Cross-Allergy of Sulfonamide-Containing Drugs in Sulfonamide Allergic Patients: A Literature Review and Case Study

Weile Feng¹, Jiawen Huang¹, Yuwen Tang¹, Zhidong Zhang¹, Jianping Zhang², Xiaofei Feng¹*

Author affiliations
¹Department of Pharmacy, The First Affiliated Hospital, Jinan University, Guangzhou 510630, Guangdong, China
²College of Pharmacy, Jinan University, Guangzhou 510630, Guangdong, China

Address reprint requests to
Jiawen Huang
Department of Pharmacy, The First Affiliated Hospital, Jinan University, Guangzhou 510630, Guangdong, China
Email: eudaemoniay@139.com

Abstract:
The purpose of this study is to find out whether there are broad cross-reactivity between antibacterial and non-antibacterial sulfonamide agents, the method of the study contained two parts, one is literature research mainly from PubMed database by using the MeSH terms ("Drug name" + allergy); ("Drug name" + hypersensitivity); ("Drug name" + cross-allergenicity) and ("Drug name + cross-reactivity), the search drugs included some commonly seen medication such as carbonic anhydrase inhibitor, COX-2 inhibitor, loop diuretic, sulfonylurea, thiazide and certain antiviral drugs; the other parts of this thesis is to conduct a statistical review, we screen out patients who have a previous allergic history of antimicrobial sulfonamides from hospital medical record system during Jan 1st, 2015 to Dec 31th, 2016, we did a descriptive statistics of general patients medical information, analyze the suspect cases which patients present potential allergic reaction after using non-antimicrobial sulfonamides agents. Result of literature research reveal there are no convincing evidences and research to confirm there are bored allergenicity between non-antimicrobial sulfonamides and antimicrobial sulfonamide in the aspects of chemical structure, immunological study, and large scale population study as well; Result of hospital patient's statistics found out there are only 3 suspected cases that the patients were having adverse effect during their pharmacotherapy from 506 cases. However, we did not found any strong correlation of broad allergenicity between non-antimicrobial sulfonamides and antimicrobial sulfonamides from these suspected cases. Conclusion: There is minimal evidence of cross-reactivity between the antimicrobial sulfonamides and the non-antimicrobial sulfonamides. However, the non-antimicrobial sulfonamides are rarely implicated in hypersensitivity reactions as well, so it is impossible to say with certainty that cross-reactivity does not occur.

Key words Sulfonamides, Non-antimicrobial sulfonamides, Cross-allergenicity.

INTRODUCTION
Sulfonamides, from a modern perspective, the term refers to a several group of drugs, all of which contain the sulfonamide(-SO₂:NH₂) moiety in their chemical structure. Sulfonamide-containing antibiotics are the second most frequent cause of allergic drug reactions, after the beta-lactams (Penicillins and Cephalosporins). In one large study, the incidence of reactions
to trimethoprim-sulfamethoxazole (TMP-SMX) was 34 per 1000 patients exposed, compared with 51 per 1000 for amoxicillin. However, the adverse reactions caused by sulfonamides differ significantly from those attributed to beta-lactams, and the evaluation and management of sulfonamide reactions are distinct. The pathophysiology of allergic (or hypersensitivity) reactions to sulfonamides is complex and poorly understood. Concerns have been raised that a history of sulfa allergy may be associated with an increased risk of adverse reactions to a wide range of non-antibacterial sulfonamides, including certain antivirals, carbonic anhydrase inhibitors, cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs, loop and thiazide diuretics, and sulfonylureas; concerns have also been raised that patients who have experienced an allergic reaction to one non-antibacterial sulfonamide may be at risk for an adverse reaction to others.

**TYPES AND CATEGORIZATION OF SULFONAMIDES**

**ANTIMICROBIAL SULFONAMIDES AND NON-ANTIMICROBIAL SULFONAMIDES**

There are two distinct groups of sulfonamides that differ in chemical structure as well as clinical use which are antimicrobial sulfonamides, the original antibacterial sulfonamides are synthetic antimicrobial agents that contain the sulfonamide group, this group includes sulfamethoxazole (in trimethoprim-sulfamethoxazole [TMP-SMX]) and other less commonly used antimicrobials, some sulfonamides are also devoid of antibacterial activity and that is belong to another group which are non-antimicrobial sulfonamides, the agents in this group include diuretics (thiazide diuretics, loop diuretics, carbonic anhydrase inhibitors), hypoglycemics, anti-inflammatories (COX-2 inhibitors), hypoglycemic agents (sulfonylures) and antihypertensive agents, such as furosemide, hydrochlorothiazide, acetazolamide, sumatriptan, glyburide, celecoxib, sulfasalazine and so on.

- **Protease inhibitors:** The human immunodeficiency virus (HIV) protease inhibitors darunavir, fosamprenavir, and tipranavir, as well as the hepatitis C virus (HCV) protease inhibitor simeprevir, contain sulfonamide moieties, but lack one or both essential functional groups implicated in sulfonamide antibiotic hypersensitivity (ie, N4 arylamine or N-containing ring substitution at N1). But most clinical evidence confirms that they do not cross-react with antimicrobial sulfonamides.
- **Sulfones:** Sulfones are a distinct class of medications from sulfonamides. Dapsone (diaminodiphenylsulphone) is the only sulfone in common clinical use. Although dapsone is not a sulfonamide, it is mention in here because the hypersensitivity reactions reported to dapsone are clinically similar to those of sulfonamide antimicrobials, may have similar pathogenesis, and may have some cross-reactivity concerns as well.

