Review Article

Sulfonamides: far from obsolete

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ABSTRACT

Sulfa drugs or sulfonamides were introduced in 1935 by the German physician Gerhard Domagk (1895-1964). Domagk worked closely with two chemists, Fritz Mietzsch and Josef Klarer. They worked together on compounds related to synthetic dyes, testing their effects on infectious diseases. Their concerted work eventually led to the discovery of Prontosil (sulfamidochrysoidine), the first sulfa drug that showed an incredible antibacterial effect on diseased laboratory mice. Soon after the introduction of sulfonamides, penicillin was discovered and hailed as a more effective and a safer alternative. The production of sulfonamides lost its enthusiasm with the introductions of even more antibiotics. However; anti-bacterial Sulfonamides are far from being obsolete despite the introduction of newer classes of antibiotics. Interest in their use has been revived in the 1980s with AIDS epidemic, when a combination of sulfamethoxazole and trimethoprim (SMX/TMP) was recognized as the drug of choice for the treatment of *Pneumocystis jirovecii* (PCP) pneumonia. This review article is intended to update clinicians with the many still current recommendations for sulfonamides both as therapeutic and prophylactic agents; with mechanism of action and resistance; and with adverse side effects that clinicians need to watch for while using this class of antimicrobial.

Keywords: Adverse reactions to sulfonamides, Diaminopyrimidines, Drug resistance to sulfonamides, Glimpse of history of sulfa drugs, Mechanism of action of sulphonamides, Sulfonamides

INTRODUCTION

Sulfa drugs or sulfonamides were introduced in 1935 by the German physician Gerhard Domagk (1895-1964). Domagk worked closely with two chemists, Fritz Mietzsch and Josef Klarer. They worked together on compounds related to synthetic dyes, testing their effects on infectious diseases. Their concerted work eventually led to the discovery of Prontosil (sulfamidochrysoidine), the first sulfa drug that showed an incredible antibacterial effect on diseased laboratory mice.[1] Prontosil was the first drug to successfully treat bacterial infections and the first of many to follow sulfa drugs, as forerunners of antibiotics. In 1936, Ernest Fourneau found out prontosil pathway in the human body and discovered that this dye was a pro-drug. Prontosil is metabolized to sulfanilamide which is the active anti-bacterial agent.[2] For three years

Prontosil had been successfully used to treat several bacterial diseases in humans of both *Streptococcal* and *Staphylococcal* origins. Among the early patients treated was Domagk's six-year-old daughter, Hildegard, who had contracted a severe *streptococcal* infection from a non-sterile needle stick. She recovered but suffered a permanent reddish discoloration of her skin due to Prontosil. Had Domagk not tested the drug on experimental laboratory mice, and just observed the drug ineffective in laboratory glassware, this discovery would have been missed. This achievement earned Domagk a Nobel Prize in 1939.

However, the Nobel committee had angered the German political authorities by awarding the 1935 Nobel Peace Prize to Carl von Ossietzky, an outspoken German pacifist. So, German citizens were forbidden by the Nazi party led by Hitler, to accept the Nobel Prize. After

Domagk accepted the prize, he was arrested by the Gestapo and forced to send a letter rejecting it. Although Domagk was able to receive his prize medal in 1947, the prize money had long since been redistributed. Soon after the introduction of sulfonamides, penicillin was discovered and hailed as a more effective and safer alternative. The production of sulfonamides lost its enthusiasm with the introductions of even more antibiotics. However; with the AIDS epidemic in the 1980s and the prevalence of *Pneumocystis jirovecii* (PCP) pneumonia, sulfa drugs emerged as the drug of choice to treat and prevent this disease.[3] The sulfonamides are derivatives of sulfanilamide, which is the nucleus common to all. Adding or substituting various functional groups result in compounds with varying physical, chemical, pharmacologic, and antibacterial properties.

