**Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics 33**

**I. FLUOROQUINOLONES**

Naladixic acid is the predecessor to all fluoroquinolones. Introduction of the first fluorinated quinolone, norfloxacin, was rapidly followed by development of other members of this group, such as ciprofloxacin, which has had wide clinical application. Today, over 10,000 analogs have been synthesized. Newer fluorinated quinolones offer greater potency, a broader spectrum of antimicrobial activity, greater in vitro efficacy against resistant organisms, and in some cases, a better safety profile than older qui- nolones and other antibiotics. Compared to ciprofloxacin, the new com- pounds are more active against gram-positive organisms, yet retain favourable activity against gram-negative microorganisms. It seems likely that the number of drugs in this class of antibiotics will increase due to its wide antibacterial spectrum, favourable pharmacokinetic properties, and relatively infrequent adverse event profile. Unfortunately, their overuse has already led to the emergence of resistance, resulting in limitations to their clinical usefulness. The fluoroquinolones and other antibiotics dis- cussed in this chapter are listed in Figure 33

**.1. A. Mechanism of action**

The fluoroquinolones enter the bacterium by passive diffusion through water-filled protein channels (porins) in the outer mem- brane. Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction. [Note: Topoisomerases are enzymes that change the configuration or topology of DNA by a nicking, pass-through, and resealing mechanism. They do not change the DNA’s primary sequence (Figure 33.2).] Binding of the quinolone to both the enzyme and the DNA forms a ternary complex that inhibits the resealing step, and can cause cell death by inducing cleavage of the DNA. Because DNA gyrase is a bac- teriospecific target for antimicrobial therapy, cross-resistance with other, more commonly used antimicrobial drugs is rare, but this is increasing in the case of multidrug-resistant organisms. The second site blocked by the fluoroquinolones—topoi somerase IV—is required by bacteria for cell division. It has been implicated in the process of segregating newly replicated DNA. In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more sig- nificant than that of topoisomerase IV, whereas in gram-positive organisms (for example, the streptococci), the opposite is true.

**B. Antimicrobial spectrum**

Fluoroquinolones are bactericidal and exhibit AUC/MIC dependent killing. Bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30-fold the minimum inhibitory concentration. In general, they are effective against gram- negative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legione lla ceae, chlamydia, mycoplasma and some mycobacteria. They are effective in the treatment of gonorrhea but not syphilis. The newer agents (for example, levofloxacin and moxifloxacin) also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae. Moxifloxacin has activity against many anaerobes. If used prophylactically before transurethral surgery, fluoroquinolones lower the incidence of postsurgical urinary tract infections (UTIs). It has become common practice to classify the fluoroquinolones into “generations,” based on their antimicrobial targets (Figure 33.3). The nonfluorinated quinolone nalidixic acid is considered to be first generation, with a narrow spectrum of susceptible organisms usually confined to the urinary tract. Ciprofloxacin and norfloxacin are assigned to the second generation because of their activity against aerobic gram-negative and atypical bacteria. In addition, these fluoroquinolones exhibit significant intra- cellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chla- mydia, mycoplasma, and legionella). Levofloxacin is classified as third generation because of its increased activity against gram-positive bacteria. Lastly, the fourth generation includes only moxifloxacin because of its activity against anaerobic, as well as, gram-positive organisms.

**C. Examples of clinically useful fluoroquinolones**

**1. Ciprofloxacin**: The serum levels of ciprofloxacin [sip-row-FLOX-a- sin] that are achieved are effective against many systemic infections, with the exception of serious infections caused by methicillin-resistant Staphylococcus aureus (MRSA), the enterococci, and pneumococci (Figure 33.4). Ciprofloxacin is particularly useful in treating infections caused by many Enterobac teriaceae and other gram-negative bacilli. For example, traveler’s diarrhea caused by E. coli can be effectively treated. It is the most potent of the fluoroquinolones for Pseudomonas aeruginosa infections and, therefore, is used in the treatment of pseudomonal infections associated with cystic fibrosis. The drug is also used as an alternative to more toxic drugs, such as the aminoglycosides. It may act synergistically with β-lactams and is also of benefit in treating resistant tuberculosis. Ciprofloxacin is also commonly used to treat typhoid fever in third-world countries.

