**Chapter 32: Protein Synthesis Inhibitors**

**I. OVERVIEW**

A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome. In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits). The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome. Thus, although drugs that interact with the bacterial target usually spare the host cells, high levels of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the host mitochondrial ribosomes. Figure 32.1 lists the drugs discussed in this chapter.

**II. TETRACYCLINES**

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings are responsible for variation in the drugs’ individual pharmacokinetics, which cause small differences in their clinical efficacy.

**A. Mechanism of action**

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Nonresistant strains concentrate the tetracyclines intracellularly. The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site. By this mechanism, bacterial protein synthesis is inhibited (Figure 32.2).

**B. Antibacterial spectrum**

As broad-spectrum bacteriostatic antibiotics, the tetracyclines are effective against gram-positive and gram-negative bacteria, as well as, against organisms other than bacteria. Tetracyclines are the drugs of choice for infections such as those shown in Figure 32.3.

**C. Resistance**

Widespread resistance to the tetracyclines limits their clinical use. The most commonly encountered, naturally occurring resistance thus producing resistance. This is accomplished by Mg2+-dependent, active effl ux of the drug, mediated by the plasmid-encoded resistance protein, TetA. Other less important mechanisms of bacterial resistance

to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Any organism resistant to one tetracycline is resistant to all.

**D. Pharmacokinetics**

**1. Absorption:** All tetracyclines are adequately, yet incompletely, absorbed after oral ingestion (Figure 32.4). However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions. Non absorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations). [Note: This presents a problem if a patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids (Figure 32.5).] *Doxycycline* [dox-I SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are almost totally absorbed on oral administration. Currently, *doxycycline* is the preferred tetracycline for parenteral administration, but *minocycline* is available intravenously as well.

**2. Distribution:** The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fl uids is adequate. Although all tetracyclines enter the cerebrospinal fl uid (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline*. *Minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva. Although useful in eradicating the meningococcal carrier state, *minocycline* is not

eff ective for central nervous system infections. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

**3. Elimination:** All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and/or its metabolites are secreted into the bile. Most tetracyclines are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration. Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives. Unlike other tetracyclines, *doxycycline* can be employed for treating infections in renally compromised patients because it is preferentially excreted via the bile into the feces. [Note: Tetracyclines are also excreted in breast milk.]

**E. Adverse effects**

**1. Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 32.6) and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.

**2. Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.

**3. Fatal hepatotoxicity:** This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.

**4. Phototoxicity:** Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with *tetracycline* [tet-rah- SYE-kleen], *doxycycline*, and *demeclocycline* [dem-e-kloe-SYE-kleen].

**5. Vestibular problems:** These side effects (for example, dizziness, nausea, and vomiting) occur particularly with *minocycline*, which concentrates in the endolymph of the ear and aff ects function. *Doxycycline* may also cause vestibular effects.

**6. Pseudotumor cerebri:** Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

**7. Superinfections:** Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

**8. Contraindications**: Renally impaired patients should not be treated with any of the tetracyclines except doxycycline. Accumulation of tetracyclines may aggravate preexisting azotemia (a higher-than- normal level of urea or other nitrogen-containing compounds in the blood) by interfering with protein synthesis, thus promoting amino acid degradation. The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age.

**III. GLYCYLCYCLINES**

Tigecycline [tye-ge-SYE-kleen] is the first available member of a new class of antimicrobial agents called glycylcyclines. Tigecycline, a derivative of minocycline, is structurally similar to the tetracyclines and has a broad-spectrum activity against multidrug-resistant gram-positive pathogens, some gram- negative organisms, and anaerobic organisms. Tigecycline is indicated for treatment of complicated skin and soft tissue infections, as well as, complicated intra-abdominal infections.

1. **Mechanism of action**

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation.

1. **Antibacterial spectrum**

Tigecycline exhibits expanded broad-spectrum activity that includes methicillin-resistant staphylococci, multidrug-resistant Streptococcus pneumoniae, and other susceptible strains of streptococcal species, vancomycin-resistant enterococci, extended-spectrum β-lactamase producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. However, tigecycline is not active against Proteus, Providencia, or Pseudomonas species.

1. **Resistance**

Tigecycline was developed to overcome the recent emergence of tetracycline class–resistant organisms that utilize efflux and ribosomal protection to confer resistance.

