University of Technology
Applied Science Department
Biotechnology Division

Antibiotics

4th Class

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Part4

Erythromycin

Erythromycin is a macrolide antibiotic that has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often used for people who have an allergy to penicillins. For respiratory tract infections, it has better coverage of atypical organisms, including *Mycoplasma* and legionellosis. It was first marketed by Eli Lilly and Company, and it is today commonly known as EES (erythromycin ethylsuccinate, an ester prodrug that is commonly administered).

In structure, this macrocyclic compound contains a 14-membered lactone ring with ten asymmetric centers and two sugars (L-cladinose and D-desosamine), making it a compound very difficult to produce via synthetic methods. Erythromycin is produced from a strain of the actinomycete *Saccharopolyspora erythraea*.

Mechanism of Action

Erythromycin displays bacteriostatic activity or inhibits growth of bacteria, especially at higher concentrations,[12] but the mechanism is not fully understood. By binding to the 50s subunit of the bacterial 70s rRNA complex, protein synthesis and subsequent structure and function processes critical for life or replication are inhibited. Erythromycin interferes with aminoacyl translocation, preventing the transfer of the tRNA bound at the A site of the rRNA complex to the P site of the rRNA complex. Without this translocation, the A site remains occupied and, thus, the addition of an incoming tRNA and its attached amino acid to the nascent polypeptide chain is inhibited. This interferes with the production of functionally useful proteins, which is the basis of this antimicrobial action.

Adverse Effects

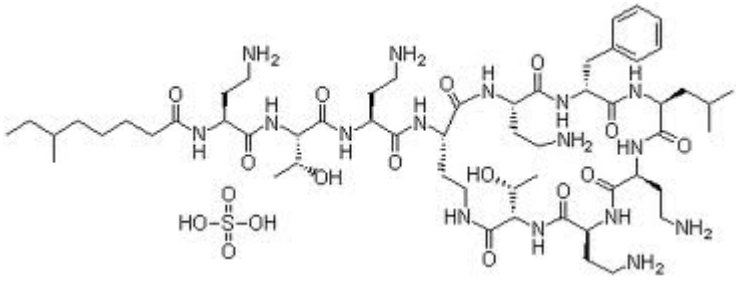
Gastrointestinal disturbances, such as diarrhea, nausea, abdominal pain, and vomiting, are very common because erythromycin is a motilin agonist. Because of this, erythromycin tends not to be prescribed as a first-line drug. However, erythromycin may be useful in treating gastroparesis due to this pro-motility effect. Intravenous erythromycin may also be used in endoscopy as an adjunct to clear gastric contents. More serious side-effects include arrhythmia with prolonged QTc intervals including Torsades de pointes and reversible deafness. Allergic reactions range from urticaria to anaphylaxis. Cholestasis, Stevens–Johnson syndrome, and toxic epidermal necrolysis are some other rare side-effects that may occur. Exposure to erythromycin (especially long courses at antimicrobial doses, and also through breastfeeding) has been linked to an increased probability of pyloric stenosis in young infants.[9] Erythromycin used for feeding intolerance in young infants has not been associated with hypertrophic pyloric stenosis.

Erythromycin estolate has been associated with reversible hepatotoxicity in pregnant women in the form of elevated serum glutamic-oxaloacetic transaminase and is not recommended during pregnancy. Some evidence suggests similar hepatotoxicity in other populations. It can also affect the central nervous system, causing psychotic reactions, nightmares and night sweats. It may also alter the effectiveness of combined oral contraceptive pills because of its effect on the gut flora. Erythromycin is an inhibitor of the cytochrome P450 system, which means that it can have a rapid effect on levels of other drugs metabolized by this system, e.g., warfarin.

Antibacterial which Inhibit Permeability of the Cell Wall

Polymyxins

Polymyxins are antibiotics, with a general structure consisting of a cyclic peptide with a long hydrophobic tail. They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids. They are produced by the Gram-positive bacterium *Bacillus polymyxa* and are selectively toxic for Gram-negative bacteria due to their specificity for the lipopolysaccharide molecule that exists within many Gram-negative outer membranes.