**2. Norfloxacin**: Norfloxacin (nor-FLOX-a-sin] is effective against both gram-negative (including P. aeruginosa) and gram-positive organ- isms in treating complicated and uncomplicated UTIs, prostatitis and traveler's diarrhea (unlabeled use). It is not effective in systemic infections.

**3. Levofloxacin**: Levofloxacin [leave-oh-FLOX-a-sin] is an isomer of ofloxacin [oh-FLOX-a-sin] and has largely replaced it clinically. It can be used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases, with the exception of syphilis. It may be used as alternative therapy in patients with gonorrhea. Additionally, due to its broad spectrum of activity, levofl oxacin is utilized in a wide range of infections, including skin infections, acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, as well as nosocomial pneumonia. Levofl oxacin has excellent activity against S. pneumoniae respiratory infections

**4. Moxifl oxacin**: Moxifl oxacin [moxie-FLOX-a-sin] not only has enhanced activity against gram-positive organisms (for example, S. pneumoniae) but also has excellent activity against many anaerobes. It has very poor activity against P. aeruginosa. Moxifloxacin does not concentrate in urine and is not indicated for the treatment of UTIs.

**D. Resistance**

When the fluoroquinolones were first introduced, there was optimism that resistance would not develop. Although no plasmid-mediated resistance has been reported, resistant MRSA, pseudomonas, coagulase- negative staphylococci, and enterococci have unfortunately emerged due to chromosomal mutations. Cross-resistance exists among the quinolones. The mechanisms responsible for this resistance include the following.

 **1. Altered target**: Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones. Topo- isomerase IV also undergoes mutations. Resistance is frequently associated with mutations in both DNA gyrase and topo- isomerase IV.

**2. Decreased accumulation**: Reduced intracellular concentration of the drugs in the bacterial cell is linked to two mechanisms. One involves a decreased number of porin proteins in the outer mem- brane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The other mechanism is associated with an energy-dependent efflux system in the cell membrane.

**E. Pharmacokinetics**

**1. Absorption**: Only 35 to 70 percent of orally administered norfloxacin is absorbed, compared with 85 to 95 percent of the other fluoroquinolones (Figure 33.5). Intravenous preparations of ciprofloxacin and levofloxacin are available. Ingestion of the fluoroquinolones with sucralfate, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents (Figure 33.6). The fluoroquinolones with the longest half-lives (levofloxacin and moxifloxacin) permit once-daily dosing.

**2. Elimination**: Binding to plasma proteins ranges from 10 to 40 per- cent. [Note: Achieved plasma levels of free norfloxacin are insufficient for treatment of systemic infections.] All the fluoroquinolones dis- tribute well into all tissues and body fluids. Levels are high in bone, urine (except moxifloxacin), kidney, and prostatic tissue (but not pro- static fluid), and concentrations in the lung exceed those in serum. Penetration into cerebrospinal fluid is relatively low except for ofloxacin, for which concentrations can be as high as 90 percent of those in the serum. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellular organisms such as Legionella pneumophila. Most fluoroquinolones are excreted renally, therefore, the dose needs to be adjusted when renal function changes. Moxifloxacin, on the other hand, is excreted primarily by the liver, and no dose adjustment is required with decreased renal functioning.

**F. Adverse reactions**

In general, these agents are very well tolerated. Toxicities similar to those for nalidixic acid have been reported for the fl uoroquinolones (Figure 33.7).

**1. Gastrointestinal**: The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea, which occur in three to six percent of patients.

**2. Central nervous system problems**: The most prominent central nervous system (CNS) effects of fluoroquinolone treatment are headache and dizziness or light-headedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs. [Note: Ciprofloxacin interferes in the metabolism of theophylline and may evoke seizures.]

**3. Phototoxicity**: Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens. However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity.

