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

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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

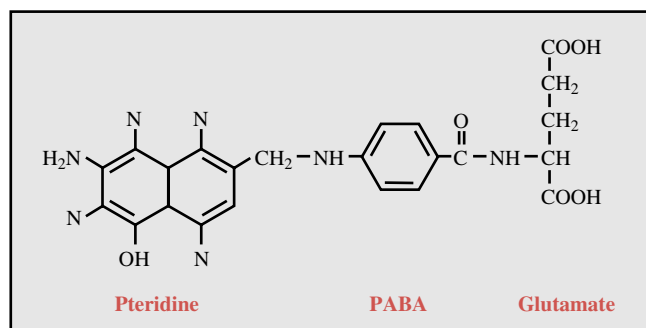


FIGURE 44.1

Folic acid and its component molecules.

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.

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

of its activity against both susceptible *Streptococcus pneumoniae* and *Haemophilus influenzae type b (Hib)*; the latter organism is now a much less frequent pathogen in otitis because of the use of the Hib vaccine.

Gonorrhea, typhoid fever, and brucellosis have been treated with TMP-SMX with cure rates comparable to those attained by standard therapy. It also has been used in the treatment of nocardial infections.

TMP-SMX remains the antimicrobial therapy of choice in both the treatment and prevention of infections caused by *P. carinii*, a protozoan that produces serious pneumonitis in patients with hematological malignancies and AIDS. In those with AIDS, treatment is more prolonged and relapse is common. These patients are at increased risk for untoward effects such as fever, hepatitis, rash, and leukopenia.

Adverse Effects and Drug Interactions

Serious adverse effects are rare except in AIDS patients. TMP-SMX can cause the same adverse effects as those associated with sulfonamide administration, including skin rashes, central nervous system (CNS) disturbances, and blood dyscrasias. Blood dyscrasias, hepatotoxicity, and skin rashes are particularly common in patients with AIDS. Most of the adverse effects of this combination are due to the sulfamethoxazole component. Trimethoprim may increase the hematological toxicity of sulfamethoxazole. Long-term use of trimethoprim in persons with borderline folic acid deficiency, such as alcoholics and the malnourished, may result in megaloblastic anemia, thrombocytopenia, and granulocytopenia.

Trimethoprim has been reported to decrease the therapeutic effect of cyclosporine with a concomitant increased risk of nephrotoxicity. Increased levels of dapsone, warfarin, methotrexate, zidovudine, and sulfonyleureas may occur when given together with trimethoprim; dosages of these drugs should be modified and the patient monitored accordingly.

Because both drugs may interfere with folic acid metabolism, their use during pregnancy is usually contraindicated by the potential for effects on the fetus, such as the development of neural tube defects associated with folate deficiency. The use of trimethoprim is contraindicated in patients with blood dyscrasias, hepatic damage, and renal impairment.

QUINOLONES: NALIDIXIC ACID AND FLUOROQUINOLONES

Chemistry, Mechanism of Action, and Classification

All clinically approved quinolones in use in the United States contain a carboxylic acid moiety in the 3-position of the basic ring structure (the 4-quinolones). The 4-

quinolones inhibit DNA synthesis through their specific action on DNA gyrases, which are composed of two A and two B subunits. DNA subunits A (gyrase A gene) have a strand-cutting function to prevent overwinding (supercoiling) of the DNA strands during separation and eventual replication of the mirror strand. The A subunits are the site of action for the 4-quinolones. Recently a second target, unique to the fluoroquinolones, has been identified as topoisomerase type IV. This enzyme is responsible for separating the daughter cells following replication.

The DNA gyrases and type IV topoisomerase both belong to the general class of DNA enzymes called topoisomerases. The effect of quinolones on these DNA enzymes is initially bacteriostatic but becomes bactericidal when bacteria are unable to repair the DNA lesions. These drug targets may be primary or secondary depending upon the organism; this observation can affect the bacterial potential for the development of drug resistance; this may require the use of another drug with a different specificity and spectrum of activity.

The quinolones are now often classified into generations, much like the cephalosporins. Each generation (first through fourth) has spectrum specificity and unique pharmacological properties, although there is considerable overlap: First, nalidixic acid and cinoxacin; second, norfloxacin, ciprofloxacin, ofloxacin, enoxacin, and lomefloxacin; third, levofloxacin, sparfloxacin, gatifloxacin; and fourth, trovafloxacin and moxifloxacin. Several of the newer quinolones have been recently removed from the market as a result of QT prolongation and serious hematological and renal problems.