**CHEMICAL STRUCTURE DIFFERENCE BETWEEN SULFONAMIDES**

For difference prospective, sulfonamides can also be divided into three types based on the chemical structure, sulfonylarylamines, non-sulfonylarylamines and sulfonamide moiety-containing drugs. In the antimicrobial sulfonamides, they all share two essential functional groups: an arylamine (an amine group linked to a benzene ring at N4) and an aromatic (N-containing) 5 or 6 member ring attached to the sulfonamide core as an N1 substituent. The presence of both moieties is essential to their mechanism of antimicrobial action (i.e., as an analog of para-aminobenzoic acid) and is also believed central to the pathogenesis of hypersensitivity reactions. The only agents that contain both moieties and produce the reactive intermediates implicated in hypersensitivity are the antimicrobial sulfonamides. The nonantimicrobial sulfonamides do not contain an arylamine group or a substituted aromatic ring.
**EPIDEMIOLOGY OF HYPERSENSITIVITY TO SULFONAMIDES**

Hypersensitivity reactions to sulfonamides have been documented since shortly after the introduction of sulfanilamide, and they occur in about 3% of patients in the general population and 60% of patients with HIV infection. The most common manifestation of sulfonamide allergy is a generalized maculopapular rash accompanied by fever and urticaria, and the most serious reactions are called hypersensitivity or idiosyncratic adverse drug reactions. Rarely, one case per million person-years, antimicrobial sulfonamides may be associated with life-threatening conditions like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Adverse reactions to trimethoprim-sulfamethoxazole (TMP-SMX) occurred in 8 percent of 1121 hospitalized patients receiving oral or parenteral treatment. Women were affected twice as often as men. This study was published before the human immunodeficiency virus (HIV) epidemic.

**Impact of HIV infection:** The epidemiology of sulfonamide reactions changed markedly with the appearance of HIV, as patients with this infection are markedly more susceptible to sulfonamide reactions. However, this review focuses on sulfonamide allergy in patients without HIV infection.

**TYPES OF HYPERSENSITIVITY REACTION TO SULFONAMIDES**

A variety of hypersensitivity reactions can occur in response to sulfonamide drugs.

**ISOLATED CUTANEOUS REACTIONS**

The most common type of hypersensitivity reaction to sulfonamides is an isolated dermatologic reaction. Signs and symptoms are variable and may include erythema, maculopapular or morbilliform rash, urticaria, and pruritus. Most of these reactions appear within the first three days of therapy and resolve promptly after drug discontinuation. The mechanisms responsible are unknown in most cases.

**MORBILLIFORM RASH WITH FEVER AND SYSTEMIC SYMPTOMS**

A more serious type of sulfonamide hypersensitivity is characterized by a pruritic, maculopapular or morbilliform rash, accompanied or preceded by fever. In some patients, this progresses to multisystem organ involvement and dysfunction. Severity can range from mild to severe to fatal. Sulfonamide antimicrobials (usually trimethoprim-sulfamethoxazole [TMP-SMX]) are most commonly implicated in this type of reaction, although non-antimicrobial sulfonamides are occasionally causative.

Symptoms generally develop one to two weeks after the start of administration, with fever usually appearing first, sometimes accompanied by malaise and pharyngitis. Peripheral blood smear may reveal an atypical lymphocytosis or eosinophilia. Organ involvement may be asymptomatic or overt, and can include hepatitis, nephritis, pulmonary infiltrates, and cytopenias. Symptoms generally resolve one to two weeks after discontinuation. With re-exposure, symptoms may appear within one to two days.

**IMMEDIATE-TYPE ALLERGY AND ANAPHYLAXIS**

Sulfonamide antimicrobials can cause type I, or immediate-type hypersensitivity reactions, although this is not common. Type I reactions are mediated primarily by specific IgE antibodies, which trigger sensitized mast cells (and basophils) to degranulate, releasing histamine and other vasoactive mediators. Typical symptoms include urticaria, angioedema, bronchospasm, laryngeal edema, and hypotension. There is some evidence that these rare reactions involve the substituted aromatic ring, rather than the arylamine portion. Non-antimicrobial sulfonamides have also been implicated, but not convincingly documented. For sulfonamides, the relevant drug antigen is usually not the intact drug itself. Instead, reactive metabolites may become
bound in large numbers to serum or cell surface carrier proteins and thereby create a multivalent immunologic stimulus, which can differ structurally from the parent drug. Thus, the utility of skin testing with the original (unmetabolized) sulfonamide is unknown. Antimicrobial sulfonamides are strongly associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, or Lyell syndrome). In contrast, the non-antimicrobial sulfonamides (including furosemide, thiazide diuretics, and sulfonylurea hypoglycemics) are not associated with an excess risk of SJS/TEN. SJS is characterized by a prodrome of malaise and fever, followed by the rapid onset of erythematous or purpuric macules and plaques and blistering of the mucous membranes. The skin lesions progress to epidermal necrosis and sloughing. TEN, or Lyell syndrome, is a similar, but more severe disorder that involves a greater percentage of the body surface area. The immunologic mechanisms of SJS/TEN remain enigmatic. These disorders are discussed in detail separately. Erythema multiforme (EM) is a milder cutaneous reaction consisting of target and vesiculobullous lesions involving the mucosal membranes and favouring the extremities (and palms and soles). SJS and severe EM are viewed by many experts, although not all, as separate entities. EM has also been reported in association with sulfonamide antibiotics.

