

SULFA DRUGS AND THE SKIN**Santhosh M Mathews, Jiju V, Irene Thomas*, Jicky T Panicker,****Linta Susan Kuriakose,**

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Accepted on 08 Sep 2015***Correspondence for****Author****Irene Thomas**Nazareth College of
Pharmacy, Othera P.O
Thiruvalla, Kerala.**ABSTRACT**

Sulpha drugs (also called sulphur drugs or sulfonamide-containing drugs) are an imprecise term that generally refers to drugs that contain a sulphonamide functional group in their chemical structure. These drugs have a variety of uses and can be classified into antibiotics and non-antibiotic drugs. Sulfonamide-containing drugs are frequently implicated in allergic and non-allergic reactions. Allergies to sulfonamide are common; hence medications containing sulfonamides are prescribed carefully. It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide

group, and do not cause the same hypersensitivity reactions seen in the sulfonamides. Adverse reactions to sulfonamide antibiotics are estimated to occur in 3-6% of treatment courses. The majority of these reactions are not of an allergic nature. Types of non-allergic reactions to sulfonamide antibiotics include nausea and diarrhoea, candidiasis, folate deficiency, and headaches. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics. Because sulfonamides displace bilirubin from albumin, kernicterus (brain damage due to excess bilirubin) is an important potential side effect of sulfonamide use.

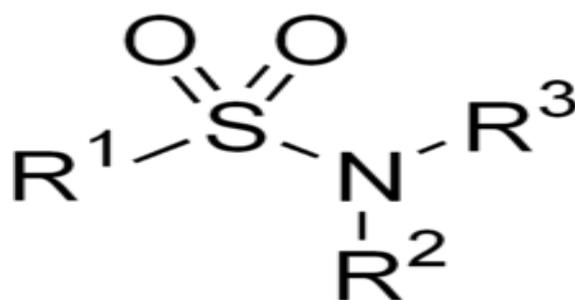
KEYWORDS: Sulphonamides-categories-sulfa allergy-non antibiotic sulphonamides.**INTRODUCTION**

Sulfonamide drugs were the first antimicrobial drugs, and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade-named Prontosil, was a prodrug.

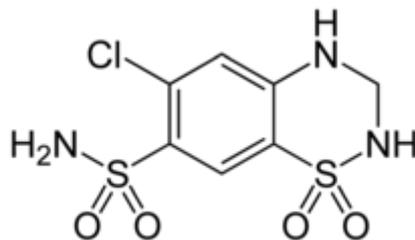
Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes which are able to bind preferentially to bacteria and parasites might be used to attack harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk^[5] (working under the general direction of Farben executive Heinrich Hörlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice. The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. The active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone. The sulfanilamide compound is more active in the protonated form. The drug has very low solubility and sometimes can crystallize in the kidneys, due to its first pK_a of around 10. This is a very painful experience, so patients are told to take the medication with copious amounts of water. Newer analogous compounds prevent this complication because they have a lower pK_a , around 5–6 making them more likely to remain in a soluble form. Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5,400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

PREPARATION

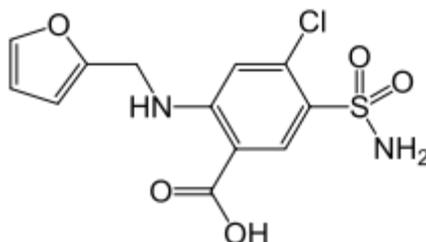
Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. Certain sulfonamides (sulfadiazine or sulfamethoxazole) are sometimes mixed with the drug trimethoprim, which acts against dihydrofolate reductase.



Sulfonamide functional group



Hydrochlorothiazide is a sulfonamide and a thiazide.



Furosemide is a sulfonamide, but not a thiazide.

Sulphonamides are categorised into.

