

Synthetic Organic Antimicrobials: Sulfonamides, Trimethoprim, Nitrofurans, Quinolones, Methenamine

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DRUG LIST

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SULFONAMIDES

Chemistry, Structure, and Function

The sulfonamides are a large group of compounds that are structural analogues of *p*-aminobenzoic acid (PABA). They differ primarily in the substituents on either the amido group ($\text{SO}_2\text{-NH-R}$) or the amino group ($-\text{NH}_2$) of the sulfanilamide nucleus. Substitutions on the sulfonamide group modify the drug's solubility characteristics, resulting in congeners with different rates of absorption and excretion. One group of sulfonamides remains largely unabsorbed in the gastrointestinal (GI)

tract following oral administration. Sulfadiazine, for example, produces changes only on local gut bacterial flora and finds wide use in presurgical bowel sterilization. Other sulfonamides, such as sulfisoxazole, are rapidly absorbed and highly soluble, and they undergo rapid urinary excretion, mainly in the unaltered form. A third group are rapidly absorbed and slowly excreted and maintain adequate blood levels for up to 24 hours (e.g., sulfamethoxazole). These drugs are useful in treating chronic urinary infections. Finally, some sulfonamides (e.g., sulfacetamide and sulfadiazine [silver salt]) are designed for topical use such as in infection of the eye and in burn patients.

Mechanism of Action and Resistance

Both sulfonamides and trimethoprim (not a sulfonamide) sequentially interfere with folic acid synthesis by bacteria. Folic acid functions as a coenzyme in the transfer of one-carbon units required for the synthesis of thymidine, purines, and some amino acids and consists of three components: a pteridine moiety, PABA, and glutamate (Fig. 44.1). The sulfonamides, as structural analogues, competitively block PABA incorporation; sulfonamides inhibit the enzyme dihydropteroate synthase, which is necessary for PABA to be incorporated into dihydropteroic acid, an intermediate compound in the formation of folinic acid. Since the sulfonamides *reversibly block* the synthesis of folic acid, *they are bacteriostatic drugs. Humans cannot synthesize folic acid and must acquire it in the diet; thus, the sulfonamides selectively inhibit microbial growth.*

Resistance to the sulfonamides can be the result of decreased bacterial permeability to the drug, increased production of PABA, or production of an altered dihydropteroate synthetase that exhibits low affinity for sulfonamides. The latter mechanism of resistance is plasmid mediated. Active efflux of the sulfonamides has also been reported to play a role in resistance. The inhibitory effect of the sulfonamides also can be reversed by the presence of pus, tissue fluids, and drugs that contain releasable PABA.

Antibacterial Spectrum and Resistance

The sulfonamides are broad-spectrum antimicrobials that are effective against gram-positive and some gram-negative organisms of the Enterobacteriaceae. There is good activity against *Escherichia coli*, moderate activity against *Proteus mirabilis* and *Enterobacter* spp.; poor activity against indole-positive *Proteus* and *Klebsiella* spp., and no inhibitory activity against *Pseudomonas aeruginosa* and *Serratia* spp. They are also effective against *Chlamydia* spp., but superior drugs are now

available. Sulfonamides are used in treating infections caused by *Toxoplasma gondii* and occasionally chloroquine-resistant *Plasmodium falciparum*.

Resistance occurs as the result of one or more alterations in the cellular metabolism of the bacteria; both mutation and plasmid-mediated resistance occurs. These changes, which can be irreversible, include alterations in the physical or enzymatic characteristics of the enzyme or enzymes that metabolize PABA and participate in the cellular synthesis of tetrahydrofolic acid. The appearance of alternative pathways for PABA synthesis within the bacteria or the development of an increased capacity to inactivate or eliminate the sulfonamide also may contribute to bacterial cell resistance. Bacteria that can use preformed folate are not inhibited by sulfonamides.