Polymyxins B and E (also known as colistin) are used in the treatment of Gram-negative bacterial infections. The global problem of advancing antimicrobial resistance has led to a renewed interest in their use recently. Polymyxin M is also known as "mattacin".

Mechanism of Action

After binding to lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes. The hydrophobic tail is important in causing membrane damage, suggesting a detergent-like mode of action. Removal of the hydrophobic tail of polymyxin B yields polymyxin nonapeptide, which still binds to LPS but no longer kills the bacterial cell. However, it still detectably increases the permeability of the bacterial cell wall to other antibiotics, indicating that it still causes some degree of membrane

disorganization.Gram-negative bacteria can develop resistance to polymyxins through various modifications of the LPS structure that inhibit the binding of polymyxins to LPS.

Clinical Use

Polymyxin antibiotics are relatively neurotoxic and nephrotoxic[6] and are usually used only as a last resort if modern antibiotics are ineffective or are contraindicated. Typical uses are for infections caused by strains of multidrug-resistant *Pseudomonas aeruginosa* or carbapenemase-producing Enterobacteriaceae.

Polymyxins are not absorbed from the gastrointestinal tract, and, therefore, another route of administration must be chosen, e.g., parenteral (often intravenously) or by inhalation (unless perhaps the target is bacteria in the gastrointestinal tract).

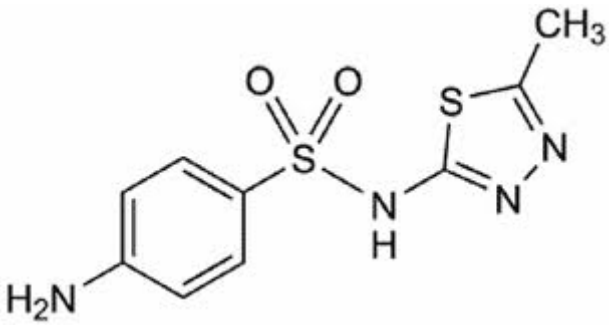
Polymyxins have less effect on Gram positive organisms, and are sometimes combined with other agents (as with Trimethoprim/polymyxin) to broaden the effective spectrum.

Antibacterial which Inhibit Folic Acid of Cell Wall

Sulfonamide

Sulfonamide or sulphonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sometimes called sulfa drugs or sulpha drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides.

Sulfa allergies are common; hence medications containing sulfonamides are prescribed carefully.



It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group, and do not cause the same hypersensitivity reactions seen in the sulfonamides.

History

Sulfonamide drugs were the first antimicrobial drugs, and paved the way for the antibiotic revolution in medicine. The first sulfonamide, trade-named Prontosil, was a prodrug. Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben. The Bayer team believed that coal-tar dyes able to preferentially bind to bacteria and parasites might be used to target harmful organisms in the body. After years of fruitless trial-and-error work on hundreds of dyes, a team led by physician/researcher Gerhard Domagk (working under the general direction of Farben executive Heinrich Hoerlein) finally found one that worked: a red dye synthesized by Bayer chemist Josef Klarer that had remarkable effects on stopping some bacterial infections in mice. The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. Prontosil, as Bayer named the new drug,

was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body. It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci. However, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later, it was accidentally discovered by a French research team, led by Ernest Fourneau, at the Pasteur Institute, that the drug was metabolized into two pieces inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulfanilamide. The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone.

The result was a sulfa craze. For several years in the late 1930s, hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulfa. This and nonexistent testing requirements led to the elixir sulfanilamide disaster in the fall of 1937, during which at least 100 people were poisoned with diethylene glycol.

This led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938. As the first and only effective antibiotic available in the years before penicillin, sulfa drugs continued to thrive through the early years of World War II.[7] They are credited with saving the lives of tens of thousands of patients, including Franklin Delano Roosevelt, Jr. (son of President Franklin Delano Roosevelt) (in 1936) and Winston Churchill. Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first-aid kit containing sulfa pills and powder, and were told to sprinkle it on any open wound. During the years

1942 to 1943, Nazi doctors conducted sulfanilamide experiments on prisoners in concentration camps.