**4. Connective tissue problems**: Fluoro quinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age, because articular cartilage erosion (arthropathy) occurs in immature experimental animals. [Note: Careful monitoring is indicated in children with cystic fibrosis, who receive fluoroquinolones for acute pulmonary exacerbations.] In 2008, FDA added a Black Box Warning to fluoroquinolones about increased risk of tendinitis or tendon rupture that may occur with systemic fl uoroquinolone use, not with ophthalmic or otic use. The Achilles tendon is the most frequent tendon associated with the occurrence of tendinitis and ten- don rupture. The adverse event can occur during fluoroquinolone treatment, or up to several months after completion of therapy. The risk of developing tendinitis or tendon rupture associated with fl uoroquinolone use is increased in patients over 60 years of age, those receiving concomitant corticosteroid therapy, and in patients with kidney, heart, or lung transplants.

**5. Contraindications**: Moxifloxacin and other fluoroquinolones, may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or are taking antiarrhythmic medications and not being actively monitored.

 **6. Drug interactions**: The effect of antacids and cations on the absorption of these agents was considered above. Ciprofl oxacin and ofloxacin can increase the serum levels of theophylline by inhibiting its metabolism (Figure 33.8). This is not the case with the third- and fourth-generation fluoroquinolones, which may raise the serum levels of warfarin, caffeine, and cyclosporine.

**II. OVERVIEW OF THE FOLATE ANTAGONISTS**

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide. To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid as a vitamin from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo. The sulfonamides (sulfa drugs) are a family of antibiotics that inhibit this de novo synthesis of folate. A second type of folate antago nist —trimetho prim—prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell’s ability to make this conversion. Thus, both sulfonamides and trimethoprim interfere with the ability of an infecting bacterium to divide. Combining the sulfonamide, sulfamethoxazole, with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic combination that is used as effective treatment of a variety of bacterial infections.

**III. SULFONAMIDES**

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and their efficacy in certain bacterial infections, such as trachoma and those of the urinary tract. However, when cotrimoxazole was introduced in the mid-1970s, there was a renewed interest in the sulfonamides. Sulfa drugs differ from each other not only in their chemical and physical properties, but also in their pharmacokinetics.

1. **Mechanism of action**

In many microorganisms, dihydrofolic acid is synthesized from p-amino- benzoic acid (PABA), pteridine, and glutamate (Figure 33.9). All the sulfonamides currently in clinical use are synthetic analogs of PABA. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate syn- thetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms. The sulfa drugs, including cotrimoxazole, are bacteriostatic.

1. **Antibacterial spectrum**

Sulfa drugs are active against selected Enterobacteria in the urinary tract and Nocardia. In addition, sulfadiazine [sul-fa-DYE-a-zeen], in com- bination with the dihydrofolate reductase inhibitor pyrimethamine [py- ri-METH-a-meen], is the preferred form of treatment for toxoplasmosis.

1. **Resistance**

Only organisms that synthesize their folate requirements de novo are sensitive to the sulfonamides. Thus, humans, who synthesize critical folate cofactors from dietary folic acid, are not affected, and bacteria that can obtain folates from their environment are naturally resistant to these drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. [Note: Organisms resistant to one member of this drug family are resistant to all.] Resistance is generally irreversible and may be due to 1) an altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA.

**D. Pharmacokinetics**

**1. Administration**: After oral administration, most sulfa drugs are well absorbed via the small intestine (Figure 33.10). An exception is sulfasalazine [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel disease (for example, Crohn’s disease or ulcerative colitis). [Note: Local intestinal fl ora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti- infl ammatory effect. Absorption of the sulfapyridine can lead to toxicity in patients who are slow acetylators (see below).] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. Because of the risk of sensitization, sulfas are not usually applied topically. However, in burn units, creams of silver sulfadiazine or mafenide [mah-FEN-ide] acetate (α-amino-p-toluene- sulfonamide) have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. Superinfections with resistant bacteria or fungi may still occur. [Note: Silver sulfadiazine is preferred because mafenide produces pain on application. Furthermore, mafenide can be absorbed in burn patients, causing an increased risk of acid-base imbalance.]

**2. Distribution**: Sulfa drugs are bound to serum albumin in the circulation, where the extent of binding depends on the particular agent’s pKa. In general, the smaller the pKa value, the greater the binding. Sulfa drugs distribute throughout the body’s water and penetrate well into cerebrospinal fluid—even in the absence of inflammation. They can also pass the placental barrier and enter fetal tissues.