Pharmacokinetic Properties

Absorption

Sulfonamides are usually given orally, although the soluble sodium salts can be given parenterally, a route that is infrequently used. Except for compounds designed for local gut effects, the sulfonamides are rapidly absorbed from the intestinal tract, primarily from the small intestine. They can usually be found in serum and urine within 30 minutes after ingestion. Peak serum levels are obtained in 2 to 6 hours; urine levels can reach above 500 $\mu\text{g/mL}$. Although absorption can occur via other routes (e.g., burned and/or abraded skin, stomach), the amounts absorbed are usually low and unpredictable. A burn area larger than 20% of total body surface can absorb enough drug to result in toxicity, especially if accompanied by renal dysfunction.

Distribution

Systemically absorbed sulfonamides readily distribute throughout body fluids. They pass the placental barrier and enter the cerebrospinal fluid (CSF) even in the absence of inflammation. The degree of protein binding, the half-life, and the drug's solubility in urine will vary considerably from one sulfonamide to another. Half-lives range from 2.5 to 17 hours, the latter exhibited by sulfadiazine. Sulfadiazine and sulfacetamide tend to have lower protein binding (about 20–30%) than the other major systemic sulfonamides, whose binding ranges from 80 to 90% (e.g., sulfamethoxazole, sulfisoxazole). The effects of high protein binding by a sulfonamide become almost negligible in body fluids with a paucity of protein (e.g., synovial, peritoneal, ocular); thus, the drug in these sites is primarily in the active unbound form. Most drugs with protein binding above 30% do not cross the placenta; while this reduces toxic potential, it concomitantly lowers drug antibacterial activity.

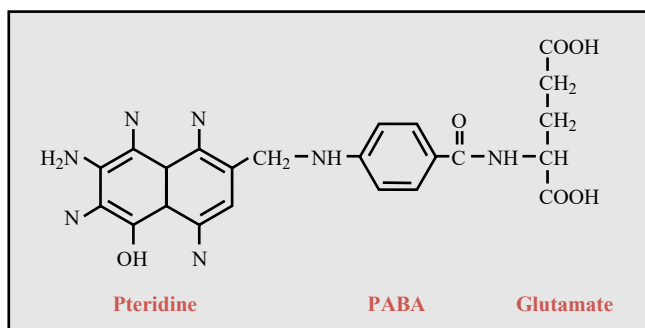


FIGURE 44.1

Folic acid and its component molecules.

Metabolism and Excretion

The sulfonamides are degraded in the liver by acetylation and oxidation; metabolites have reduced bacteriological activity. The parent compound and the metabolites are excreted in the urine, primarily by glomerular filtration followed by tubular reabsorption. Some sulfonamides exhibit diurnal variations in excretion, being three times greater at night than during the day.

Clinical Uses

Sulfonamides have a long record of successful use in the treatment of a wide range of both gram-positive and gram-negative bacterial infections. They are also active against some of the less frequently encountered infections, such as leprosy, malaria, toxoplasmosis, and nocardiosis. Current indications are more limited, especially to the treatment of urinary tract and ear infections, because of frequently encountered resistance and the availability of better and safer agents for infections such as shigellosis, salmonellosis, and meningococcal meningitis. In contrast, the growth of rickettsial organisms is actually stimulated.

Acute uncomplicated urinary tract infections caused by *E. coli* and other pathogens generally respond promptly to one of the short-acting sulfonamides. Recurrent urinary tract infections (UTIs), when related to some structural abnormality in the tract, are frequently caused by sulfonamide-resistant bacteria.

Sulfadiazine and sulfisoxazole still play a useful role in the prophylaxis of group A streptococcal infections in patients with rheumatic fever who are hypersensitive to penicillin. This is tempered with the potential for toxicity and infection with resistant *Streptococcus pyogenes*.

Trisulfapyrimidine (a combination of sulfadiazine, sulfamerazine, and sulfamethazine), trimethoprim-sulfamethoxazole, or sulfisoxazole can be used as an alternative drug for the treatment of melioidosis caused by *Pseudomonas pseudomallei* and for infections produced by *Nocardia* spp.

A number of infections caused by *Chlamydia trachomatis*, such as trachoma, inclusion conjunctivitis, pneumonia, and urethritis, can be treated with topical or systemic sulfonamides, although tetracycline or erythromycin is preferred.