OTHER UNCOMMON REACTIONS

Sulfonamide drugs, usually the antimicrobials, are infrequently associated with several other types of reactions, including serum sickness, hemolytic anemia, and aseptic meningitis.

- **Serum sickness:** Serum sickness, a type III immunologic reaction, is occasionally caused by sulfonamide antimicrobials. These reactions present approximately 10 days to 2 weeks after initiation of therapy, with fever, rash (which is often urticarial), arthralgia, and lymphadenopathy. Serum sickness is a self-limited response following discontinuation of the drug.

- **Hemolytic anemia:** Glucose-6-phosphate dehydrogenase (G6PD) deficiency is generally considered a contraindication to the use of sulfonamide drugs, as these agents can cause hemolytic anemia. This is a genetic metabolic-type adverse drug reaction rather than an immunologic reaction. The different sulfonamides vary in their risk of causing hemolysis in patients with G6PD deficiency. Several of the antimicrobials are considered high risk, whereas few of the non-antimicrobials are. Probenecid is one exception that is considered high risk. Dapsone also carries significant risk.

- **Aseptic meningitis:**TMP-SMX is among the most common antibiotics to cause drug-induced aseptic meningitis. The clinical presentation of aseptic meningitis involves fever and headache, sometimes accompanied by nausea and vomiting, change in mental status, photophobia, or stiff neck. Patients may display a range of other neurologic and systemic symptoms and signs. In a literature review of 41 cases, most patients developed symptoms to the combination of TMP and SMX, although cases were identified that were triggered by TMP alone or SMX alone. Evaluation of the cerebrospinal fluid typically showed elevated white blood cells (usually in the range of 100 to 1000/mcL), with neutrophil predominance, elevated protein, and normal glucose. After the drug was discontinued, patients began to improve within 24 hours, with resolution of the headache within two to three days. Several case reports exist of patients who were challenged to TMP alone after reacting to TMP-SMX and experienced recurrent symptoms. Of the 15 patients in the review who received the TMP-SMX again, 91 percent developed symptoms within 6 hours, and all did within 24 hours, even when the initial reaction developed after days to weeks of therapy.

PATHOPHYSIOLOGY

The pathophysiology of the most prevalent type of sulfonamide hypersensitivity reaction (i.e., fever and nonblistering rash) has not been conclusively defined and is likely multifactorial. Metabolism of sulfonamide antimicrobials results in intermediate forms of the drug that are
believed to be critical in the pathogenesis of some reactions, although interactions between unmetabolized sulfonamide antimicrobials and T cell receptors have also been proposed. It is unclear if the mechanisms described herein are involved in fever and nonblistering rash only, or also in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), although cytotoxic mechanisms are likely more prominent in SJS/TEN.

**SULFONAMIDE METABOLISM**

Sulfonamide antimicrobials are metabolized along several pathways. Some of the drug becomes acetylated (via N-acetyl transferase) at the arylamine moiety to form nontoxic metabolites that are excreted in the urine. Alternatively, the arylamine group may undergo N-oxidation via cytochrome P<sub>450</sub> to form reactive metabolites. These reactive metabolites can act as hapten, or small molecules that become covalently linked to large host proteins. These hapten-protein complexes may be recognized as foreign and initiate an immunologic reaction. Other intermediate metabolites may be directly cytotoxic. Factors that slow metabolism, such as slow acetylation and/or glutathione deficiency states (such as human immunodeficiency virus [HIV] infection), may increase exposure to these metabolites and thus enhance the likelihood of hypersensitivity reactions.

**EVALUATION AND DIAGNOSIS OF SULFONAMIDES HYPERSENSITIVITY**

A thorough and detailed history is the most important component of the evaluation of a patient who reports sulfonamide allergy because there are no definitive in vivo or in vitro tests for either confirming or excluding the allergy to these medications.  

**History:** The general approach to information gathering in a patient with possible drug allergy (eg, clinical history and review of records) is presented separately. The primary goals in taking a history about past reactions to sulfonamides are:

- Assessing what type of reaction the patient likely experienced in the past.
- Assuring that the reaction was not suggestive of severe forms of hypersensitivity, such as Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or anaphylaxis.

Accordingly, patients who report emergency department (ED) visits or hospitalizations, blistering or peeling of the skin or mucous membranes, or use specific phrases such as "anaphylaxis" or "nearly died," in association with prior sulfonamide reactions, must be taken very seriously.

**Testing:** There are no reliable, valid, and practical testing techniques to evaluate patients with past sulfonamide reactions, although a variety of immunologic testing techniques have been tried experimentally, including in vivo tests such as skin testing and patch testing, as well as in vitro tests such as lymphocyte toxicity assays, enzyme-linked immunosorbent assays (ELISA), radioallergosorbent tests (RAST), and drug-specific immunoglobulin G (IgG) and IgE testing.

**Trimethoprim allergy:** A subset of patients who react to a trimethoprim-sulfamethoxazole (TMP-SMX) combination product are sensitive to the trimethoprim component. This has mostly been documented in human immunodeficiency virus (HIV)-infected patients, in whom up to 20 percent of reactions were due to TMP allergy. However, both generalized erythematous skin eruptions and fixed drug eruption in response to trimethoprim have been reported in patients without HIV infection. Careful graded challenge with trimethoprim is often required to clarify the situation.