Antibacterial Spectrum and Resistance

The first-generation and oldest quinolones exhibit limited gram-negative activity. Nalidixic acid and cinoxacin do not achieve systemic antibacterial levels and are thus restricted to therapy of bladder infections caused by urinary pathogens, such as *E. coli* and *Klebsiella* and *Proteus* spp. Although they are bactericidal agents, their use is restricted by resistance.

The second-generation drugs demonstrate their most reliable activity against gram-negative organisms, including Enterobacteriaceae. *Haemophilus* spp. and sexually transmitted disease (STD) agents, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Moraxella catarrhalis* (formerly *Neisseria catarrhalis*; causes otitis media) are also susceptible. The antipseudomonal activity of ciprofloxacin, norfloxacin, ofloxacin, and lomefloxacin is due to their piperazine moiety; resistance to these agents, however, is becoming more prevalent.

Significantly greater activity against gram-positive organisms, such as *S. pneumoniae*, is demonstrated by

the third and fourth generations. Methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium* are resistant. The fourth-generation quinolones also possess activity against anaerobes.

With the exception of the first generation, the quinolones are active against a variety of pathogens associated with respiratory tract infections, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Mycobacterial* spp., although these drugs are not FDA-approved for the latter. Recently, ciprofloxacin has gained popular attention in providing coverage for *Bacillus anthracis*, a major bioterrorism agent.

Resistance is related to mutations in the DNA gyrase, with the gyrase gene A (*gyrA*) being the predominant site. The primary mutation sites affected by organisms are topoisomerase IV and *gyrA*. Mutations at these points influence the degree of resistance, with lower levels of resistance associated with topoisomerase IV and higher levels with *gyrA*. Alterations in porins (gram-negative bacteria) that result in a decreased uptake of the drug and the appearance of an active efflux system for transport of the drug out of the cell also contribute to resistance. Resistance is chromosomally mediated; plasmid-associated resistance has not been reported. Killing by quinolones is concentration dependent, while that for the β -lactams is time dependent; thus the quinolones demonstrate a long postantibiotic effect. Cross-resistance between the quinolones can occur, particularly if resistance is strong. Moxifloxacin appears less susceptible to the appearance of cross-resistance.

Absorption, Metabolism, and Excretion

The quinolones are rapidly and almost completely absorbed after oral administration and are widely distributed in body tissues. Levels in extravascular spaces can often exceed serum levels. Levels lower than those found in serum occur in CSF, bone, and prostatic fluids. Ciprofloxacin and ofloxacin have been detected in breast milk and ofloxacin levels in ascites fluid are close to serum levels. Food ingestion does not affect bioavailability, which ranges from 50 to 95%. The half-life for most quinolones is 3 to 4 hours.

Elimination of the fluoroquinolones is through glomerular filtration and tubular secretion. In patients with moderate to severe renal insufficiency, quinolone dosages should be modified. The fluoroquinolones are also metabolized by hepatic conjugation and glucuronidation. Caution should be observed with administration of trovafloxacin because of its potential to induce hepatic toxicity. Dosage, peak serum levels, percent protein binding, urine concentrations, and degree of metabolism differ to varying degrees among the quinolones.

Clinical Uses

Therapeutic uses of the quinolones include urinary and respiratory tract infections, GI and abdominal infections, STDs, and bone, joint, and soft tissue infections. Nalidixic acid is effective for urinary tract infections; however, bacteria can become resistant, particularly if the drug is used for long periods. The second-generation fluoroquinolones are all equally efficacious in UTIs, and their activity is comparable to that of TMP-SMX. These drugs have shown efficacy in treating prostatitis and can serve as an alternative therapy for patients not responding to TMP-SMX.

The fluoroquinolones have a variety of indications in the treatment of respiratory infections, although they may not be the drugs of choice; these infections include acute and chronic bacterial sinusitis. A second-generation cephalosporin, such as cefuroxime, is usually the drug of choice in acute sinusitis associated with *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae*. The second-generation quinolones usually have poor activity in treating community-acquired pneumonia (CAP) because of their poor activity against *S. pneumoniae*. The third- and fourth-generation fluoroquinolones are significantly more effective in treating CAP because of their activity against *S. pneumoniae*. The fluoroquinolones are also indicated for nosocomial pneumonia, chronic bronchitis (acute exacerbations), and chronic otitis media.