Sulfonamides, such as sulfadiazine, in combination with pyrimethamine, are considered the treatment of choice of symptomatic toxoplasmosis. Patients should be well hydrated to prevent crystalluria; this problem may be reduced with the use of triple sulfas (trisulfapyrimidine). Some regimens have included a sulfonamide (sulfadoxine) in combination with pyrimethamine (*Fansidar*) for the treatment of chloroquine-resistant malaria caused by *P. falciparum*.

Topically active sulfonamides are useful in preventing infections in burn patients. Mafenide acetate

(*Sulfamylon Cream*), the most widely used compound, is effective against *P. aeruginosa*, an organism that frequently colonizes burns. It is less effective against staphylococci, which also colonize burns. Local absorption of the acetate preparation, which is acidic, can result in respiratory alkalosis. Silver sulfadiazine in a 1% cream can be used as an alternative to mafenide and has good activity against gram-negative bacteria.

Sulfacetamide is used topically for treatment of ocular infections.

Adverse Effects and Drug Interactions

If the concentration of the sulfonamide is sufficiently high and its aqueous solubility is sufficiently low, the free drug or its metabolites may form crystals and cause bleeding or complete obstruction of the kidneys. Combinations of sulfa compounds have been developed for the purpose of lowering the dosage of individual components to reduce the chance of crystalluria (e.g., triple sulfas, such as the trisulfapyrimidines).

The sulfonamides do cause hypersensitivity reactions (e.g., rashes, eosinophilia, and drug fever) in a small number of patients. Other rare allergic reactions include vasculitis, photosensitivity, agranulocytosis, and thrombocytopenia. Stevens-Johnson syndrome is also associated with sulfonamide use; it is characterized by fever, malaise, erythema multiforme, and ulceration of the mucous membranes of the mouth and genitalia. Hemolytic anemia may develop in persons with a genetic deficiency of red blood cell glucose-6-phosphate dehydrogenase (G6PD).

Sulfonamides compete for sites on plasma proteins that are responsible for the binding of bilirubin. As a result, less bilirubin is bound, and in the newborn, the unbound bilirubin can be deposited in the basal ganglia and subthalamic nuclei, causing *kernicterus*, a toxic encephalopathy. For this reason, *sulfonamides should not be administered to newborns or to women during the last 2 months of pregnancy*.

Significant drug-drug interactions are those that potentiate the effects of other agents and require dosage modification. These include certain anticoagulants, hypoglycemic sulfonylureas, and hydantoin anticonvulsants.

TRIMETHOPRIM

Chemistry, Structure, and Mechanism of Action

Trimethoprim (*Trimplex*, *Proloprim*) is a structural analogue of the *pteridine* portion of dihydrofolic acid. It differs from the sulfonamides in that it acts at a second step in the folic acid synthetic pathway; that is, it

competitively inhibits dihydrofolate reductase. This is the enzyme that catalyzes the reduction of dihydrofolic acid to tetrahydrofolic acid, the active form of folate. Dihydrofolate reductase is present in both mammalian tissue and bacteria, but 20,000 to 60,000 times more drug is required to inhibit the mammalian enzyme; this accounts for its *selective toxicity* against bacteria.

Trimethoprim-sulfamethoxazole (TMP-SMX) was introduced as a fixed dose combination in 1968. Trimethoprim was added to sulfamethoxazole to synergistically and sequentially inhibit bacterial synthesis of tetrahydrofolic acid. The combination was also designed to delay development of bacterial resistance. Sulfamethoxazole was selected in part because it is a congener of the frequently used sulfisoxazole but exhibits slower enteric absorption and urinary excretion. Sulfamethoxazole has a half-life similar to that of trimethoprim.

Antibacterial Spectrum and Resistance

Trimethoprim exhibits broad-spectrum activity. It is most commonly used in combination with sulfamethoxazole and is active against most gram-positive and gram-negative organisms, especially the Enterobacteriaceae. There is little activity against *anaerobic* bacteria; *P. aeruginosa*, enterococci, and methicillin-resistant staphylococci should be considered resistant to trimethoprim.