The sulfanilamide compound is more active in the protonated form. The solubility of the drug is very low and sometimes can crystallize in the kidneys. This is a very painful experience, so patients are told to take the medication with copious amounts of water.

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5,400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

Uses of Sulfonamide

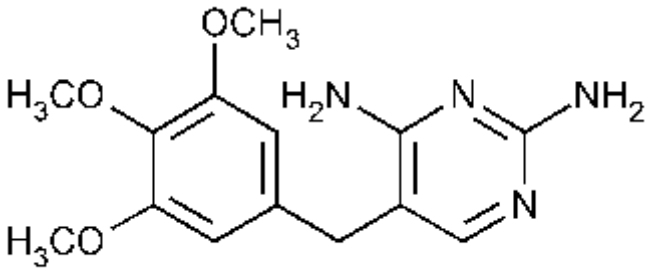
The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide, and torsemide), sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e.g., celecoxib), and acetazolamide.

Sulfasalazine, in addition to its use as an antibiotic, is also used in the treatment of inflammatory bowel disease.

In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis. As such, the microorganism will be "starved" of folate and die.

Trimethoprim

Trimethoprim is a bacteriostatic antibiotic mainly used in the prophylaxis and treatment of urinary tract infections. It belongs to the class of chemotherapeutic agents known as dihydrofolate reductase inhibitors. Trimethoprim was formerly marketed by GlaxoSmithKline under trade names including Proloprim, Monotrim and Triprim; but these trade names have been licensed to various generic pharmaceutical manufacturers.



Mechanism of Action

Trimethoprim acts by interfering with the action of bacterial dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid. Tetrahydrofolic acid is an essential precursor in the *de novo* synthesis of the intermediate Thymidine monophosphate (dTMP), precursor of DNA metabolite Thymidine triphosphate. Bacteria are unable to take up folic acid from the environment (i.e. the infection host) and are thus dependent on their own synthesis. Inhibition of the enzyme starves the bacteria of nucleotides necessary for DNA replication causing, in certain circumstances, cell lethality due to thymineless death. This drug was developed by George H. Hitchings and collaborators, who shared the

Nobel Prize for Physiology or Medicine in 1988 for the discovery of antifolates.

Clinical Indications

Trimethoprim, used as monotherapy (since 1980 in the UK), is indicated for the prophylaxis and treatment of urinary tract infections. (Co-trimoxazole, with its greater efficacy against a limited number of bacteria, and parasites remains indicated for some infections).

Contraindications and Reactions

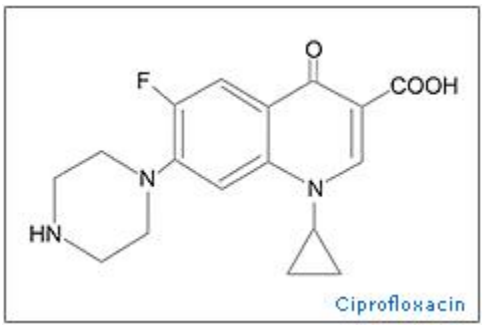
Trimethoprim can cause thrombocytopenia (low levels of platelets) by lowering folic acid levels; this may also cause megaloblastic anemia. Trimethoprim antagonizes the epithelial sodium channel (ENaC) in the distal tubule, thus acting like amiloride, this can cause hyperkalemia. Trimethoprim also competes with creatinine for secretion into the renal tubule, this can cause an art factual rise in the serum creatinine. Use in EHEC infections may lead to an increase in expression of Shiga toxin.[12] Due to the fact that it crosses the placenta and can affect folate metabolism, trimethoprim is relatively contraindicated during pregnancy, especially the first trimester. It may be involved in a reaction similar to disulfiram when alcohol is consumed after it is used, particularly when used in combination with sulfamethoxazole.