CATEGORY	TYPE	EXAMPLES
Child antibacterial drugs		Pediazole
Antimicrobial	Short-acting	<ul style="list-style-type: none"> • Sulfacetamide • Sulfadiazine • Sulfadimidine • Sulfafurazole • Sulfisomidine (also known as sulfaisodimidine)
	Intermediate-acting	<ul style="list-style-type: none"> • Sulfadoxine • Sulfamethoxazole • Sulfamoxole
	Long-acting	<ul style="list-style-type: none"> • Sulfadimethoxine • Sulfamethoxypyridazine • Sulfametoxydiazine • Sulfadoxine • Sulfametopyrazine
	Ultra long-acting	
Sulfonylureas (anti-diabetic agents)		<ul style="list-style-type: none"> • Acetohexamide • Carbutamide • Chlorpropamide • Glibenclamide (also known as glyburide) • Glibornuride

		<ul style="list-style-type: none"> • Gliclazide • Glycopyramide • Glimepiride • Glipizide • Gliquidone • Glisoxepide • Tolazamide • Tolbutamide
Diuretics		<ul style="list-style-type: none"> • Acetazolamide • Bumetanide • Chlorthalidone • Clopamide • Dorzolamide • Furosemide • Hydrochlorothiazide (HCT, HCTZ, HZT) • Indapamide • Mefruside • Metolazone • Xipamide
Anticonvulsants		<ul style="list-style-type: none"> • Ethoxzolamide • Sultiame • Topiramate • Zonisamide
Dermatologicals		<ul style="list-style-type: none"> • Mafenide
Antiretrovirals		<ul style="list-style-type: none"> • Amprenavir (protease inhibitor) • Darunavir (protease inhibitor) • Delavirdine (non-nucleoside reverse transcriptase inhibitor) • Fosamprenavir (protease inhibitor) • Tipranavir (protease inhibitor)
Stimulant		Azabon
Other		<ul style="list-style-type: none"> • Apricoxib (COX-2 inhibitor) • Bosentan (endothelin receptor antagonist) • Celecoxib (COX-2 inhibitor) • Dofetilide (class III antiarrhythmic) • Dronedarone (class III antiarrhythmic) • Ibutilide (class III antiarrhythmic) • Parecoxib (COX-2 inhibitor) • Probenecid (PBN) • Sotalol (beta blocker) • Sulfasalazine (SSZ) • Sumatriptan (SMT) • Tamsulosin (alpha blocker) • Udenafil (PDE5 inhibitor)

Sulfa allergy

The term “sulfa allergy” (or “sulphur allergy”) most commonly refers to an immunological response to sulfonamide antibiotics. The most commonly prescribed sulfonamide antibiotics include.

- Sulfamethoxazole, often combined with trimethoprim as co-trimoxazole. This is the most common sulfonamide antibiotic in New Zealand; current brand names include Trimel™, Trisul™, and Deprim™.
- Sulfasalazine, a drug used to treat inflammatory bowel disease and rheumatoid arthritis; the current New Zealand brand name is Salazopyrin™.
- Sulfacetamide, used topically to treat eye infections; current New Zealand brand names include Acetopt™ Eye drops and Bleph 10™ Eye drops.
- Sulfadiazine silver, a topical cream used to prevent and treat infection in burns and other types of wounds; the current New Zealand brand name is Flamazine™ Cream.

Sulfonamide antibiotic-associated drug eruptions occur in 1.5-3% of patients in the general population and in up to 30% of patients infected with HIV.

Types of immunological skin reactions to sulfonamide antibiotics.

Reaction	Symptoms
Sulfonamide drug hypersensitivity syndrome	<ul style="list-style-type: none"> • Symptoms usually develop 7-14 days after starting the drug and include fever, generalised maculopapular rash, and internal organ involvement • The rash spreads to varying degrees over the trunk and extremities
Fixed drug eruption	<ul style="list-style-type: none"> • Well-defined, round or oval patches of redness and swelling of the skin, sometimes surmounted by a blister • Develops within 30 minutes to 8 hours of taking the drug
Type I (immediate, IgE-mediated, true allergic response)*	<ul style="list-style-type: none"> • Urticaria (hives) • Anaphylaxis (rare) • Occurs within 30 minutes of drug administration
Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)	<ul style="list-style-type: none"> • Usually develops within the first week of taking the drug • Serious and potentially fatal skin reaction with sheet-like skin and mucosal loss • Rare immune-complex-mediated hypersensitivity
Erythema nodosum	<ul style="list-style-type: none"> • Red, hot and painful lumps on the shins or about the knees and ankles • Associated with joint pains and systemic symptoms
Erythema multiforme	<ul style="list-style-type: none"> • Target (iris) lesions • May involve mucous membranes • Self-limiting, usually resolves without complications

*Trimethoprim, on its own, can rarely cause anaphylaxis and TEN. Patients who have had a hypersensitivity reaction to trimethoprim-sulfamethoxazole should avoid both sulfonamide antibiotics and trimethoprim.