**Diagnosis:** The diagnosis of the most common forms of sulfonamide allergy (ie, simple rash and rash with fever) are made clinically.
LITERATURE SEARCH

METHODS

A list of sulfonamide-containing medications was created by literature search from the PubMed/PubChem compound database. Each sulfonamide-containing medication was searched for the up to date drug monograph available in the online drug product databases. Food and Drug Administration (FDA)-approved labeling for various drugs was reviewed for supporting data.

In order to assess the level of published support for sulfonamide cross-reactivity, a comprehensive search of PubMed databases from the year of 1966 to the year of 2017 to examine how the information about cross-reactivity among sulfonamide-containing medications is reflected in the primary literature, we used the MeSH terms (“Drug name” + allergy); (“Drug name” + hypersensitivity); (“Drug name” + cross-allergenicity) and (“Drug name + cross-reactivity) for each sulfonamide-containing medication to search the databases.

Search drugs included but not completed in the following: sulfonamide, carbonic anhydrase inhibitor, COX-2 inhibitor, loop diuretic, sulfonylurea, thiazide, triptan, indapamide, tamsulosin, zonisamide, amprenavir, tipranavir, darunavir, probenecid, and mafenide. Relevant references from PubMed literature database articles were also examined.

RESULT AND ANALYSIS OF LITERATURE RESEARCH

The literature search identified some articles on research pertaining to potential cross-reactivity among sulfonamide antibiotics and non-antibiotics and various drugs from other medication classes.

CROSS-REACTIVITY

There is minimal evidence of cross-reactivity between sulfonamide antimicrobials and non-antimicrobials. However, the available information about cross-reactivity between these two groups is limited to observational studies, as there are no validated skin tests or serologic tests to diagnose or confirm sulfonamide allergy.

CONFOUNDING IN STUDIES OF CROSS-REACTIVITY

Studies of cross-reactivity among related medications are often confounded by the fact that a clinical history of drug allergy, by itself, identifies a subgroup of patients who are at increased risk of reactions to medications in general, even in the absence of actual cross-reactivity among the implicated drugs. Patients with immunologic reactions to two or more chemically distinct types of drugs are said to have “multiple drug allergy syndrome.”

The propensity of certain patients to develop drug reactions was demonstrated in a large, retrospective cohort study performed on a medical database of over eight million patients spanning a 12-year period. Individuals who had a documented allergic reaction to a sulfonamide antibiotic in the past did indeed react more commonly to a sulfonamide non-antibiotic (10 percent) compared with those who tolerated sulfonamide antibiotics (1.6 percent). However, those same individuals with documented sulfonamide antibiotic reactions reacted to the chemically distinct penicillins even more often (14 percent). In addition, there was a higher risk of reaction to sulfonamide non-antibiotics in those with a history of reactions to penicillins than those with a history of reactions to sulfonamide antibiotics. This strongly suggests that a predisposition of drug hypersensitivity reactions, in general, is a better predictor for sulfonamide allergy than a past reaction to a different type of sulfonamide.

BETWEEN SULFONAMIDE ANTIMICROBIALS AND NON-ANTIMICROBIALS

Available evidence does not support the existence of cross-reactivity between sulfonamide antimicrobials (e.g., sulfamethoxazole) and non-antimicrobials (e.g., loop diuretics, thiazide
Sulfonamide cross allergy

diuretics, sulfonylurea hypoglycemics, carbonic anhydrase inhibitors, and protease inhibitors). The strongest evidence supporting this statement is the large database study described in the preceding section 10.

Other evidence includes small studies and series demonstrating that most patients with a history of reacting to an antimicrobial sulfonamide will tolerate non-antimicrobial sulfonamides11:

- A prospective observational study of 94 hospitalized adults with reported "sulfa allergy" noted that 40 patients had taken a non-antimicrobial sulfonamide, most often furosemide, as outpatients for a median duration of 6.2 years, and nine patients had received non-antimicrobial sulfonamides as inpatients, all without adverse reactions 12.
- A retrospective series described 34 patients with reported "sulfa allergy" who were treated with furosemide and/or acetazolamide (non-antimicrobial sulfonamides) for intracranial hypertension 13. There were no reactions in those who received furosemide. Urticaria developed in two patients treated with acetazolamide, although no patients experienced severe reactions.
- Despite these data, the US Food and Drug Administration (FDA)-approved product information for many non-antimicrobial sulfonamide drugs contains warnings concerning possible cross-reactions (Table 1). A data synthesis of the cases of suspected cross-reactions, including published reports and manufacturers' data on file from 1966 to 2004, noted that the FDA product information for 17 of 33 nonantimicrobial sulfonamide drugs included varying statements, warnings, or actual contraindication statements against their use in patients with "sulfonamide" allergy 14. The authors of this analysis concluded that, when subjected to closer examination, these data did not establish a reasonable probability of immunologic or hypersensitivity syndrome cross-reactivity between the two sulfonamide groups 14.