Antibacterial which Inhibit Neucleic Acid Synthesis

Ciprofloxacin

Ciprofloxacin is a synthetic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It kills bacteria by

interfering with the enzymes that cause DNA to rewind after being copied, which stops synthesis of DNA and of protein.



Ciprofloxacin was first patented in 1983 by Bayer A.G. and subsequently approved by the U.S. Food and Drug Administration (FDA) in 1987. Ciprofloxacin has 12 FDA-approved human uses and other veterinary uses, but it is often used for unapproved uses (off-label). Ciprofloxacin interacts with other drugs, herbal and natural supplements, a characteristic it shares with other widely used antibacterial drugs such as amoxicillin, trimethoprim, azithromycin, cephalexin, and doxycycline.[4]

Mechanism of Action

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division.

This mechanism can also affect mammalian cell replication. In particular, some congeners of this drug family display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and *in vivo* tumor models.

Although quinolones are highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is not known. Quinolone-induced DNA damage was first reported in 1986 (Hussy and others.).

Recent studies have demonstrated a correlation between mammalian cell cytotoxicity of the quinolones and the induction of micronuclei. As such, some fluoroquinolones may cause injury to the chromosome of eukaryotic cells. There continues to be debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe adverse reactions experienced by some patients following fluoroquinolone therapy.

Bacterial Resistance

Ciprofloxacin is commonly used for urinary tract and intestinal infections (traveler's diarrhea) and was once considered a powerful antibiotic of last resort, used to treat especially tenacious infections. Not all physicians agreed with this assessment, as evidenced by its widespread use to treat minor infections as well as non-approved uses. As a result in recent years many bacteria have developed resistance to this drug, leaving it significantly less effective than it would have been otherwise. Resistance to ciprofloxacin and other fluoroquinolones may evolve rapidly, even during a course of treatment. Numerous pathogens, including *Staphylococcus aureus*, enterococci, *Streptococcus pyogenes* and *Klebsiella pneumoniae (quinolone-resistant)* now exhibit resistance worldwide.Widespread veterinary usage of the fluoroquinolones, particularly in Europe, has been implicated. In the meanwhile, some *Burkholderia cepacia*, *Clostridium innocuum* and *Enterococcus faecium* have developed resistance to Ciprofloxacin to varying degrees.

Fluoroquinolones had become the most commonly prescribed class of antibiotics to adults in 2002. Nearly half (42%) of those prescriptions were for conditions not approved by the FDA, such as acute bronchitis, otitis media, and acute upper respiratory tract infection, according to a study that was supported in part by the Agency for Healthcare Research and Quality. Additionally, they were commonly prescribed for medical conditions that were not even bacterial to begin with, such as viral infections, or those to which no proven benefit existed.

Medical Uses

Ciprofloxacin is used to treat a number of infections including: infections of bones and joints, endocarditis, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, chancroid, among others.

- Urinary tract infections (not recommended as a first-line antibiotic)
- Acute uncomplicated cystitis in females
- Chronic bacterial prostatitis (not recommended as a first-line antibiotic choice)
- Lower respiratory tract infections (not recommended as a first-line antibiotic choice)
- Acute sinusitis (not recommended as a first-line antibiotic choice)
- Skin and skin structure infections
- Bone and joint infections
- Infectious diarrhea
- Typhoid fever (enteric fever) caused by *Salmonella typhi*
- Uncomplicated cervical and urethra gonorrhea (due to *N. gonorrhoeae*) – however, this indication is no longer effective in some areas (for example, Asian countries, United States (including

Hawaii), Canada, and Scotland) due to bacterial resistance. Fluoroquinolones are no longer recommended in the USA for this indication.

Ciprofloxacin is not recommended for the treatment of tuberculosis. As well as in combination with other specific drugs:

- Complicated intra-abdominal infections (in combination with metronidazole);
- Empirical therapy for febrile neutropenic patients (in combination with piperacillin)

Oral and intravenous fluoroquinolones are not licensed by the U.S. FDA for use in children due to the risk of permanent injury to the musculoskeletal system, with two exceptions as outlined below. Within the studies submitted in response to a Pediatric Written Request (ciprofloxacin, circa 2004) the rate of arthropathy was reported to be 9.3% at one month and 13.6% at one year.[19] As such the pediatric use of ciprofloxacin is restricted to proven complicated urinary tract infections and pyelonephritis due to *E. coli* and inhalation anthrax.