Mechanism of action

The sulfonamides are structural analogs of para-aminobenzoic acid (PABA) resulting in competitive inhibition of dihydropteroate synthase (DHPS), an enzyme that converts PABA as a substrate to dihydrofolic acid (folic acid). Another enzyme, dihydrofolate reductase, sequentially converts dihydrofolate to tetrahydrofolate (folinic acid). Diaminopyrimidines such as trimethoprim inhibits dihydrofolate reductase, which is further into the folic acid synthesis pathway. The combination of a sulfonamide and a diaminopyrimidine, e.g. trimethoprim, ormethoprim, methoprim, or pyrimethamine, is referred to as a "potentiated" sulfonamide
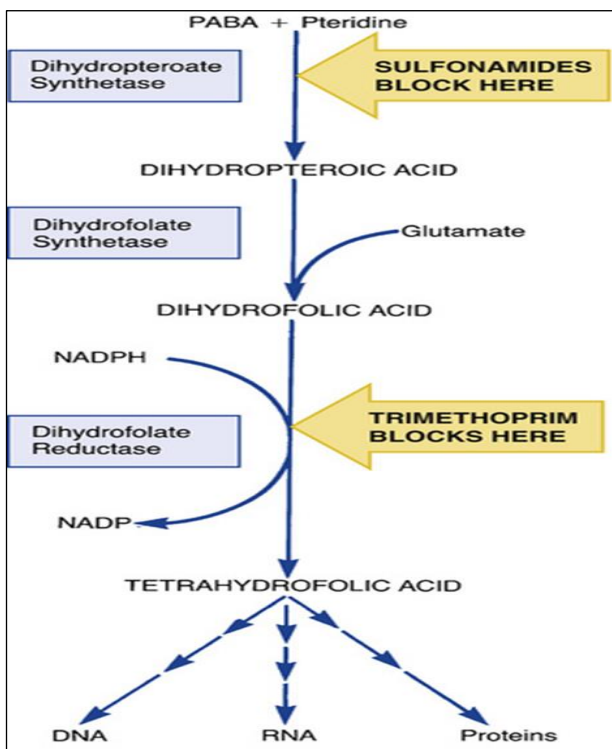

Figure 1: Mechanism of action of sulphonamides.

The addition of any of these dihydrofolate reductase inhibitors to a sulfonamide provides sequential blockade of the enzymes resulting in the ultimate synergistic inhibition of biogenesis purine bases that are the building blocks of nucleic acids thus interfering with protein synthesis and ability of a cell to replicate (Figure 1).

Note sequential inhibition of the enzymes Dihydropteroate synthase and Dihydrofolate reductase when a diaminopyrimidine is added.

Bacterial resistance

Resistance to sulfonamides is both chromosomally and plasmid mediated. Altered enzymes such that affinity for the substrate is reduced, appear to be the most common mechanism of resistance. For example, in *staphylococci*, chromosomally mediated resistance involves a mutation in genes encoding dihydropteroate synthase (DHPS). These mutant DHPS enzymes exhibit pronounced insensitivity to sulfonamides while maintaining normal binding to the p-aminobenzoic acid substrate, despite the close structural similarity between inhibitor and substrate. In addition to chromosomally mediated resistance, four mobile sulfonamide resistance genes have been discovered to date and named Sul1, Sul2, Sul3 and most recently Sul4 and each encodes for an altered enzyme with reduced affinity.[4]

Another plasmid-borne resistance is executed by genes encoding alternative dihydrofolate reductase, with the latter causing high-level resistance to trimethoprim. *Staphylococci* may have acquired some mechanisms of sulfonamide resistance from *enterococci*.