Table 1 Nonantibacterial Sulfonamides Marketed in the United States, by Class11

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of Approval by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals</td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>1999</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2006</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>2003</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>2005</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>1953</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>1998</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>1994</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>1959</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1998</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1999</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>2001</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1983</td>
</tr>
<tr>
<td>Furosemide</td>
<td>1966</td>
</tr>
<tr>
<td>Torsemide</td>
<td>1993</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>1964</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>1958</td>
</tr>
<tr>
<td>Drug</td>
<td>Year</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>1958</td>
</tr>
<tr>
<td>Glipizide</td>
<td>1984</td>
</tr>
<tr>
<td>Glyburide</td>
<td>1984</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>1966</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>1961</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>1959</td>
</tr>
<tr>
<td>Benzthiazide</td>
<td>1960</td>
</tr>
<tr>
<td>Cyclothiazide</td>
<td>1982</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>1961</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>1960</td>
</tr>
<tr>
<td>Hydrobenzthiazide</td>
<td>1959</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1959</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>1960</td>
</tr>
<tr>
<td>Methylthiazide</td>
<td>1961</td>
</tr>
<tr>
<td>Polythiazide</td>
<td>1963</td>
</tr>
<tr>
<td>Quinethazone</td>
<td>1960</td>
</tr>
<tr>
<td>Triptans (5-HT₃ receptor agonists)</td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>2001</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>2002</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2001</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>1998</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>1998</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>1992</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>1997</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td>1973</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1983</td>
</tr>
<tr>
<td>Metolazone</td>
<td>1973</td>
</tr>
<tr>
<td>Probenecid</td>
<td>1951</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>1997</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2002</td>
</tr>
</tbody>
</table>

We agree with this conclusion.

- **Sulfasalazine**: Sulfasalazine represents a possible exception to the general conclusion that cross-reactivity between antimicrobial and non-antimicrobial sulfonamides is unlikely. Sulfasalazine is a non-antimicrobial that releases sulfapyridine, an antimicrobial, upon exposure to gut bacteria. Although there is a small in vitro study demonstrating immunologic cross-reactivity between sulfonamide antibiotics and sulfasalazine, there remains no convincing clinical evidence.

- **Celecoxib**: The available evidence suggests a lack of cross-reactivity between antimicrobial sulfonamides and celecoxib, a non-arylamine sulfonamide selective COX-2 inhibitor. However, there are separate concerns about the selective COX-2 inhibitors and Stevens-Johnson syndrome (SJS) that warrant caution in patients with past febrile or blistering reactions to sulfonamide antimicrobials.
A prospective pilot study of 28 patients with a history of reactions to antimicrobial sulfonamides were challenged with celecoxib, initially with a small test dose and followed by a full dose, after extensive allergy evaluation. None experienced allergic reactions.

In a large meta-analysis of over 11,000 patients from double-blinded trials of celecoxib used for arthritis, the rate of allergic reactions specifically to celecoxib was not statistically different from placebo or active alternate therapy (other nonsteroidal anti-inflammatory drugs [NSAIDs]) 17. Although sulfonamide hypersensitivity was part of the exclusion criteria for those trials, 135 patients were included despite histories of sulfonamide hypersensitivity. Subgroup analysis of those patients did reveal a higher rate of dermatologic reactions compared with the group as a whole. However, the three- to six-fold elevation in rate of reactions was also seen in patients receiving other NSAIDs and placebo, indicating that these patients were at higher risk for hypersensitivity drug reactions in general.

In light of the above studies, we would consider the use of celecoxib in patients with past sulfonamide cutaneous reactions that were mild, although we would avoid celecoxib in a patient with past fever to sulfonamides. Because of the possible association between celecoxib and SJS, we should probably avoid celecoxib in a patient with past blistering reactions to any medication.

**BETWEEN SULFONAMIDE ANTIMICROBIALS AND DAPSONE**

As previously mentioned, dapsone is a sulfone, not a sulfonamide. However, hypersensitivity to dapsone (or the "sulfone syndrome") is characterized by symptoms similar to those seen in sulfonamide reactions (such as fever and rash, sometimes accompanied by hepatitis, lymphadenopathy, and/or hemolytic anemia), and it can be even more severe. It is unclear if there is cross-reactivity between sulfones and sulfonamide antimicrobials, but it seems prudent to avoid both types of agents whenever possible in patients who have had serious reactions (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], rash with fever and systemic symptoms, serum sickness, or hemolytic anemia) to one or the other.

**AMONG NON-ANTIMICROBIAL SULFONAMIDES**

The non-antimicrobial sulfonamides have been associated with far fewer immunologic reactions. Information about cross-reactivity among various agents within this class is derived from case reports, and the paucity of such reports suggests that cross-sensitivity is very low. Thus, when justified by clinical need, a patient with a past nonanaphylactic reaction to a non-antimicrobial sulfonamide can receive a different non-antimicrobial sulfonamide.

**CHEMICAL STRUCTURE PERSPECTIVE**

In a study of chemical characteristic between non-antimicrobial sulfonamides and antimicrobial sulfonamides found out that the antimicrobial sulfonamides contain an arylamine group that undergoes metabolic changes believed critical to the development of hypersensitivity reactions. A key component to the allergic response to sulfonamide antibiotics is the arylamine group at N4, found in sulfamethoxazole, sulfasalazine, sulfadiazine, and the anti-retrovirals amprenavir and fosamprenavir. Other sulfonamide drugs do not contain this arylamine group and are associated only rarely with hypersensitivity reactions. This study suggests that patients who are allergic to arylamine sulfonamides do not cross-react to sulfonamides that lack the arylamine group, and may therefore safely take non-arylamine sulfonamides.

**RETROETROSPECTIVE STUDY OF CLINICAL CASES**

**METHOD**

From Jinan university first affiliated hospital, we select patients who have a past history of allergic reaction to antimicrobial sulfonamides from Jan 1st, 2015 to Dec 31st, 2016 by using nosocomial medical recorded system, then, we did a second screening and mainly look at and statistics how many patients had been received non-antimicrobial sulfonamides during
hospitalization, what non-antimicrobial sulfonamides and how many non-antimicrobial sulfonamides had been taken by these patients and how their health condition changed after taking those drugs from the first screening, we recorded patient’s physiological values (height, weight, age, gender) and analysed any suspects cases which patient occur any dermatological adverse reaction (such as itchiness, angioedema, urticaria, etc.) from the second screening.