**3. Metabolism**: The sulfa drugs are acetylated, primarily in the liver. The product is devoid of antimicrobial activity, but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria (“stone formation”; see below) and, therefore, potential damage to the kidney.

**4. Excretion**: Sulfa drugs are eliminated by glomerular filtration and require dose adjustments for renal dysfunction. Depressed kidney function causes accumulation of both the parent compounds and their metabolites necessitating dose adjustment. The sulfonamides may also be eliminated in breast milk.

**E. Adverse effects**

 **1. Crystalluria**: Nephrotoxicity develops as a result of crystalluria (Figure 33.11). Adequate hydration and alkalinization of urine pre- vent the problem by reducing the concentration of drug and pro- moting its ionization. Agents, such as sulfi soxazole [sul-fi -SOX-a-zole] and sulfamethoxazole [sul-fa-meth-OX-a-zole] are more soluble at urinary pH than are the older sulfonamides (for example, sulfadiazine) and are less liable to cause crystalluria.

 **2. Hypersensitivity**: Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, are potential problems. The latter occurs more frequently with the longer-acting agents. When patients report previous sulfa allergy, it is paramount to acquire a description of the reaction to direct appropriate therapy.

**3. Hemopoietic disturbances**: Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase defi ciency. Granulocytopenia and thrombocytopenia can also occur. **4. Kernicterus**: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the baby’s blood- brain barrier is not fully developed (see below).

**5. Drug potentiation**: Transient potentiation of the anticoagulant effect of warfarin results from their displacement from binding sites on serum albumin. Free methotrexate levels may also rise through displacement.

**6. Contraindications**: Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving methenamine for UTIs (Figure 33.12).

**IV. TRIMETHOPRIM**

Trimethoprim [trye METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sul- fonamides. Trimethoprim is most often compounded with sulfamethoxazole, producing the combination called cotrimoxazole. **A. Mechanism of action**

The active form of folate is the tetrahydro-derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction (see Figure 33.9) is inhibited by trimethoprim, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for trimethoprim than does the mammalian enzyme, which accounts for the drug’s selective toxicity. [Note: Examples of other drugs that function as folate reductase inhibitors include pyrimethamine, which is used with sulfonamides in treating parasitic infections, and methotrexate, which is used in the treatment of cancer, rheumatoid arthritis, and psoriasis].

**B. Antibacterial spectrum**

The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole. However, trimethoprim is 20- to 50-fold more potent than the sulfonamide. Trimethoprim may be used alone in the treatment of acute UTIs and in the treatment of bacterial prostatitis (although fluoroquino- lones are preferred) and vaginitis.

1. **Resistance**

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim. Overproduction of the enzyme may also lead to resistance, because this can decrease drug permeability.

1. **Pharmacokinetics**

The half-life of trimethoprim is similar to that of sulfamethoxazole. However, because the drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids. The drug also penetrates the cerebro spinal fluid. Trimethoprim undergoes some O-demethylation, but most of it is excreted unchanged through the kidney.

1. **Adverse effects**

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those having very poor diets. These blood disorders can be reversed by the simultaneous administration of folinic acid, which does not enter bacteria.

**V. COTRIMOXAZOLE**

The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (see Figure 33.13). The combination was selected because of their synergistic activity and the similarity in the half-lives of the two drugs.

1. **Mechanism of action**

The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate (see Figure 33.9).

1. **Antibacterial spectrum**

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs (Figure 33.14). It is effective in treating UTIs and respiratory tract infections as well as in Pneumocystis jiroveci pneumonia and ampicillin- or chlorampheni col-resistant systemic salmonella infections. It has activity versus MRSA, and can be particularly useful for community acquired skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible Nocardia species and Stenotrophamonas maltophilia.

1. **Resistance**

Resistance to the trimethoprim-sulfamethoxazole combination is less frequently encountered than resistance to either of the drugs alone, because it would require that the bacterium have simultaneous resistance to both drugs.