The fluoroquinolones have indications for a variety of GI infections, including traveler's diarrhea due to *E. coli*, shigellosis, and typhoid fever. In the AIDS patient these drugs are effective in treating bacteremias and eradicating the carrier state due to nontyphoidal organisms. *Importantly, the fluoroquinolones are contraindicated in the treatment of enterohemorrhagic E. coli because they can induce the cytotoxic Shiga-like toxin.*

Primary cervicitis, urethritis, and extended infections, such as pelvic inflammatory disease due to the STD agents *N. gonorrhoeae* and *C. trachomatis*, are successfully treated with fluoroquinolones. Both ciprofloxacin and ofloxacin appear to be more effective than other fluoroquinolones, although resistance has been reported to be emerging. Because coinfections in patients treated with ciprofloxacin and ofloxacin are frequent, especially in women ($\geq 50\%$), caution should be observed in using these agents if resistance becomes predominant in either infecting organism. Ciprofloxacin and ofloxacin are ineffective against *Treponema pallidum* but are active against the less common *Haemophilus ducreyi*.

The use of fluoroquinolones in bone and joint infections is influenced by the causative agent and the rate of resistance development. The use of the oral route for administration of the fluoroquinolones is especially ad-

vantageous in treating chronic infections that often require long-term therapy.

Adverse Effects and Drug Interactions

In general, the quinolones and fluoroquinolones are well tolerated. The most frequently reported side effects are associated with the GI tract (2–13%); these include nausea, vomiting, diarrhea, and abdominal pain. CNS effects (1–8%), such as drowsiness, weakness, headache, dizziness, and in severe cases, convulsions and toxic psychosis, have been reported. Some side effects, such as photosensitivity, correlate with specific chemical structures, including the halogen substitution on the eighth position, as found in sparfloxacin and lomefloxacin. Adverse cardiovascular effects (6–7%; vascular embolism, cardiac insufficiency, hypotension) also occur with sparfloxacin. Sparfloxacin, moxifloxacin, and gatifloxacin can exacerbate QT prolongations. Fulminant hepatotoxicity associated with trovafloxacin has resulted in acute liver failure, and the FDA has recommended limiting therapy to life-threatening infections.

The use of the quinolones in pregnant or breast-feeding women and children whose epiphyseal plates have not closed is generally contraindicated. Their use for treating young cystic fibrosis children infected with *Pseudomonas* spp. is an exception; the patient should be monitored carefully for untoward effects.

All quinolones interact with multivalent cations, forming chelation complexes resulting in reduced absorption. Major offenders are antacids; vitamins containing calcium and iron can also be problematic. All fluoroquinolones interact with warfarin, didanosine (ddi), and phenytoin, resulting in decreased absorption or metabolism. Ciprofloxacin and other second-generation drugs interact with theophylline by decreasing its clearance, which leads to theophylline toxicity.

Allergic reactions (e.g., rashes, urticaria, and eosinophilia) have been observed. These drugs have occasionally been associated with cholestatic jaundice, blood dyscrasias, hemolytic anemia, hypoglycemia, and nephrotoxicity. Recently the use of ciprofloxacin for prophylaxis protection against anthrax infection has been associated with damage to muscle ligaments.

URINARY ANTISEPTICS

Urinary antiseptics are drugs that exert their antimicrobial effect in the urine and are devoid of virtually any significant systemic effect. Prolonged use for prophylaxis and/or suppression is common in recurrent or chronic UTIs where other antimicrobials can be used only for short durations because they do not sustain sterility.

Nitrofurans (Nitrofurantoin) Chemistry and Mechanism of Action

A number of 5-nitro-2-furaldehyde derivatives, called *nitrofurans*, are used in the treatment and/or prophylaxis of microbial infections, primarily in the urinary tract. Recent evidence suggests that the reduction of the 5-nitro group to the nitro anion results in bacterial toxicity. Intermediate metabolites modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis); this observation may explain the lack of resistance development to these drugs. Evidence also indicates that the nitro anion undergoes recycling with the production of superoxide and other toxic oxygen compounds. It is presumed that the nitrofurans are selectively toxic to microbial cells because in humans, the slower reduction by mammalian cells prevents high serum concentrations.