RESULT
INITIAL SCREENING
From jinan university first affiliated hospital medical recorded system, we identified a total of 508 cases with reported allergy to sulfonamides during the period from Jan 1st, 2015 to Dec 31th, 2016. From the 508 case reports, only 364 patients were included for participation in the statistical study because certain patients were re-hospitalisation for more than one time during the selected period (Table 2). In certain patients, they were not only allergy to sulfonamides but also allergy to some other drugs or foods, the following table included the statistics of patient’s sulfonamides allergic symptoms and other drugs or foods allergic histories other than sulfonamides. A study shows that patients who had a past history of penicillin allergy had a greater risk of getting non-antimicrobial sulfonamides allergies than those patients who allergy to antimicrobial sulfonamides 10.

Table 2 Statistics of Patient’s Past Allergic History

<table>
<thead>
<tr>
<th>Symptoms of sulfonamides allergy and other allergic history</th>
<th>Patients Counts (Total n=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Patients Counts (Total n=364)</td>
</tr>
<tr>
<td>No Records</td>
<td>317(87.1%)</td>
</tr>
<tr>
<td>Skin rashes/Hives</td>
<td>22(6.0%)</td>
</tr>
<tr>
<td>Anaphylaxis reaction</td>
<td>13(3.6%)</td>
</tr>
<tr>
<td>Rare symptoms (blisters on the lip, swollen and redness of the lip, oral ulcer, blister on the body, dermatitis, numbness of the limbs, and hematuria)</td>
<td>1(2.7%)</td>
</tr>
<tr>
<td>Gastrointestinal Discomfort</td>
<td>2(0.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allergic history other than sulfonamides</th>
<th>Patients Counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other foods or drugs allergy other than sulfonamides</td>
<td>267(74%)</td>
</tr>
<tr>
<td>Penicillins or Cephalosporins allergy</td>
<td>48(13%)</td>
</tr>
<tr>
<td>Other foods or drugs allergy</td>
<td>30(8%)</td>
</tr>
<tr>
<td>(Penicillin or Cephalosporins) + (Other drugs or foods)</td>
<td>18(5%)</td>
</tr>
</tbody>
</table>

SECOND SCREENING
From the first screening of 364 sulfonamides allergies patients, there were 146(40.1%) patients who had been received non-antimicrobial sulfonamides during their hospitalization, 90(61.6%) are male, the average age is 66.3 years old range from (24 years to 92 years). On the other hand, 56(38.4%) are female, average age is 68.7 years old range from (34 years old~91 years old), and the median length of hospitalization is 6 days’ range from(1~27days).

Figure 1 and 2 show statistics of various non-antimicrobial sulfonamides that were used on these 146 patients and the statistics of how many non-antimicrobial sulfonamides that a patient had been received during hospitalization.
SUSPECTED CASES ANALYSIS

From 145 patients who had been received non-antimicrobial sulfonamides during their hospitalization, three of them were occur suspects dermatological reaction. The following are detailed information of each patients general health condition, treatment process and their pharmacotherapy records, theirs name were replaced by A, B, C.

PATIENT A

PATIENT HEALTH CONDITION

Patient A was an 84 years old male who have a history of hypertension for two years and the patient was taking benidipine to control his blood pressure, and he also taking warfarin for long term for his thrombosis. He was coming to the hospital for his cardiovascular problem, and he had been given three types of non-antimicrobial sulfonamides during his treatment in “cardiovascular ward”, the first one is meloxicam 7.5mg/PO bid start from 4/10~4/24; and another three days prescription start from 4/24~4/27, the second one is Fondaparinux sodium 2.5mg/IH qd start from 4/2~4/7 and another three days prescription start from 4/24~4/27, the third one is torsemide 20mg/IV for one day from 4/17, the allergic reaction was first occur from 4/6 with symptoms of itchy skin eruption and skin rash all over the body, loratadine and
chlorphenamine were given to patient A after the day of reaction, and some glucocorticoids also been given to the patient but the skin rash was persist until patient discharge on April 26th, only the symptom of itchiness was slightly relieved.

**PHARMACOTHERAPY RECORDS**
From the medical record data of patient A stated, the complain of itchiness of whole body accompany with skin rash was first present in April 6th and before these discomfort occurs, patient had taken the following drugs since April 2nd: Alprostadil, aspirin, atorvastatin, fondaparinux, warfarin. all of the above drugs can cause dermatologic adverse reaction except alprostadil, the following are information about dermatologic adverse reaction and possible hypersensitivity reaction of these drugs which retrieved from various data base: Aspirin can cause skin rash, urticaria and hypersensitivity included anaphylaxis, angioedema but many adverse effects of aspirin are dose related and are rare at low dosages but the patient was only taking 100mg of aspirin PO/qd since till April 3rd; the another drug that patient had took is 20mg of atorvastatin PO for every night till April 24th, it have some adverse effect that could cause anaphylaxis, angioedema which both are less than two percent ratio; patient had took 2.5mg of fondaparinux qd till April 7th and it has less than one percent ratio of reports say it may cause anaphylactoid reaction, anaphylaxis, angioedema and injection site reaction (bleeding at injection site, skin rash, pruritus); patient had took 1.5mg of warfarin since April 3rd till April 6th and it has 1%~10% could cause dermatitis, pruritus, skin necrosis, urticaria, and hypersensitivity: (anaphylaxis, hypersensitivity reaction). Only the adverse reaction of aspirin, fondaparinux and warfarin have match the symptoms that the patient had encounter but none of these have chemical structure that related to sulfa moiety and something should be notice, it is fondaparinux contain quite a few sulfur atom in its structure. After April 6th ward round record, doctor had order loratadine, chlorpheniramine, halometasone and thalidomide for relieving patient discomfort, even though, the complain of itching and skin rash were only got a slightly better and the complains were still accompany with the patient till discharge according to the ward round record, during the therapy, the patient also received 7.5mg of meloxicam PO in April 10th and 20mg of torsemide IV in April 17th, these two drugs contain a sulfonamide moiety in their structure but it dose not seem to have close relation to the suspects "allergic reaction" this time due to the occurrence date of the “reaction” and the drugs that patient had taken. After all, it seems the "allergic reaction" is cause by this three drugs: aspirin, fondaparinux and warfarin, because all these drugs could cause skin rash and the patient had taken these three days before the “skin problem” had occur, therefor, this “allergic reaction” may have nothing to do with sulfonamides cross-allergenicity but probably mere drugs adverse reaction of those drugs.