1. **Pharmacokinetics**

Following a 30- to 60-minute intravenous infusion every 12 hours, tigecycline rapidly distributes into the body tissues, and thus should never be used to treat bacteremia. It does not undergo significant liver metabolism, but it is primarily eliminated via biliary/fecal excretion. No dose adjustment is necessary for patients who are renally impaired. However, dose adjustment is needed in severe hepatic dysfunction.

1. **Adverse effects**

Tigecycline is associated with significant nausea and vomitting. Other adverse effect are similar to those of the tetracycline class. Other similar tetracycline adverse effects that may occur with tigecycline include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered to a pregnant woman.

**F. Drug interactions**

The cytochrome P450 liver enzymes do not metabolize *tigecycline*; therefore, it will not be affected by medications that induce or inhibit these enzymes. Although *tigecycline* does not affect prothrombin time significantly, it has been found to inhibit the clearance of *warfarin*. Therefore, it is recommended that anticoagulation be monitored closely when *tigecycline* is coadministered with *warfarin*. No dose adjustment of *digoxin* is necessary with concomitant use of *tigecycline* even though *digoxin* Cmax is increased. However, another method of contraception is suggested when *tigecycline* and oral contraceptives are co-administered because the oral contraceptives may become less effective.

**IV. AMINOGLYCOSIDES**

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones, and the carbapenems. Aminoglycosides that are derived from Streptomyces have -mycinsuffixes, whereas those derived from Micromonospora end in -micin. The terms “aminoglycoside” and “aminocyclitol” stem from their structure—two amino sugars joined by a glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their polycationic nature precludes their easy passage across tissue membranes. All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for *streptomycin* [strep-toe-MYE-sin] as described below.

**A. Mechanism of action**

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation (Figure 32.7). There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code. Polysomes become depleted because the aminoglycosides interrupt the process of polysome disaggregation and assembly. [Note: The aminoglycosides synergize with β-lactam antibiotics because of the latter’s action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium.]

**B. Antibacterial spectrum**

The aminoglycosides are effective in combination for the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa. To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, *vancomycin*, or a drug active against anaerobic bacteria. Aminoglycosides are bactericidal. The exact mechanism of their lethality is unknown because other antibiotics that affect protein synthesis are generally bacteriostatic. [Note: The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen requiring drug transport system.] Some therapeutic applications of four commonly used aminoglycosides—*amikacin* [am-i KAYsin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin*—are shown in Figure 32.8. Aminoglycosides may only be used as monotherapy for UTIs.

**C. Resistance**

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides is absent and 2) plasmid-associated synthesis of enzymes (for example, acetyl transferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is not an invariable rule. [Note: *Amikacin* is less vulnerable to these enzymes than are the other antibiotics of this group.]

**D. Pharmacokinetics**

**1. Administration:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration (Figure 32.9). Therefore, all aminoglycosides (except *neomycin* [neeoh- MYE-sin]) must be given parenterally to achieve adequate serum levels. [Note: The severe nephrotoxicity associated with *neomycin* precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery.] The bactericidal effect of amino glycosides is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die. They also have a postantibiotic effect. Because of these properties, once daily dosing with the aminoglycosides can be employed. This results in less toxicity, and is less expensive to administer. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours. [Note: The dose that is administered is calculated based on lean body mass, because these drugs do not distribute into fat.]

**2. Distribution:** All the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for *neomycin*, the aminoglycosides may be administered intrathecally or intraventricularly. High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

**3. Fate:** Metabolism of the aminoglycosides does not occur in the host. All are rapidly excreted into the urine, predominantly by glomerular filtration (see Figure 32.9). Accumulation occurs in patients with renal failure and requires dose modification.

**E. Adverse effects**

It is important to monitor plasma levels of *gentamicin*, *tobramycin*, and *amikacin* to avoid concentrations that cause dose-related toxicities (Figure 32.10). [Note: When the drugs are administered two to three times daily, both peak and trough levels are measured. Peak levels are defined as those obtained 30 minutes to 1 hour after infusion. Trough levels are obtained immediately before the next dose. When once-daily dosing is employed, only the trough concentrations are monitored for toxicity.] Patient factors, such as old age, previous exposure to aminoglycosides, and liver disease, tend to predispose patients to adverse reactions. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

**1. Ototoxicity:** Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti. Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as *cisplatin* or the loop diuretics, *furosemide*, *bumetanide*, or *ethacrynic acid,* are particularly at risk. Vertigo and loss of balance (especially in patients receiving *streptomycin*) may also occur because these drugs affect the vestibular apparatus.