Because sulfonamides act competitively, overproduction of PABA can also override competitive inhibition of dihydropteroate synthase. Alternate pathways of folic acid synthesis may also contribute to low-level resistance. Cross-resistance between sulfonamides is common and in general, resistance to one sulfonamide indicates resistance to all. Plasmid-mediated sulfonamide resistance in intestinal gram-negative bacteria is often linked with ampicillin and tetracycline resistance. Organisms that can absorb folic acid from surrounding environment e.g. *Enterococci* are inherently resistant to sulfonamides. Strains of *Pseudomonas*, *Klebsiella*, and *Proteus* are most often highly resistant, as are *Rickettsiae*, *Mycoplasmas*, and most *Chlamydia*.

Pharmacokinetic features

The sulfonamides are classically subdivided on the basis of their elimination time into short-acting (plasma half-life, t $1/2$ <8h), medium acting (t $1/2$ = 8-16 h), long-acting (t $1/2$ = 17-48 h) and ultra-long acting (t $1/2$ >48 h). Sulfonamides used as single agents today are short- or medium- acting. Sulfonamides may be administered orally, parenterally or topically.

Apart from the poorly absorbed derivatives that are intended for local intestinal use, most sulfonamides are well and rapidly absorbed following oral administration. They are highly distributed throughout the body. The degree of distribution is governed by water solubility, tissue vascularity, and the degree of plasma protein binding. Sulfonamides are bound to plasma proteins to a greater or lesser extent depending on the particular drug, and it is the unbound fraction that is freely diffusible. Concentration in the urine usually exceeds the plasma concentration.

Sulfonamide is metabolized in the liver by several oxidative pathways, acetylation, and conjugation with sulfate or glucuronic acid. Metabolites and some unchanged drugs are eliminated by the kidney via glomerular filtration and tubular excretion, but some tubular reabsorption occurs. Tubular reabsorption depends on the inherent lipid solubility of the specific drug, and urinary PH.

In a mixture of sulfonamides, each component drug has its solubility; therefore, a combination of sulfonamides is more water-soluble than a single drug at the same total concentration. This character is utilized clinically by using combination therapy to reduce crystalluria. N-4 acetylated sulfonamides, except the sulfa pyrimidine group, are less soluble than unchanged drug or other metabolites. Alkalization of the urine promotes sulfonamide excretion, and urinary acidification increases the risk of crystalluria.[5]

Therapeutic use sulfonamides

Sulfonamides are divided into two groups, antibacterial sulfonamides, and non-antibacterial sulfonamides. The anti-bacterial group is further classified as oral absorbable, oral non-absorbable and topical agents.[6] Oral absorbable agents are further divided into short-acting agents such as sulfisoxazole, medium acting agents such as sulfamethoxazole and long-acting agents such as sulfasalazine. Non-antimicrobial sulfa drugs will not be discussed in this article.

Anti-bacterial Sulfonamides are far from being obsolete despite the introduction of newer classes of antibiotics. Interest in their use has been revived in the 1980s with AIDS epidemic when a combination of sulfamethoxazole and trimethoprim (SMX/TMP) was recognized as the drug of choice for the treatment of *Pneumocystis jirovecii* (PJP) pneumonia.[7]

Sulfonamides in combination with trimethoprim also provide excellent coverage for *Staphylococcus aureus* including Methicillin-Resistant *Staphylococcus aureus* (MRSA) with susceptibility rate in the high nineties. They provide an excellent oral alternative to treat skin and soft tissue infections caused by MRSA particularly with increasing resistance to clindamycin.[8] The combination plays a role in the management of acute

exacerbations in patients with cystic fibrosis infected with *Staphylococcus aureus*.[9]

Highly water-soluble sulfonamides, such as sulfisoxazole (sulfafurazole), sulfadimidine (sulfamethazine) and sulfamethoxazole are rapidly eliminated via the kidneys by glomerular filtration and tubular secretion. 20% of Sulfamethoxazole in urine is eliminated unchanged, and in combination with TMP, is used to treat urinary tract infections.

The combination of SMX/TMP also considered the drug of choice for the treatment of Nocardia infections. SMX/TMP with rifampin is the preferred regimen to treat brucellosis in women during early pregnancy.