Antibacterial Spectrum and Resistance

Nitrofurantoin (*Furadantin*, *Macrochantin*) is primarily active against gram-negative bacteria (*E. coli*, *P. mirabilis* is variable) and some susceptible gram-positive organisms, such as *S. aureus* and *Enterococcus faecalis*. In vitro activity is demonstrated against *Staphylococcus saprophyticus* and *Staphylococcus epidermidis*, but it may not be helpful in predicting patient response; the same applies for certain species of *Klebsiella* and *Citrobacter*. Most *Proteus* (indole positive), *Serratia*, and *Pseudomonas* spp. are resistant. Development of resistant strains is virtually unknown, and cross-resistance with other antimicrobials has not been reported.

Absorption, Metabolism, and Excretion

Nitrofurantoin is administered orally and is rapidly and almost completely absorbed from the small intestine; only low levels of activity are achieved in serum because the drug is rapidly metabolized. Relatively high protein binding (about 70%) also affects serum levels, reducing potential for systemic toxicity and alteration of intestinal flora. Relative tissue penetration is much lower than other antimicrobials for UTIs, and therefore, nitrofurantoin is not indicated in the therapy of infections such as pyelonephritis and renal cortical or perinephric abscesses. Nitrofurantoin is rapidly excreted by glomerular filtration and tubular secretion to yield effective urinary levels. In moderate to severe renal dysfunction, toxic blood levels may occur while urinary levels may be inadequate. The drug is inactivated in the liver.

Nitrofurazone (*Furacin*) is used topically and is not readily absorbed from the skin.

Clinical Use

The singular indication for nitrofurantoin is the treatment and long-term prophylaxis of lower UTIs caused by susceptible bacteria; it is not used as a bacterial suppressant. It is often used prophylactically post intercourse in women with chronic UTIs. Although serum drug concentrations are low, concentrations (100–200 $\mu\text{g}/\text{mL}$) are found in urine that are well above the minimum inhibitory concentration for susceptible bacteria. The bacteriostatic or bactericidal activity of nitrofurantoin is concentration dependent; a urinary concentration greater than 100 $\mu\text{g}/\text{mL}$ ensures bactericidal activity. Because nitrofurantoin lacks the broad tissue distribution of other antimicrobial agents, urine cultures should be obtained before and after therapy. Alkalinization of the urine increases urinary concentrations of the drug but decreases its antibacterial efficacy; acidifying agents, including cranberry juice, can be useful.

Nitrofurazone, a topical antibiotic, is occasionally used in the treatment of burns or skin grafts in which bacterial contamination may cause tissue rejection.

Adverse Effects and Drug Interactions

Nausea and vomiting are the most commonly observed adverse effects. Pulmonary hypersensitivity reactions can result in chronic morbidity, usually after therapy lasting at least 6 months. Findings can include *chronic desquamative interstitial pneumonia with fibrosis*. Resolution may not occur with discontinuation of therapy; fever is absent. Reactions may also be acute or subacute. Patients may present acutely with findings resembling acute respiratory distress syndrome. Infiltrates (especially at the base of the lung) and/or effusions may develop but are usually reversible when the drug is stopped; fever is a common finding. In contrast, resolution of pulmonary disease may require several months, especially in subacute reactions, with which fever is not frequent. These reaction types have all been reported as contributing factors in mortality. *When a patient taking nitrofurantoin develops pulmonary symptoms, a suspicion of drug-associated toxicity must be entertained.*

Intrahepatic cholestasis and hepatitis similar to that seen in chronic active hepatitis can rarely occur; fatalities have been reported. Nitrofurantoin can interfere with immature red blood cell enzyme systems found in babies less than 1 month of age and in nursing infants. This leads to cellular damage and anemia. Nitro-

furantoin use is also contraindicated in pregnant women near term.

In vitro antagonism between nitrofurantoin and the quinolones has been shown, but a demonstration of clinical relevance warrants further study. Certain drugs used in treating gout, which inhibit tubular secretion, can affect UTI therapy by raising serum levels of nitrofurantoin with concomitant diminished urinary levels.

Nitrofurazone is a relatively safe topical agent. Skin sensitization has been reported.