**2. Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

**3. Neuromuscular paralysis:** This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate*

 r *neostigmine* can reverse the block that causes neuromuscular paralysis.

**4. Allergic reactions:** Contact dermatitis is a common reaction to topically applied *neomycin*.

**V. MACROLIDES**

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-roe- MYE-sin] was the fi rst of these drugs to find clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals who are allergic to β-lactam antibiotics. The newer members of this family, *clarithromycin* [kla-rith-roe MYE-sin] (a methylated form of *erythromycin*) and *azithromycin* [az-ith-roe-MYE sin] (having a larger lactone ring), have some features in common with, and others that improve on, *erythromycin*. *Telithro mycin* [tel-ith-roe-MYE-sin], a semisynthetic derivative of *erythromycin*, is the fi rst “ketolide” antimicrobial agent that has been approved and is now in clinical use. Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant grampositive strains.

**A. Mechanism of action**

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis (Figure 32.11). They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical or in close proximity to that for *clindamycin* and *chloramphenicol*.

**B. Antibacterial spectrum**

**1. Erythromycin:** This drug is effective against many of the same organisms as *penicillin G* (Figure 32.12); therefore, it may be used in patients who are allergic to the penicillins.

**2. Clarithromycin:** This antibiotic has a spectrum of antibacterial activity similar to that of *erythromycin*, but it is also effective against Haemophilus influenzae. Its activity against intracellular patho gens,

such as Chlamydia, Legionella, Moraxella, and Ureaplasma species and Helicobacter pylori, is higher than that of *erythromycin*.

**3. Azithromycin:** Although less active against streptococci and staphylococci than *erythromycin*, *azithromycin* is far more active against respiratory infections due to H. infl uenzae and Moraxella catarrhalis.

 *Azithromycin* is now the preferred therapy for urethritis caused by Chlamydia trachomatis. It also has activity against Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections.

**4. Telithromycin:** This ketolide drug has an antibacterial spectrum similar to that of *azithromycin*. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective.

**C. Resistance**

Resistance to *erythromycin* is becoming a serious clinical problem. For example, most strains of staphylococci in hospital isolates are resistant to this drug. Several mechanisms have been identified: 1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug; 2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and 3) the presence of a plasmid-associated *erythromycin* esterase. Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*, but *telithromycin* can be effective against macrolide-resistant organisms.

**D. Pharmacokinetics**

**1. Administration:** The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration (Figure 32.13). *Clarithromycin, azithromycin*, and *telithromycin* are stable to stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin,* but can increase that of *clarithromycin*. Intravenous administration of *erythromycin* is associated with a high incidence of thrombophlebitis. However, the incidence of thrombophlebitis reported with intravenous administration of *azithromycin* is less than one percent.

**2. Distribution:** *Erythromycin* distributes well to all body fkuids excepe CSF. It is one of the few antibiotics that diff uses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages.

All four drugs concentrate in the liver. Inflammation allows for greater tissue penetration. Similarly, *clarithromycin, azithromycin*, and *telithromycin* are widely distributed in the tissues. Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts. *Azithromycin* has the longest half-life and largest volume of distribution of the four drugs (Figure 32.14).

**3. Elimination:** *Erythromycin* and *telithromycin* are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system (see p. 14). Interference with the metabolism of drugs such as *theophylline* and *carbamazepine* has been reported for *clarithromycin* (see Figure 32.16). *Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.

**4. Excretion:** *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile (see Figure 32.13). Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

**E. Adverse effects**

**1. Epigastric distress:** This side effect is common and can lead to poor patient compliance for *erythromycin*. *Clarithromycin* and *azithromycin* seem to be better tolerated by the patient, but gastrointestinal problems are their most common side effects (Figure 32.15).

**2. Cholestatic jaundice:** This side effect occurs especially with the estolate form (not used in the U.S.) of *erythromycin*, presumably as the result of a hypersensitivity reaction to the estolate form (the lauryl salt of the propionyl ester of *erythromycin*). It has also been reported for other forms of the drug.