Sulfonamides also are used to treat some protozoal diseases. The combination of SMX/TMP is the drug of choice for the treatment of cyclosporiasis. Because pyrimethamine is a better inhibitor of dihydrofolate reductase in protozoa, sulfadiazine or sulfadoxine in combination with pyrimethamine are used to treat toxoplasmosis and malaria respectively.

The protease inhibitors amprenavir and fosamprenavir are also sulfonamide drugs that are used in the treatment of Human immunodeficiency virus as part of combination therapy.[10,11] It is worth mentioning that because of increased resistance to sulfonamides among Strep pneumoniae and group A Strep, these class of antimicrobial is no longer recommended to treat infections caused by these organisms.

Prophylactic use

The combination of sulfamethoxazole and trimethoprim (SMX/TMP) is highly water-soluble and are eliminated by the kidneys, with the unchanged fraction achieving high concentrations in urine. For this reason, they are used to treat urinary tract infections as well as to prevent recurrent infections in predisposed children and adults. However; current data do not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTIs in infants without vesicoureteral reflux (VUR).[12]

Chemoprophylaxis with trimethoprim-sulfamethoxazole compared with placebo decreased recurrent UTI from 27% to 15% in children with grade I through grade IV VUR, following a first or second febrile or symptomatic UTI. However; resistance among causative organisms increased from 25% to 68%. The proportion of children with renal scarring after 2 years was not affected by prophylaxis.[13]

SMX/TMP combination also is used for PCP prophylaxis in AIDS patients and other immunocompromised patients at risk for this opportunistic pneumonia. The combination also protects against toxoplasmosis, and malaria in those living in endemic areas.[14]

However; the use of SMX/TMP for PCP prophylaxis in infants born to HIV infected mothers is no longer recommended as the risk of perinatal transmission of HIV is very low, and its use may aggravate anemia and neutropenia associated with zidovudine prophylaxis.

Because they achieve good intracellular concentration in macrophages, SMX/TMP combination also, are used in patients with chronic granulomatous disease to prevent infections caused by catalase-positive bacteria as they enhance the intracellular killing of these organisms.[15]

Sulfadiazine is no longer recommended for prophylaxis to prevent secondary cases of meningitis in close contacts and during outbreaks because of emerged resistance to sulfonamides among *Strep. pneumoniae*, *N. meningitides*, and *Haemophilus influenzae* type b.[16]

Poorly absorbed sulfonamides used to treat intestinal diseases

Poorly soluble sulfonamide derivatives, such as sulfaguanidine which is a guanidine derivative of sulfanilamide, are so insoluble that they are not absorbed from the GI tract (<5%), but soluble enough to achieve a local bacteriostatic effect on some intestinal pathogens and may be used to treat bacillary dysentery in animals.

Phthalylsulfathiazole and succinylsulfathiazole undergo bacterial hydrolysis in the lower GI tract with the consequent release of active sulfathiazole. Sulfasalazine (Salicylazosulfapyridine) is also poorly absorbed and hydrolyzed in the large intestine to sulfapyridine and 5-aminosalicylic acid and is used as an anti-inflammatory for management of ulcerative colitis.

Topical use

Several sulfonamides are used topically for specific purposes. Sulfacetamide is not highly efficacious but is occasionally used to treat ophthalmic infections. Mafenide acetate and silver sulfadiazine are used on burn wounds to prevent invasion by many gram-negative and gram-positive organisms. Sulfathiazole is commonly included in wound powders for the same purpose. Topical sulfadiazine vaginal cream for yeast infection is less commonly used now with the availability of effective single oral dose therapy with fluconazole.[17]

Adverse effects and toxicity

Adverse effects of sulfonamides can result from systemic use and sometimes with topical application. These reactions are either due to allergy or drug toxicity. Incidence of adverse effects is different for the various sulfonamides, but cross-sensitivity is common.