Although claimed to be effective, ciprofloxacin is not to be considered a first line agent for inhalation anthrax in the pediatric population. However, the fluoroquinolones are licensed to treat lower respiratory infections in children with cystic fibrosis in the UK. Current recommendations by the American Academy of Pediatrics note the systemic use of ciprofloxacin in children should be restricted to infections caused by multidrug resistant pathogens or when no safe or effective alternatives are available.

Indications include:

- Complicated urinary tract infections and pyelonephritis due to *Escherichia coli*.
- Inhalational anthrax (postexposure).

Ciprofloxacin is not recommended to treat community acquired pneumonia (CAP) as a stand-alone first-line agent. The current guidelines (Infectious Diseases Society of America 2007) state, in very limited circumstances, ciprofloxacin or levofloxacin should be combined with other drugs such as a beta-lactam drug to treat specific CAP infections, but neither drug is recommended to be used separately as a stand-alone first-line agent. In addition, the current guidelines state: "Data exist suggesting that resistance to macrolides and older fluoroquinolones (ciprofloxacin and levofloxacin) results in clinical failure. Other studies have shown that repeated use of fluoroquinolones predicts an increased risk of infection with fluoroquinolone-resistant pneumococci. As such, the general opinion stated in 1994 that ciprofloxacin "is not to be considered a suitable agent for use in general practice for the blind initial treatment of chest infections...." does not appear to have changed within these current guidelines.

Antibiotics may not improve the long-term clinical outcome for sinusitis. When prescribed for chronic bronchitis and acute bacterial sinusitis, the use of the fluoroquinolone class offers no compelling advantages over established treatment. Nor does antibiotic treatment help sore throats. The use of antibiotics such as ciprofloxacin to treat bronchitis is to be considered unnecessary and as such exposes the patient to an unacceptable risk of suffering a severe adverse reaction. Additionally, antibiotics have no effect upon viral infections, such as the common head cold or viral respiratory infections.

Ciprofloxacin should not be used in infants as they have not developed sufficient enzymes to metabolize the drug. Severe adverse reaction may occur in this patient group. Ciprofloxacin may be licensed for other uses, or restricted, by the various regulatory agencies worldwide.

Contraindications

As noted above, under licensed use, ciprofloxacin is also now considered to be contraindicated for the treatment of certain sexually transmitted diseases by some experts due to bacterial resistance.

There are only four contraindications found within the 2009 package insert:

- "Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug."
- "Concomitant administration with tizanidine is contraindicated."
- "Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components."
- "Local I.V. site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions that resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen."

Ciprofloxacin is also considered to be contraindicated within the pediatric population (except for the indications outlined under licensed use above), pregnancy, nursing mothers, and in patients with epilepsy or other seizure disorders.

- **Pregnancy**

The fluoroquinolones rapidly cross the blood-placenta and blood-milk barriers, and are extensively distributed into the fetal tissues. For this reason, the fluoroquinolones are contraindicated during pregnancy due to the risk of spontaneous abortions and birth defects. The fluoroquinolones have also been reported as being present in the mother's milk and are passed on to the nursing child, which may increases the risk of the child suffering from this syndrome as well, even though the child had never been prescribed or taken any of the drugs found within this class.

- **Pediatric population**

Fluoroquinolones are not licensed by the U.S. FDA for use in children due to the risk of fatalities[38] as well as permanent injury to the musculoskeletal system, with two exceptions. Ciprofloxacin is being licensed for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*, and inhalational anthrax (postexposure), and levofloxacin was recently licensed for the treatment of inhalational anthrax (postexposure). However, the fluoroquinolones are licensed to treat lower respiratory infections in children with cystic fibrosis in the UK.