**3. Ototoxicity:** Transient deafness has been associated with *erythromycin*, especially at high dosages.

**4. Contraindications:** Patients with hepatic dysfunction should be treated cautiously—if at all—with *erythromycin*, *telithromycin*, or *azithromycin*, because these drugs accumulate in the liver. Recent cases of severe hepatotoxicity with *telithromycin* use have emphasized the caution needed when utilizing this agent. Additionally, *telithromycin* has the potential to prolongate the QTc interval in some patients. Therefore, it should be avoided in patients with congenital prolongation of the QTc interval and in those patients with proarrhythmic conditions. Similarly, patients who are renally compromised should be given *telithromycin* with caution. *Telithromycin* is contraindicated in patients with myasthenia gravis.

**5. Interactions:** *Erythromycin*, *telithromycin*, and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulations of these compounds (Figure 32.16). An interaction with *digoxin* may occur in some patients. In this case, the antibiotic eliminates a species of intestinal fl ora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation. No interactions have been reported for *azithromycin*.

**VI. CHLORAMPHENICOL**

*Chloramphenicol* [klor-am-FEN-i-kole] is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

**A. Mechanism of action**

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 32.17). Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone marrow toxicity.

**B. Antimicrobial spectrum**

*Chloramphenicol*, a broad-spectrum antibiotic, is active not only against bacteria, but also against other microorganisms, such as Rickettsia. Pseudomonas aeruginosa is not aff ected, nor are the Chlamydiae.

*Chloramphenicol* has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

**C. Resistance**

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol.* Another mechanism for resistance is associated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

**D. Pharmacokinetics**

*Chloramphenicol* may be administered either intravenously or orally (Figure 32.18). It is completely absorbed via the oral route because of its lipophilic nature, and is widely distributed throughout the body. It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about 10 percent of the parent compound is excreted by glomerular filtration. *Chloramphenicol* is also secreted into breast milk.

**E. Adverse effects**

The clinical use of *chloramphenicol* is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appear on mucous membranes.

**1. Anemias:** Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of *chloramphenicol* include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

**2. Gray baby syndrome:** This adverse eff ect occurs in neonates if the dosage regimen of *chloramphenicol* is not properly adjusted. Neonates have a low capacity to glucuronylated the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term “gray baby”), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.

**3. Interactions:** *Chloramphenicol* is able to inhibit some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of such drugs as *warfarin*, *phenytoin*, *tolbutamide,* and *chlorpropamide*, thereby elevating their concentrations and potentiating their effects (Figure 32.19).

**VII. CLINDAMYCIN**

*Clindamycin* [klin-da-MYE-sin] has a mechanism of action that is the same as that of *erythromycin*. *Clindamycin* is employed primarily in the treatment of infections caused by anaerobic bacteria, such as Bacteroides fragilis, which often causes abdominal infections associated with trauma. However, it is also significantly active against nonenterococcal, gram-positive cocci, including some MRSA strains. Resistance mechanisms are the same as those for *erythromycin,* and cross-resistance has been described. [Note: Clostridium difficile is always resistant to *clindamycin*.] *Clindamycin* is well absorbed by the oral route. It distributes well into all body f uids except the CSF. Adequate levels of *clindamycin* are not achieved in the brain, even when meninges are inflamed. Penetration into bone is good and occurs even in the absence of inflammation. *Clindamycin* undergoes extensive oxidative metabolism to inactive products. The drug is excreted into the bile or urine by glomerular filtration, but therapeutically effective levels of the parent drug are not achieved in the urine (Figure 32.20). Accumulation has been reported in patients with either severely compromised renal function or hepatic failure. In addition to skin rashes, the most serious adverse effect is potentially fatal pseudomembranous colitis caused by overgrowth of C. difficile, which elaborates necrotizing toxins. Oral administration of either *metronidazole* or *vancomycin* is usually effective in controlling this serious problem. [Note: *Vancomycin* should be reserved for a condition that does not respond to *metronidazole*.] Impaired liver function has also been reported.

**VIII. QUINUPRISTIN/DALFOPRISTIN**

*Quinupristin/dalfopristin* [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of thirty to seventy, respectively. They are derived from a streptomycete and then chemically modified. The drug is normally reserved for the treatment of *vancomycin*-resistant Entero coccus faecium (VRE).