Methenamine

Methenamine (hexamethylenetetramine) is an aromatic acid that is hydrolyzed at an acid pH (<6) to liberate ammonia and the active alkylating agent formaldehyde, which denatures protein and is bactericidal. Methenamine is usually administered as a salt of either mandelic (*Mandelamine*) or hippuric (*Hiprex, Urex*) acid. Not only do these acids acidify the urine, which is necessary to generate formaldehyde, but also, the resulting low urine pH is by itself bacteriostatic for some organisms.

Methenamine is administered orally and is well absorbed from the intestinal tract. However, 10 to 30% decomposes in the stomach unless the tablets are protected by an enteric coating. The inactive form (methenamine) is distributed to virtually every body fluid. Almost all of the methenamine moiety is excreted into the urine by 24 hours, having reached the urine by both glomerular filtration and tubular secretion.

Methenamine is primarily used for the long-term prophylactic or suppressive therapy of recurring UTIs. *It is not a primary drug for therapy of acute infections.* It should be used to maintain sterile urine after appropriate antimicrobial agents have been employed to eradicate the infection.

Gastric distress (nausea and vomiting) is one of the most frequently reported adverse reactions. Bladder irritation (e.g., dysuria, polyuria, hematuria, and urgency) may occur. The mandelic salt can crystallize in urine if there is inadequate urine flow and should not be given to patients with renal failure. Patients with preexisting hepatic insufficiency may develop acute hepatic failure due to the small quantities of ammonia formed during methenamine hydrolysis.

The coadministration of methenamine with certain sulfonamides (sulfamethizole or sulfathiazole) can form a urine precipitate resulting in drug antagonism.

Study QUESTIONS

- A 24-year-old AIDS patient is interested in starting chemoprophylaxis for *Pneumocystis pneumonia* (PCP) and cerebral toxoplasmosis. He has no drug allergies. Which of the following prophylactic agents is appropriate for the prevention of both PCP and cerebral toxoplasmosis?

 - Nitrofurantoin
 - Trimethoprim–sulfamethoxazole
 - Norfloxacin
 - Methenamine
 - Nalidixic acid
- Urinalysis of a 38-year-old woman with recurrent UTIs revealed pH 6.8, 30 to 50 WBC per high-power field, and gram-negative bacilli identified as *Proteus mirabilis*. Which of the following produces a bacteriostatic urinary environment for *P. mirabilis*?

 - Urease enzyme
 - Hippuric acid
 - Catalase enzyme
 - Folic acid
 - Coagulase enzyme
- A 3-day-old baby is given a presumptive diagnosis of kernicterus. Which of the following mechanisms is involved in sulfonamide-induced kernicterus?

 - Competes for the bilirubin-binding sites on plasma proteins
 - Defective bilirubin hepatic conjugation and metabolism
 - Physiological jaundice due to destruction of fetal red blood mass
 - Pregnancy-induced hepatic congestion and cholestasis
 - Primary biliary cirrhosis of the liver
- A 6-year-old relatively healthy boy is diagnosed with external otitis and was prescribed a 7-day course of TMP-SMX. Which of the following is the basic mechanism of action of the sulfonamides?

 - Selective inhibition of incorporation of PABA into human cell folic acid synthesis.
 - Competitive inhibition of incorporation of PABA into microbial folic acid.
 - Inhibition of transpeptidation reaction in bacterial cell wall synthesis.
 - Changes in DNA gyrases and active efflux transport system resulting in decreased permeability of drug.
 - Structural changes in dihydropteroate synthase and overproduction of PABA.
- Evaluation of a yearly chest radiograph of a 73-year-old patient taking nitrofurantoin prophylactically for recurrent UTIs revealed new findings of bilateral interstitial fibrosis. What is the possible explanation for the patient's pulmonary presentation and what is the next step?

 - Acute urosepsis; add a broad-spectrum antibiotic to nitrofurantoin.
 - Possible allergic reaction to nitrofurantoin; stop it immediately.
 - Nitrofurantoin-resistant *E. coli* infection; stop it immediately.
 - Acute community-acquired streptococcal pneumonia; treat accordingly.
 - Nitrofurantoin-induced hemolysis; requires permanent urinary catheter.
- A 16-year-old girl, a cystic fibrosis patient, is diagnosed with a ciprofloxacin-resistant *Pseudomonas aeruginosa* lower respiratory tract infection. Bacteria acquire quinolone resistance by which of the following mechanisms?