Within the studies submitted in response to a Pediatric Written Request (ciprofloxacin, circa 2004), the rate of atrophy was reported to be 9.3%. Within the BPCA Pediatric Studies Summary for ciprofloxacin, it was stated that the overall incidence of adverse events at six weeks was 41%.

This would be consistent with the safety profile found with the other fluoroquinolones studied in the pediatric population. As such, the current ban on the use of the fluoroquinolones in the pediatric population is both reasonable and supported by various clinical studies. The most recent long term study, *BAY 0 9867 Cipro Pediatric Use Study (QUIP)*, which followed pediatric patients from 1999–2008, supports the current expert opinion that the risk of permanent injury continues to outweigh the potential benefits of ciprofloxacin therapy in the pediatric population.

Within the United States, the FDA has stated it is their intention to pursue the licensing of the fluoroquinolones for pediatric use in spite of the evidence presented at that 62 Meeting of the Anti-Infective Drugs Advisory Committee that the fluoroquinolones cause irreversible joint damage in the pediatric population.

Adverse Effects

The safety of fluoroquinolones is similar to that of other antibiotics. In most, adverse reactions are mild to moderate; however, occasionally serious adverse effects occur. There have been a number of regulatory actions taken as a result of such adverse reactions, which included published warnings, Subsequent to this, on 25 June 2007, the U.S. FDA required manufacturers to add an additional warning to the package inserts that stated "Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported in patients receiving therapy with quinolones, including ciprofloxacin."[48] It was not until 2008, (four years later) that the label revisions for ciprofloxacin included any warnings concerning heart problems (prolonged QT interval / torsade de pointes). Warnings concerning

rhabdomyolysis and Stevens–Johnson syndrome was still absent from the package inserts as of September 2009.

The serious adverse effects that may occur as a result of ciprofloxacin therapy include irreversible peripheral neuropathy, spontaneous tendon rupture and tendonitis, acute liver failure or serious liver injury (hepatitis), QTc prolongation/torsades de pointes, toxic epidermal necrolysis (TEN), and Stevens–Johnson syndrome, severe central nervous system disorders (CNS)[25] and Clostridium difficile associated disease as well as photosensitivity/phototoxicity reactions.

Psychotic reactions and confusional states, acute pancreatitis, bone marrow depression, interstitial nephritis and hemolytic anemia may also occur during ciprofloxacin therapy. Additional serious adverse reactions include temporary, as well as permanent, loss of vision, irreversible double vision, drug induced psychosis and chorea (involuntary muscle movements), impaired color vision, exanthema, abdominal pain, malaise, drug fever, dysaesthesia and eosinophilia. Pseudotumor cerebri, commonly known as idiopathic intracranial hypertension (IIH), (also referred to as increased intracranial pressure), has been reported to occur as a serious adverse reaction to ciprofloxacin. Children and the elderly are at a much greater risk of experiencing such adverse reactions. Tendonitis and other forms of tendon damage may manifest during fluoroquinolone therapy, and long after it had been discontinued.

Serious visual complications have also been reported to occur with ophthalmic fluoroquinolone therapy, which may also occur with ciprofloxacin eye drops, especially corneal perforation, but also evisceration and enucleation. This increased incident of corneal perforation may be due to fluoroquinolones causing alterations in stromal collagen, leading to a reduction in tectonic strength. As noted previously

permanent double vision (diplopia) has also been reported. An unusual case of seizures has also been reported with ciprofloxacin ear drops in an elderly patient. Some groups refer to these adverse events as "fluoroquinolone toxicity". These groups of people claim to have suffered serious long term harm to their health from using fluoroquinolones. This has led to a class action lawsuit by people harmed by the use of fluoroquinolones, as well as legal action by the consumer advocate group Public Citizen. Partly as a result of the efforts of the State of Illinois and Public Citizen, the FDA ordered black box warnings on all fluoroquinolones advising consumers of the possible toxic effects of fluoroquinolones on tendons.

II. Antifungal Drugs

An antifungal medication is a medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Such drugs are usually obtained by a doctor's prescription or purchased over-the-counter.