1. **Pharmacokinetics**

Trimethoprim is more lipid soluble than sulfamethoxazole and has a greater volume of distribution. Administration of one part trimethoprim to five parts of the sulfa drug produces a ratio of the drugs in the plasma of twenty parts sulfamethoxazole to one part trimethoprim. This ratio is optimal for the antibiotic effect. Cotrimoxazole is generally administered orally (Figure 33.15). Exceptions involve intravenous administration to patients with bloodstream infections or severe pneumonia caused by P. jiroveci, or to patients who cannot take the drug by mouth. Both agents distribute throughout the body. Trimethoprim concentrates in the relatively acidic milieu of prostatic and vaginal fluids, and it accounts for the use of the trimethoprim-sulfamethoxazole combination in infections at these sites. Both parent drugs and their metabolites are excreted in the urine.

**E. Adverse effects**

**1. Dermatologic**: Reactions involving the skin are very common and may be severe in the elderly (Figure 33.16).

**2. Gastrointestinal**: Nausea, vomiting, as well as, glossitis and stomatitis are not unusual.

**3. Hematologic**: Megaloblastic anemia, leukopenia, and thrombocytopenia may occur. All these effects may be reversed by the con- current administration of folinic acid, which protects the patient and does not enter the microorganism. Hemolytic anemia may occur in patients with glucose 6-phosphate dehydrogenase deficiency due to the sulfamethoxazole.

**4. Patients infected with human immunodeficiency virus**: Immuno- compromised patients with P. jiroveci pneumonia frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.

**5. Drug interactions**: Prolonged prothrombin times (increased INR) in patients receiving both sulfamethoxazole and warfarin have been reported. The plasma half-life of phenytoin may be increased due to an inhibition of its metabolism. Methotrexate levels may rise due to displacement from albumin-binding sites by sulfamethoxazole.

**VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS**

Urinary tract infections (most commonly uncomplicated acute cystitis and pyelonephritis) in women of child-bearing age and in the elderly are one of the most common problems seen by primary care physicians. Escherichia coli is the most common pathogen, causing about 80 percent of uncomplicated upper and lower UTIs. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs, with other common causes including Klebsiella pneumoniae and Proteus mirabilis. These infections may be treated with any one of a group of agents called urinary tract antiseptics, including methenamine, nitrofurantoin, and the quinolone nalidixicacid. These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

 **A. Methenamine**

**1. Mechanism of action**: To act, methenamine [meth-EN-a-meen] must decompose at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria (Figure 33.17). Methenamine should not be used in patients with indwelling catheters. Bacteria do not develop resistance to formaldehyde. [Note: Methenamine is frequently formulated with a weak acid, such as mandelic acid or hippuric acid. Ascorbic acid (vita- min C), and cranberry juice have been used to reduce urinary pH. Non-prescription antacids, such as sodium bicarbonate should be avoided.]

**2. Antibacterial spectrum**: Methenamine is primarily used for chronic suppressive therapy. Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of meth- enamine. Methenamine is used to treat lower UTIs but is not effective in upper UTIs. It is most useful when the causative organism is E. coli, however it can suppress other organisms.

**3. Pharmacokinetics**: Methenamine is administered orally. In addition to formaldehyde, ammonium ion is produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, meth- enamine is contraindicated in patients with hepatic insufficiency, in which elevated levels of circulating ammonium ions would be toxic to the CNS. Methenamine is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur and the drug is eliminated in the urine.

**4. Adverse effects**: The major side effect of methenamine treatment is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. Methenamine mandelate is con- traindicated in patients with renal insufficiency, because mandelic acid may precipitate. [Note: Sulfonamides, such as cotrimoxazole, react with form aldehyde and must not be used concomitantly with methenamine. The combination increases the risk of crystalluria and mutual antagonism.]

**B. Nitrofurantoin**

Nitrofurantoin [nye-troe-FYOOR-an-toyn] sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA. Bacteria that are susceptible rarely become resistant during therapy. Antibiotic activity is greater in acidic urine. It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci are susceptible. Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase defciency. Other adverse effects include gas- trointestinal disturbances, acute pneumonitis, and neurologic problems. Interstitial pulmonary fibrosis has occurred in patients who take nitrofurantoin chronically. This is of critical importance, especially in the elderly. Contraindications: Anuria, oliguria, significant impairment of renal function (not to be used in patients with creatinine clearance less than 60 mL/min or significantly elevated serum creatinine), pregnancy at term or ≥ 38 weeks pregnant.