Resistance can develop from alterations in dihydrofolate reductase, bacterial impermeability to the drug, and by overproduction of the dihydrofolate reductase. The most important mechanism of bacterial resistance to trimethoprim clinically is the production of plasmid-encoded trimethoprim-resistant forms of dihydrofolate reductase.

Because trimethoprim and sulfamethoxazole have their effects at different points in the folic acid synthetic pathway, a synergistic effect results when the two are administered together. The incidence of bacterial resistance to the combination is less than that observed when the drugs are used individually. Resistance is an increasing problem in a number of bacteria, but is especially problematic in the Enterobacteriaceae, against which the combination is used in AIDS patients for *Pneumocystis carinii* pneumonia prophylaxis.

Absorption, Metabolism, and Excretion

Trimethoprim is well absorbed from the GI tract, and peak blood levels are achieved in about 2 hours. Tissue levels often exceed those of plasma, and the urine concentration of trimethoprim may be 100 times that of the plasma. Trimethoprim readily enters the CSF if inflammation is present. The half-life of the drug is approximately 11 hours. Sulfamethoxazole ($t_{1/2}$ = 10 hours) is frequently coadministered with trimethoprim in a fixed dose ratio of 1:5 (trimethoprim to sulfamethoxazole).

Peak drug levels in plasma are achieved in 1 to 4 hours following oral administration and 1 to 1.5 hours after IV infusion. At this time, the TMP-SMX plasma ratio is 1:20, which is the ratio most effective for producing a synergistic effect against most susceptible pathogens. The ratio is also influenced by the greater lipid solubility of trimethoprim, which results in its larger volume of distribution. Both trimethoprim and sulfamethoxazole bind to plasma protein (45 and 66% respectively) and both are metabolized in the liver. Approximately 40 to 60% of both parent drugs and their metabolites is excreted by the kidney within 24 hours; in moderate to severe renal dysfunction the dose should be reduced by approximately one-half. Only the parent compounds are excreted in the bile. Both drugs cross the placenta and are found in breast milk (see adverse effects).

Clinical Use of Trimethoprim-Sulfamethoxazole

TMP-SMX (*Septra*, *Bactrim*) is used in the treatment of genitourinary, GI, and respiratory tract infections caused by susceptible bacteria. *E. coli*, enterococci, *P. mirabilis*, some indole-positive strains of *Proteus* spp., and *Klebsiella pneumoniae* are usually sensitive to this combination therapy for both chronic and recurrent UTIs. Trimethoprim is present in vaginal secretions in high enough levels to be active against many of the organisms found in the introital area that are often responsible for recurrent UTIs. In some patients with recurrent UTIs, most notably women of childbearing age, the long-term use of one tablet taken at night is an effective form of chemoprophylaxis. The drug is approved for use by the U. S. Food and Drug Administration (FDA) for treating UTIs in both children and adults.

TMP-SMX is also used in the treatment of infection caused by ampicillin-resistant *Shigella* spp. and for antibiotic-resistant *Salmonella* spp.. The combination is also effective for covering the carrier state of *Salmonella typhi*, the agent of typhoid fever, and other *Salmonella* spp.. Successful treatment of traveler's diarrhea due to susceptible *E. coli* is another advantage of the use of this combination. The combination is not indicated in the therapy of enterohemorrhagic *E. coli* strains such as O157:H7 because of the risk of developing hemolytic-uremic syndrome associated with the release of the cytotoxic enterotoxin by the drugs.

Because trimethoprim accumulates in the prostate, TMP-SMX is used to treat prostatitis caused by sensitive organisms. Therapy can be prolonged (4–6 weeks) and repeat courses of therapy may be necessary. Trimethoprim alone, because of its lipid solubility, can be effectively used when patients exhibit an allergic response to the sulfonamide component.

Otitis media in children and purulent exacerbations of chronic bronchitis respond well to TMP-SMX because

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