Mechanism of Action

Antifungal work by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effects on the host. Unlike bacteria, both fungi and humans are eukaryotes. Thus fungal and human cells are similar at the molecular level. This makes it more difficult to find or design drugs that target fungi without affecting human cells. As a consequence, many antifungal drugs cause side-effects. Some of these side-effects can be life-threatening if the drugs are not used properly.

Classes

1. Polyene Antifungal

A polyene is a molecule with multiple conjugated double bonds. A polyene antifungal is a macrocyclic polyene with a heavily hydroxylated region on the ring opposite the conjugated system. This makes polyene antifungals amphiphilic. The polyene antimycotics bind with sterols in the fungal cell membrane, principally ergosterol. This changes the transition temperature of the cell membrane, thereby placing the membrane in a less fluid, more crystalline state. As a result, the cell's contents including monovalent ions (K+, Na+, H+, and Cl-), small organic molecules leak and this is regarded one of the primary ways cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible.

However, at therapeutic doses, some amphotericin B may bind to animal membrane cholesterol, increasing the risk of human toxicity. Amphotericin B is nephrotoxic when given intravenously. As a polyene's hydrophobic chain is shortened, its sterol binding activity is increased. Therefore, further reduction of the hydrophobic chain may result in it binding to cholesterol, making it toxic to animals. This group includes Nystatin and Amphotericin B.

2. Imidazole, triazole, and thiazole antifungals

Azole antifungal drugs inhibit the enzyme lanosterol 14 α-demethylase; the enzyme necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth.

3. Allylamines

Allylamines inhibit squalene epoxidase, another enzyme required for ergosterol synthesis.

4. Echinocandins

Echinocandins may be used for systemic fungal infections in immunocompromised patients, they inhibit the synthesis of glucan in the cell wall via the enzyme 1,3-β glucan synthase:

- Anidulafungin
- Caspofungin
- Micafungin

Echinocandins are poorly absorbed when administered orally. When administered by injection they will reach most tissues and organs with concentrations sufficient to treat localized and systemic fungal infections.

Nystatin

Nystatin (originally named Fungicidin) is a polyene antifungal medication to which many molds and yeast infections are sensitive, including *Candida*. Due to its toxicity profile, there are currently no injectable formulations of this drug on the US market. However, nystatin may be safely given orally as well as applied topically due to its minimal absorption through mucocutaneous membranes such as the gut and the skin.

Mechanism of action

Like amphotericin B and natamycin, nystatin binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K^+ leakage

and death of the fungus. Ergosterol is fairly unique to fungi, so the drug does not have such catastrophic effects on animals or plants.

Uses

Cutaneous, vaginal, mucosal and esophageal *Candida* infections usually respond well to treatment with nystatin. *Cryptococcus* is also sensitive to nystatin. In the UK its licence for treating neonatal oral thrush is restricted to those over the age of one month (miconazole is an appropriate alternative for younger babies).

Nystatin is often used as prophylaxis in patients who are at risk for fungal infections, such as AIDS patients with a low $CD4^+$ count and patients receiving chemotherapy. It is prescribed in *units*, with doses varying from 100,000 (for oral infections) to 1 million (for intestinal ones). As it is not absorbed from the gut, it is safe for oral use and does not have problems of drug interactions.

It is also used in cellular biology as an inhibitor of the lipid raft-caveolae endocytosis pathway on mammalian cells, at concentrations around 3 µg/mL. Nystatin is also used as a tool by scientists performing "perforated" patch-clamp electrophysiologic recordings of cells. When loaded in the recording pipette, it allows for measurement of electrical currents without washing out the intracellular contents, because it forms pores in the cell membrane that are permeable to only monovalent ions.