**PATIENT B**

**PATIENT HEALTH CONDITION**
Patient B was 80 years old female who have a history of hypertension for 7 years which was being control it by hydrochlorothiazide(HCTZ), and two years of type 2 diabetes which was being control by gliclazide and acarbose. She was coming to hospital for her respiratory infection and during her treatment, she was been given to two type of non-antimicrobial sulfonamides, one is HTCZ 62.mg/PO qd start from 1/6~1/14 and the other one is gliclazide 30mg/PO start from 1/6~1/7, the patient already have skin rash exist before the admission physical examination, Triamcinolone acetonide was given to the patient during hospitalization but symptom exist till the patient discharge (1/14).

**PHARMACOTHERAPY RECORDS**
From the medical record of patient B, we found out that she has a history of hypertension and diabetes because of that she was taking losartan/ hydrochlorothiazide to control her blood pressure and also taking gliclazide and acarbose to control her blood glucose level.
Furthermore, the medical record also show the patients had skin rash on her abdomen and bottom during her admission physical examination and the skin rash on her body was persist until the last ward round record before patient discharge. The drug which patient was taking during her therapy and also have a potential to could cause skin rash are the following: Gliclazide, hydrochlorothiazide, acarbose, cefixime, atorvastatin, cefazolin, azithromycin. In addition, gliclzaide and hydrochlorothiazide both contain a sulfa moiety in their structure. Doctor had given mizolastine and pevisone to relieve the symptoms. In our opinion, the symptom could be cause by the adverse reaction of gliclzaide or hydrochlorothizde or both of them, or it could be cause by fungi infection because of pevisone is mainly used to treat fungi infection.

**PATIENT C**

**PATIENT HEALTH CONDITION**

Patient C was 85 years old male who have a history of hypertension for 30 years and it was control by amlodipine, and he was also taking atorvastatin and clopidogrel, what’s more, the patient not only allergy to sulfonamides but terramycin. The patient was received three type of non-antimicrobial sulfonamides during his treatment period, the first one is tamsulosin 0.2mg/PO for a day at 6/3, the second one is torsemide 10mg/IV or 20mg/IV first start from 5/29 for one day; 6/5 for one day; and ten consecutive days from 6/12~6/22, the third one is parecoxib 40mg/IV start from 6/12~6/17 except the day at 14th. furthermore, the patient was also taking a sulfur-containing medicine which are amlodipine at 5/30~6/22 and Etamsylate at 5/29~6/2 after that patient occur intensive itchy skin eruption which it first occur from 5/31 and the itchiness continue to 6/3 before it got relief after taking another antihistamine drugs and glucocorticoids, and there also had lab report that point out the patient have an elevation of eosinophil which suggests potential allergic reaction may occur, loratadine 8.8mg/PO was given to the patient at 5/31 till 6/4 and it did not have significant effect to symptoms.

**PHARMACOTHERAPY RECORDS**

From the medical record of patient C, patient present itching of the whole body on May 31th and before this discomfort occur, patient had taken the following drugs: 30mg of lansoprazole IV/GTT q12 from May 28th till June 3rd; 2g of cefmetazole IV q8h from May 28th till May 30th; 5mg of amlodipine PO from May 30th till June 2nd; 10mg of torsemide IV on May 29th. From these drugs, only lansoprazole has a less than one percent ratio could cause hypersensitivity. In addition, torsemide have a sulfa moiety in its structure. After then, doctor given patient calamine lotion for potential chronic eczema and loratadine to relieve the symptom, after that day, the itching dose not get any better, on Jun 3rd some blood sample had sent to laboratory for further investigation, the lab result gave out there have an elevation of eosinophil value which mean the patient may have hypersensitivity. Doctor given addition drugs which included halometasone and cyproheptadine to relieve his itchiness, the itchiness had got better after the therapy but these condition still persist until patient discharge on June 22th. In this period, lansoprazole had not given to the patient after June 3rd, only 10mg of torsemide IV was given to patient on June 5th and June 10th respectively, since then, 10mg of torsemide IV was given to the patient until June 22th. From above result, it dose not seems have an evidence point toward sulfa cross-allergenicity was the cause of hypersensitivity of this patient, it was to complicate to identify the cause of this allergic reaction because patient was taking multiple drugs at the same short period.