Management of sulfa drug allergy depends on the type and severity of the reaction. Mild reactions may simply require cessation of the drug and antihistamines for symptom relief. More severe reactions may require topical or oral steroids or even hospital admission e.g. for drug hypersensitivity syndrome or rare and serious reactions such as SJS-TEN).

Non-antibiotic sulfonamides

Many commonly used drugs contain a sulfonamide group in their chemical structure, including frusemide/ furosemide; thiazide diuretics e.g. hydrochlorothiazide and indapamide; sulfonylureas e.g. gliclazide, glipizide and glibenclamide; celecoxib; acetazolamide; probenecid; sumatriptan; amprenavir (this drug has structural similarities to sulfonamide antibiotics). Non-antibiotic sulfonamides are thought to be less likely to cause severe allergic reactions.



Patient suffering from Stevens–Johnson syndrome

Sulfonamides have the potential to cause a variety of untoward reactions, including urinary tract disorders, haemopoietic disorders, porphyria, and hypersensitivity reactions. When used in large doses, they may cause a strong allergic reaction. Two of the most serious are Stevens–Johnson syndrome and toxic epidermal necrolysis (also known as Lyell syndrome). Approximately 3% of the general population have adverse reactions when treated with sulfonamide antimicrobials. Of note is the observation that patients with HIV have a much higher prevalence, at about 60%.

Hypersensitivity reactions are less common in nonantibiotic sulfonamides, and, though controversial, the available evidence suggests those with hypersensitivity to sulfonamide antibiotics do not have an increased risk of hypersensitivity reaction to the nonantibiotic agents. 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; available evidence 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. It has therefore been argued that the terms 'sulfonamide allergy' or 'sulfa allergy' are misleading, and should be replaced by a reference to a specific drug (e.g. 'cotrimoxazole allergy').



Allergic urticaria on the skin induced by an antibiotic.

Two regions of the sulfonamide antibiotic chemical structure are implicated in the hypersensitivity reactions associated with the class.

- The first is the N1 heterocyclic ring, which causes a type I hypersensitivity reaction.
- The second is the N4 amino nitrogen that, in a stereospecific process, forms reactive metabolites that cause either direct cytotoxicity or immunologic response.

The nonantibiotic sulfonamides lack both of these structures.^[19]

The most common manifestations of a hypersensitivity reaction to sulfa drugs are rash and hives. However, there are several life-threatening manifestations of hypersensitivity to sulfa drugs, including Stevens–Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, hemolytic anemia, thrombocytopenia, fulminant hepatic necrosis, and acute pancreatitis, among others.^[20]

Cross-reactivity

Patients that are allergic to one sulfonamide antibiotic are likely to be allergic to other sulfonamide antibiotics. Until recently, it was thought that these patients were also likely to be allergic to non-antibiotic sulfonamides (called cross-reactivity).

There are important chemical differences between sulfonamide antibiotics and non-antibiotics. More recent evidence suggests that patients with an allergy to sulfonamide antibiotics do not react to the sulfonamide group of the chemical structure, but rather to other portions. Therefore, it is thought that cross-reactivity between sulfonamide antibiotics and non-antibiotics is unlikely (with the exception of drugs such as amprenavir, which have structural similarities to sulfonamide antibiotics).

However, patients who have had an allergic reaction to one drug, are much more likely to experience an allergic reaction to other (even unrelated) drugs, so caution should be used when administering any future medications to these patients.

Other drugs and products with names stemming from ‘sulfur’

Some drugs contain a sulfhydryl group (e.g. penicillamine, captopril) or sulfate group (e.g. morphine sulfate, heparin sulfate) in their chemical structure. These drugs have no relationship to sulfonamide allergy. However sulfhydryl containing drugs can cause unrelated adverse skin reactions such as a rash or pemphigus (a rare autoimmune blistering disease). Sulfates are also commonly found in soaps and cosmetics; allergies to sulfates are extremely rare. Sulfites are chemicals used as preservatives in food and drugs, e.g. sulfur dioxide and sodium sulfite. Allergy to sulfite preservatives can cause anaphylaxis, other rashes, asthma, seizures and death. People with asthma are at higher risk of sulfite allergy. Allergy to sulfites bears no relationship to sulfonamide allergy. People who have had allergic reactions to sulfonamide-containing drugs do not need to avoid sulfhydryl drugs, sulfates or sulfites. To prevent confusion, the general term ‘sulfa allergy’ should not be used. Instead it is better to note the exact drug and reaction involved.

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