Hypersensitivity reactions, such as rashes, Stevens-Johnson syndrome, vasculitis, serum sickness, drug fever, anaphylaxis, and angioedema

Crystalluria, oliguria, and anuria make complicate high dose administration with inadequate hydration, especially with low urine PH. Bone marrow suppression with agranulocytosis and thrombocytopenia; and in patients with G6PD deficiency, hemolytic anemia is hematologic toxicities that need to be monitored with long term use of sulfonamides.

The protein binding of the sulfonamides varies from less than 50% for sulfadiazine to more than 90% for sulfadoxine. Importantly, sulfonamides bind firmly to albumin and may displace other compounds leading to increased pharmacologic effects of these drugs. For example, the anticoagulant, warfarin may be displaced resulting in decreased blood coagulability and dose adjustment may be needed. The anticonvulsant phenytoin also may be displaced with increased toxicity and sedation. Displacement of bilirubin may result in Kernicterus in neonates. For this reason, the use of sulfonamides is not recommended in late pregnancy and newborns.

Photosensitivity reactions may occur, and the patient may avoid excessive exposure to the sun while on these medications. These drugs can exacerbate porphyria. Neurologic effects, such as insomnia, and headache are known side effects. Hypothyroidism, necrotic hepatitis, and activation of quiescent SLE may occur in patients taking sulfonamides.

Sulfasalazine can reduce the intestinal absorption of folate (folic acid). Thus, use of this drug may trigger folate deficiency in patients with inflammatory bowel disease, which also reduces absorption, especially if dietary intake is inadequate.

Mafenide may cause metabolic acidosis by inhibiting carbonic anhydrase.

Drug interactions

Antacids interfere with sulfonamide absorption when co-administered orally. Sulfonamide solutions are incompatible with calcium-containing fluids and mixing should be avoided for IV infusion. Sulfonamides may be displaced from their plasma-protein-binding sites by other acidic drugs with higher binding affinities. Some sulfonamides act as microsomal enzyme inhibitors, which may lead to toxic manifestations of concurrently administered drugs such as phenytoin.

Effects on laboratory tests

Bilirubin, BUN, AST, and ALT may be elevated. Methemoglobin may be detectable with prolonged use of sulfa drugs. Platelet, RBC, and WBC counts are often decreased due to bone marrow suppression. Urinalysis may show a change in color secondary to increased porphyrins, and urobilinogen. Glucosuria and sulfonamide crystals may also be found.

DISCUSSION

Sulfonamides are most effective in the early stages of acute infections when organisms are rapidly multiplying. They are not active against quiescent bacteria.

The use of sulfonamide alone is bacteriostatic, and typically there is a lag period before this bacteriostatic effect is observed. This is because bacteria have to consume existing stores of folic acids, folinic acid, purines, thymidine, and amino acids. Potentiated sulfonamides are bactericidal, and this bactericidal effect is more evident at high concentrations found for example in the urine. However; this bactericidal effect is time dependent.[4] In either case, adequate cellular and humoral defense mechanisms are critical to achieving complete eradication of infection.

The optimal ratio in vitro for the combination of trimethoprim or ormetoprim and a sulfonamide depends on the type of microorganism but is usually ~1:20. However, the commercially available preparations use a ratio of 1:5 because of pharmacokinetic considerations that presumably result in the optimal ratio at the site of infection.[18]

Although all of the sulfonamides have the same mechanism of action, differences are evident concerning activity, pharmacokinetic fate, and even antimicrobial spectrum at usual concentrations. The differences are due to the variety of physiochemical characteristics seen among the sulfonamides.

New promising small-molecule inhibitors of the enzyme DHPS are in the horizon to replace the sulfa drugs that are the only currently available inhibitors of this enzyme. They are believed to a safer alternative, however; these drugs are still early in their investigative phases.[19]

The efficacy of sulfonamides can be reduced radically by excess PABA, folic acid, thymine, purine, methionine, plasma, blood, albumin, tissue auto lysates, and endogenous protein-degradation products.

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