPI includes any statement concerning their use in SA allergy. We identified three COX-2 inhibitors. Only celecoxib and valdecoxib MPI contain a statement concerning their use in SA allergy, whereas this group generated the largest number of studies concerning their cross-reactivity with SA and all concluded that there is no cross-reactivity (Patterson *et al.*, 1999). Nine drugs were identified in miscellaneous group. Only amprenavir, fosamprenavir, sulfasalazine and zonisamide MPI have cautionary statements. The protease-inhibitors are sulfonamides with an N4 arylamine, like the sulfonylarylamine antibiotics. The product labeling for amprenavir and fosamprenavir state that the potential for cross-sensitivity with other sulfonamides is unknown, but they should be used with caution in people with SA allergy.

## 2. DISCUSSION

The story started in 1955 when Mosely and Baroody (1955) reported that a patient with congestive heart failure and sulfa allergy experienced neurological side effects following administration of oral acetazolamide. Upon readministration of acetazolamide patient experienced same neurological symptoms accompanied by respiratory distress and limb edema. Authors concluded that patient experienced hypersensitive reaction to acetazolamide and since acetazolamide is chemically related to SA; patient with sulfonamide allergy should not receive acetazolamide. As mentioned by the authors neurological symptoms were related to hypokalemia. Stock (1999) interpreted this case as being inconclusive stating that the second episode could have been due to congestive heart failure exacerbation.

Most of the data regarding cross-reactivity theory consist of case reports suggesting that patients who are allergic to sulfonylarylamines are at an increased risk of allergic reaction to the other sulfonamide group medications (Hemstreet, 2006; Landor and Rosenstreich,

1993; Bretza, 1982; Hansbrough *et al.*, 1987). However, the allergic response to two different drugs may represent either true cross-allergenicity, or an independent immune response to each drug. According to Sullivan (1991), multiple, independent drug allergies are quite common and patients who are allergic to one antimicrobial drug have at least a 10-fold increased risk of reacting to another structurally unrelated drug. Clinical presentation of immunologically mediated reactions is very diverse, hypersensitivity response to structurally similar drugs cannot automatically be attributed to cross-allergenicity. This way, case reports develop a body of evidence but are unable to discriminate immunologically linked reactions from concurrent unrelated drug hypersensitivities.

The co-existence of hypersensitivity reactions to several drugs does not prove cross-reactivity between them. As concluded by Strom *et al.* (2003) patients with a prior sulfa allergy are even more likely to have an allergic reaction to penicillin; a structurally unrelated drug, than they are to a SNA. Additionally, the risk of an allergic reaction after receiving a SNA was higher in patients with a history of penicillin allergy than in those with a history of hypersensitivity to SA. One should understand that there is a marked difference between cross-reactivity and the likelihood of mounting an immune response to a wide range of haptens.

Most of the available evidence suggests that SNA need not to be routinely avoided in patients with a history of allergy to SA (Strom *et al.*, 2003; Johnson *et al.*, 2005; Brackett *et al.*, 2004). SNA may cause an allergic reaction themselves due to stereo specificity with sulfonarylamines, cross-reactivity though is unlikely (Brackett *et al.*, 2004). Unfortunately, the product labeling of many SNA do not correlate with what is known scientifically. For instance, many diuretics are either contraindicated or contain warnings regarding their use in patients with a history of allergic reaction to SA (**Table 1B**).

This confliction with the product information of drugs confuses many medical practitioners and pharmacists. In another study authors studied the knowledge and attitudes of American pharmacists concerning sulfonamide allergy cross-reactivity (Wall *et al.* 2010). They suggested significant diversity in knowledge and attitudes of pharmacists concerning cross-reactivity of SA and SNA.

We can end this discussion with the conclusion that there is no theoretical or practical evidence to support cross-reactivity between SA and SNA. However, the clinicians must remain alert to the possibility of multiple and severe drug sensitivities in patients who experienced an allergic response to a SA. Ultimately a clinician needs

to make the decision of whether to initiate a sulfa drug in SA allergic patient, on a risk to benefit basis.

### 3. CONCLUSION

To corroborate the cross-sensitivity reaction of SA and SNA, we did not find any strong documentation in literature supporting this reaction. All of the reported cases of reactions, on close inspection, do not provide any cause-effect relationship. Although case reports describe numerous apparently linked hypersensitivity reactions to SA and SNA, no investigation to date has identified a plausible mechanism for such cross-reactivity.

After reviewing all the available literature we conclude that sulfa drug allergy label is misleading, it is a very vague medical terminology. Sulfa drug allergy is a misnomer. It should be obsolete from the medical dictionary. We are withholding appropriate therapies from patients without any evidence and we are complicating the medical decision making.

Now the question is can we use SNA in SA sensitive patients? The best answer is “probably yes” because susceptible individuals also have a much greater incidence of concurrent allergy to other drugs and drug classes. Administering first dose under supervision, close monitoring, starting with low dose and patient counseling of the potential problem and benefit of the therapy in high risk patients should be employed during the initial stage of therapy. Also it is vital to recognize the allergic reactions correctly, not documenting common side effects of medications like nausea, vomiting, diarrhea, photo dermatitis, as allergic reactions. As a general principle, all allergic adverse reactions to medications should be recorded in the patient’s file with the specific name of the drug or drugs to which the patient has reacted and the nature of the reaction. Allergies should not be attributed to classes or groups of drugs unless proven.

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