 - Overproduction of PABA
 - Changes in the synthesis of DNA gyrases
 - Plasmid-mediated changes in efflux transport system
 - Inhibition of synthesis of peptidoglycan subunits in bacterial cell walls
 - Inhibition of folic acid synthesis by blocking different steps

ANSWERS

- B.** Nitrofurantoin (A) is a urinary antiseptic agent active against many of the Enterobacteriaceae. Nitrofurantoin has no effect on *Toxoplasma* or *P. carinii*, as both are protozoans. TMP-SMX (B) daily or three times a week has proved to prevent both PCP and toxoplasmosis in AIDS patients. Norfloxacin (C) and other second-generation fluoroquinolones are known for their antipseudomonal and Enterobacteriaceae activity. The antimicrobial activity is exerted through inhibition of DNA gyrase A and type IV topoisomerase. Methenamine (D) is active against various Enterobacteriaceae; it has no activity against protozoa. Formaldehyde denatures proteins and is bactericidal. Nalidixic acid (E) is used in urinary tract infections caused by Enterobacteriaceae (e.g., *E. coli*, *Klebsiella*, and *Proteus*). It has no activity against protozoa.
- B.** *Proteus* species produce urease (A) that produces ammonia and urea, alkalizing urine. Urine requires acidification for effective therapy. Hippuric (B), mandelic, or ascorbic acids or methionine are urinary acidifying agents. The normal acidic urinary environment is disturbed by recurrent *Proteus* in-

fections. Catalase (C) is produced by staphylococcal spp. The catalase test differentiates Staphylococci from Streptococci. It has no urinary activity. Folic acid (D) is a water-soluble vitamin and has no effect on urinary pH or acidification. Humans cannot synthesize folic acid, which must be obtained from the diet. A coagulase enzyme (E) is produced by *Staphylococcus aureus*. Coagulase test differentiates *S. aureus* from other staphylococci. It has no urinary antimicrobial activity.

3. **A.** Sulfonamides (A) compete for bilirubin binding sites on plasma albumin and increase fetal blood levels of unconjugated bilirubin. Unbound bilirubin crosses the blood-brain barrier and can be deposited in the basal ganglia and subthalamic nuclei causing kernicterus, a toxic encephalopathy. Defective bilirubin hepatic conjugation (B) is due to glucuronyl transferase deficiency resulting in Gilbert's syndrome. When seen in adults it usually presents with jaundice that is precipitated by fasting. Physiological jaundice (C) usually occurs in the newborn within a week of birth. It is due to the immature fetal acetyltransferase system resulting in peripheral destruction of a large fetal red cell mass. Pregnancy-induced hepatic congestion (D), cholestasis, and acute cholecystitis are seen in pregnant women, not in the newborn. Primary biliary cirrhosis (E) is commonly seen in middle-aged women. It is a chronic progressive autoimmune disorder requiring steroids and sometimes liver transplant.
4. **B.** Humans cannot synthesize folic acid (A); diet is their main source. Sulfonamides selectively inhibit microbially synthesized folic acid. Incorporation (B) of PABA into microbial folic acid is competitively inhibited by sulfonamides. The TMP-SMX combination is synergistic because it acts at different steps in microbial folic acid synthesis. All sulfonamides are bacteriostatic. Inhibition of the transpeptidation reaction (C) involved in the synthesis of the bacterial cell wall is the basic mechanism of action of β -lactam antibiotics. Changes in DNA gyrases (D) and active efflux transport system are mechanisms for resistance to quinolones. Structural changes (E) in dihydropteroate synthetase and overproduction of PABA are mechanisms of resistance to the sulfonamides.
5. **B.** Acute urosepsis (A) is possible, but the patient's physical examination produced benign findings. Adding a broad-spectrum antibiotic has no benefit without evidence of active disease. Possible allergic reaction (B) to nitrofurantoin; it is appropriate to stop the drug immediately to guard against one of three potential pulmonary reactions: (1) acute pres-

entation with basilar infiltrate and pleural effusion, (2) chronic progressive bilateral interstitial fibrosis; (3) a subacute presentation. Nitrofurantoin-resistant *E. coli* infection (C) and urosepsis are possible in patients who are taking chronic prophylaxis, but his examination produced benign findings. Acute community-acquired streptococcal pneumonia (D) shows one or more lobar infiltrates on radiography. The patient described has bilateral interstitial fibrosis. Nitrofurantoin-induced hemolysis (E) is possible in G6PD patients, but physical examination produced benign findings; G6PD patients usually present with hematuria.