**SUMMARY OF THESE SUSPECTED CASES**

There was no obvious clue point toward the adverse dermatological reaction of these patients were cause by the cross-reaction between antimicrobial sulfonamides and non-antimicrobial sulfonamides because there was no any laboratory test to support the result, and patients receiving multiply drug treatments at the same time and some of those non-sulfonamides drugs
which do not contained any sulfa moiety could also cause similar dermatological reaction. In addition, the allergic symptoms of sulfonamides were missing in their medical records, we not sure these dermatological reactions were cause by cross-allergenicity or merely cause by other drugs adverse reaction. In conclusion, the incidence rates of cross-allergenicity is zero in this clinical cases retrospective study.

CONCLUSION
A review of the professional literature and clinical cases retrospective study, we did not find any convincing evidence of broad cross-reactivity between antibacterial and non-antibacterial sulfonamide agents, we do not think there are enough evidences to support the cross-allergenicity of non-antimicrobial sulfonamides in sulfonamides allergic patients as well. Although allergy to a sulfonamide antibiotic is indeed a risk factor for a subsequent allergic reaction to a sulfonamide non-antibiotic, a history of multiply antibiotic and other non-antibiotic allergy is at least as strong a risk factor. The association with the sulfonamide non-antibiotics might be explainable by a general predisposition to allergic reactions among certain patients rather than a specific cross-reactivity with drugs containing the sulfa moiety. Thus, prescribers should simply understand that patients with a history of any type of allergic reaction after the receipt of sulfonamides may be at increased risk for reactions to other drugs, rather than consider sulfonamides a specific contraindication. From clinical cases retrospective study, if patients who had the exposure of interest were more closely monitored for the outcome of interest than those without this exposure; that is, if physicians were more likely to monitor patients with a history of sulfa allergies for allergic reactions after administering a non-antibiotic sulfonamide, we may get more cases to studies with and get a more accurate outcome. Even though we did not found any convincing evidence of broad cross-reactivity between antibacterial and non-antibacterial sulfonamide agents but there are some suggestions for future use of sulfonamides.

SUGGESTION FOR FUTURE USE OF SULFONAMIDES

General strategies: There are three general approaches to the future use of sulfonamide drugs in patients with past reactions to a specific agent: avoidance, test dosing to confirm lack of allergy, and desensitization if allergy is likely. The choice of strategy depends upon the type and severity of the past reaction, and on the risks and benefits of alternative treatments.

- Avoidance
  Use of an alternative medication of a distinct pharmacologic class is obviously the safest and simplest option in most patients with past sulfonamide reactions. Avoidance is the only safe approach if a patient describes symptoms consistent with any type of blistering dermatitis or diffuse erythroderma. These patients should almost never undergo test dosing or desensitization, except in very unusual circumstances. Case series have noted that Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can recur and may be more severe with even minor re-exposures.

- Test dosing
  Test dosing (or graded drug challenge) is a term used to describe the cautious administration of small and increasing doses of a medication under medical observation. Test dosing is appropriate for patients who are unlikely to be allergic to the drug in question. It does not alter the patient’s immune response to the drug, so patients who tolerate a graded challenge prove that they are not allergic to that drug. The starting dose used is influenced by the severity and remoteness of the past reaction, and may range from one-thousandth to one-tenth of the therapeutic dose. This amount is then gradually increased by 3- to 10-fold at each step. The steps are administered at time intervals
that are long enough to allow for the development of symptoms, and these intervals are
determined by the nature of the past reaction.
As an example, a patient who had previously developed a maculopapular rash in response to
hydrochlorothiazide and now required glyburide would be an appropriate candidate for test
dosing, as cross-sensitivity between these two non-antimicrobial sulfonamides is unlikely, but
not impossible. If the patient reports that the rash to hydrochlorothiazide had appeared
within two to four hours of the last administered dose, then it would be appropriate to give
test doses at intervals of six to eight hours, beginning at one-tenth of the target dose. In this
example, a relatively large initial dose is acceptable, because the original reaction to
hydrochlorothiazide was not severe.

- **Desensitization**
The term desensitization is used to describe the cautious administration of small and
increasing doses of a medication under careful medical observation to patients who are likely
to be allergic to the drug in question. Desensitization alters the patient's underlying response
to the drug, although only temporarily, as long as there is uninterrupted exposure to the
medication. Desensitization is appropriate when there are no acceptable alternative
medications. Desensitization is most often used in patients with immunoglobulin E (IgE)-
mediated, type I hypersensitivity reactions, although in the case of sulfonamide drugs,
protocols have been developed for use in patients with the more common presentation of rash
and fever.

**ACKNOWLEDGMENTS**
This work was supported by Hospital Pharmaceutical Research Fund of Guangdong
Pharmaceutical Association (2018LR07).

**REFERENCES**
2. Knowles S, Shapiro L, Shear NH. Should Celecoxib Be Contraindicated in Patients Who Are Allergic
3. Hemstreet BA, Page RL. Sulfonamide Allergies and Outcomes Related to Use of Potentially Cross-
5. Knowles S, Shapiro L, Shear NH. Should Celecoxib Be Contraindicated in Patients Who Are Allergic
6. Hemstreet BA, Page RL. Sulfonamide Allergies and Outcomes Related to Use of Potentially Cross-
8. Knowles S, Shapiro L, Shear NH. Should Celecoxib Be Contraindicated in Patients Who Are Allergic
9. Hemstreet BA, Page RL. Sulfonamide Allergies and Outcomes Related to Use of Potentially Cross-

**Volume 10, Issue 03, 2020**