**A. Mechanism of action**

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex. Thus, they synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long postantibiotic effect.

**B. Resistance**

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates *dalfopristin.* An active efflux pump can also decrease levels of the antibiotics in bacteria.

**C. Antibacterial spectrum**

The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics (for example, *methicillin*resistant staphylococci). Its primary use is in the treatment of E. faecium infections, including VRE strains. [Note: In the latter case, the effect is bacteriostatic rather than bactericidal.] The drug is not effective against Enterococcus faecalis.

**D. Pharmacokinetics**

*Quinupristin/dalfopristin* is injected intravenously (the drug is incompatible with a saline medium). The combination drug penetrates macrophages and polymorpho nucleocytes, a property that is important, because VRE are intracellular. Levels in the CSF are low. Both compounds undergo metabolism. The products are less active than the parent in the case of *quinupristin* and are equally active in the case of *dalfopristin*. Most of the parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces (Figure 32.21). Urinary excretion is secondary.

**E. Adverse eff ects**

**1. Venous irritation:** This commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.

**2. Arthralgia and myalgia:** These have been reported when higher levels of the drugs are employed.

**3. Hyperbilirubinemia:** Total bilirubin is elevated in about 25 percent of patients, resulting from a competition with the antibiotic for excretion.

**4. Interactions:** Because of the ability of *quinupristin/dalfopristin* to inhibit the cytochrome P450 (CYP3A4) isozyme, concomitant administration with drugs that are metabolized by this pathway may lead toxicities (Figure 32.22). A drug interaction with *digoxin* appears to occur by the same mechanism as that caused by *erythromycin*.

**IX. LINEZOLID**

*Linezolid* [lih-NEH-zo-lid] was introduced to combat resistant gram-positive organisms, such as *methicillin*- and *vancomycin*-resistant Staphylococcus aureus, v*ancomycin*-resistant E. faecium and E. faecalis, and *penicillin*-resistant streptococci. *Linezolid* is a synthetic oxazolidinone.

**A. Mechanism of action**

The drug inhibits bacterial protein synthesis by inhibiting the formation of the 70S initiation complex. *Linezolid* binds to a site on the 50S subunit near the interface with the 30S subunit (Figure 32.23).

**B. Resistance**

Decreased binding to the target site confers resistance on the organism. Cross-resistance with other antibiotics does not occur.

**C. Antibacterial spectrum**

The antibacterial action of *linezolid* is directed primarily against grampositive organisms, such as staphylococci, streptococci, and enterococci, as well as Corynebacterium species and Listeria monocytogenes (Figure 32.24). It is also moderately active against Mycobacterium tuberculosis. However, its main clinical use is against the resistant organisms mentioned above. Like other agents that interfere with bacterial protein synthesis, *linezolid* is bacteriostatic. However, it is cidal against streptococci and Clostridium perfringens. At this time, *linezolid* is considered non-inferior to *vancomycin* for the treatment of MRSA pneumonia. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. *Linezolid* should **not** be used for the treatment of MRSA bacteremia.

**D. Pharmacokinetics**

*Linezolid* is completely absorbed on oral administration and this formulation can be considered for treatment of bacteremia caused by VRE. An intravenous preparation is also available. The drug is widely distributed throughout the body, having a volume of distribution of 40 to 50 liters. Two metabolites that are oxidation products have been identified, one of which has antimicrobial activity. However, cytochrome P450 enzymes are not involved in their formation. The drug is excreted both by renal and nonrenal routes.

**E. Adverse effects**

*Linezolid* is well-tolerated, with some reports of gastrointestinal upset, nausea, and diarrhea, as well as headaches and rash. Thrombocytopenia was found to occur in about 2 percent of patients who were on the drug for longer than 10 days. Although no reports have appeared that *linezolid* inhibits monoamine oxidase activity, patients are cautioned not to consume large quantities of tyramine-containing foods. Early oxazolidinones had been shown to inhibit monoamine oxidase activity, and can precipitate serotonin syndrome in patients concomitantly taking SSRIs. The condition was reversible when the drug was suspended. Irreversible peripheral neuropathies and optic neuritis (causing blindness) is associated with greater than 28 days of use.