6. **B.** Overproduction (A) of PABA is one of the resistance mechanisms of sulfonamides. Changes in the synthesis of DNA gyrases (B) is a well-described mechanism for quinolone resistance. Plasmid-mediated resistance (C) does not occur with quinolones. An active efflux system for transport of drug out of the cell has been described for quinolone resistance, but it is not plasmid mediated. Inhibition of structural blocks (D) in bacterial cell wall synthesis is a basic mechanism of action of β -lactam antibiotics. Inhibition of folic acid synthesis (E) by blocking different steps is the basic mechanism of action of sulfonamides.

SUPPLEMENTAL READING

- Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. [Review]. *Drugs* 2001;61:353–364.
- Hooper DC. New uses for new and old fluoroquinolones and the challenge of resistance. *Infect Dis* 2000;30:243–254.
- Hooper DC. Urinary tract agents: Nitrofurantoin and methenamine. In Mandell GL, Dolin R, and Bennett JE (Eds.). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 5th ed. New York: Churchill Livingstone, 2000.
- Lipsky BA and Baker CA. Fluoroquinolone toxicity profiles: A review focusing on newer agents. *Clin Infect Dis* 1999;28:352–364.
- Martin JN et al. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era. *J Infect Dis* 1999;180:1809–1818.
- Smith JM, Curi AL, and Pavesio CE. Crystalluria with sulphadiazine. *Br J Ophthalmol* 2001;85:1265–1269.
- Walker RC. The fluoroquinolones. *Mayo Clin Proc* 1999;74:1030–1037.
- Wright SW, Wrenn KD, and Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med* 1999;14:606–609.

CASE Study Synthetic Organic Antimicrobials

A 62-year-old man with a history of benign hypertrophic prostate (BPH) has deep pelvic pain and a low-grade fever. He has a history of chronic bilateral osteoarthritis of the knees and was recently diagnosed with diet-controllable diabetes mellitus. The patient denies any drug allergy but is an active smoker and drinks three or four cans of beers daily.

Physical examination: elderly man is not in acute distress. His oral temperature is 37.7°C (100.1°F); blood pressure is 110/70 and heart rate is 90/minute. His prostate gland was enlarged and very tender, consistent with acute prostatitis. His routine blood work and liver function test findings were within normal limits. A urine sample was sent for analysis and cultures; ciprofloxacin 750 mg twice a day was started.

About a week later, the patient was admitted to the hospital with acute onset of confusion and possible seizurelike activity. His wife states that he is compliant with medications and even felt well after initiation of antibiotics. Possible ciprofloxacin-induced acute CNS toxicity or drug interaction was suspected, and all his medications were discontinued. Which of the following is the possible explanation for the patient's acute onset of CNS toxicity?

- (A) Ciprofloxacin can displace GABA from its receptors resulting in neuroexcitation.
- (B) Acute alcohol withdrawal was precipitated by ciprofloxacin due to an alcohol-drug interaction.

(C) He has fulminant gram-negative urosepsis with possible ciprofloxacin-resistant bacteria.

(D) He has cumulative CNS toxicity of ciprofloxacin secondary to poor urinary and prostatic tissue penetration.

(E) He has delayed stomach absorption and metabolism of the drug secondary to diabetic gastroparesis.

ANSWER: A. Ciprofloxacin can significantly interfere with the normal physiology of GABA. Displacement of GABA from its receptors by ciprofloxacin results in increased levels of the neuroexcitatory transmitter and acute CNS toxicity. The neuroexcitation can range from irritability, confusion, and agitation to seizures and toxic psychosis. Ciprofloxacin has no interaction with alcohol. A disulfiramlike reaction (flushing, nausea, vomiting, and profuse sweating) is associated with alcohol and metronidazole. Avoid alcohol and metronidazole coadministration.

Cumulative CNS toxicity secondary to poor tissue concentration is incorrect. In fact, high tissue concentrations are achieved with oral ciprofloxacin, especially in the prostate and urinary tract. For this reason, it is widely used for prostatitis and UTIs. Diabetic gastroparesis is seen in long-standing severe diabetes. Drug absorption problems are seen in these patients secondary to delayed gastric emptying and frequent vomiting. The patient described has newly diagnosed diet-controlled diabetes mellitus, so this does not explain his symptoms.