Amphotericin B

Amphotericin B is a polyene antifungal drug, often used intravenously for systemic fungal infections. It was originally extracted from *Streptomyces nodosus*, a filamentous bacterium, in 1955 at the Squibb Institute for Medical Research from cultures of an undescribed streptomycete isolated

from the soil collected in the Orinoco River region of Venezuela. Its name originates from the chemical's amphoteric properties. Two amphotericins, amphotericin A and amphotericin B are known, but only B is used clinically, because it is significantly more active in vivo. Amphotericin A is almost identical to amphotericin B (having a double C=C bond between the 27th and 28th carbons), but has little antifungal activity. Currently, the drug is available as plain amphotericin B, as a cholesteryl sulfate complex (ABCD), as a lipid complex (ABLC), and as a liposomal formulation (LAmB). The latter formulations have been developed to improve tolerability for the patient, but may show considerably different pharmacokinetic characteristics compared to plain amphotericin B.

Mechanism of action

As with other polyene antifungals, amphotericin B binds with ergosterol, a component of fungal cell membranes, forming a transmembrane channel that leads to monovalent ion (K^+, Na^+, H^+ and Cl^-) leakage, which is the primary effect leading to fungal cell death. Recently, however, researchers found evidence that pore formation is not necessarily linked to cell death (i.e. Angewandte Chemie Int. Ed. Engl. 2004). The actual mechanism of action may be more complex and multifaceted.

Mechanism of Toxicity

Mammalian and fungal membranes both contain sterols, a primary membrane target for amphotericin B. Because mammalian and fungal membranes are similar in structure and composition, this is one mechanism by which amphotericin B causes cellular toxicity. Amphotericin B molecules can form pores in the host membrane as well

as the fungal membrane. This impairment in membrane barrier function can have lethal effects. Bacteria are not affected as their cell membrane does not contain sterols. Amphotericin administration is limited by infusion-related toxicity. This is thought to result from innate immune production of pro inflammatory cytokines.

Uses

Antifungal

Oral preparations of amphotericin B are used to treat thrush; these are virtually nontoxic, in contrast to typical intravenous therapy (IV) doses. One of the main intravenous uses is in treating various systemic fungal infections (e.g., in critically ill, comorbidly infected or immunocompromised patients), including cryptococcal meningitis.

Amphotericin B is also commonly used in tissue culture to prevent fungi from contaminating cell cultures. It is usually sold in a concentrated solution, either on its own or in combination with the antibiotics penicillin and streptomycin.

Antiprotozoa

Another IV use is as a drug of last resort in otherwise-untreatable parasitic protozoan infections such as visceral leishmaniasis and primary amoebic meningoencephalitis.

Side Effects

Amphotericin B is well known for its severe and potentially lethal side-effects. Very often, a serious acute reaction after the infusion (1 to 3 hours later) is noted, consisting of high fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, dyspnea and tachypnea, drowsiness, and generalized weakness. This reaction sometimes subsides

with later applications of the drug, and may in part be due to histamine liberation. An increase in prostaglandin synthesis may also play a role. This nearly universal febrile response necessitates a critical (and diagnostically difficult) professional determination as to whether the onset of high fever is a novel symptom of a fast-progressing disease, or merely the induced effect of the drug. To decrease the likelihood and severity of the symptoms, initial doses should be low, and increased slowly. Acetaminophen, pethidine, diphenhydramine, and/or hydrocortisone have all been used to treat or prevent the syndrome, but the prophylactic use of these drugs is often limited by the patient's condition.

Intravenously administered amphotericin B has also been associated with multiple organ damage in therapeutic doses. Nephrotoxicity (kidney damage) is a frequently reported side-effect, and can be severe and/or irreversible. It is much milder when delivered via liposomes (AmBisome), and this is, therefore, the preferred method (see below). The integrity of the liposome is disrupted when it binds to the fungal cell wall, but is not affected by the mammalian cell membrane, thus less toxicity is seen.[9] The association with liposomes decreases the exposure of the kidneys to amphotericin B, which explains less nephrotoxic effects.[10] In addition, electrolyte imbalances (e.g., hypokalemia and hypomagnesemia) may also result. In the liver, increased liver enzymes and hepatotoxicity (up to and including fulminant liver failure) are common. In the circulatory system, several forms of anemia and other blood dyscrasias (leukopenia, thrombopenia), serious cardiac arrhythmias (including ventricular fibrillation), and even frank cardiac failure have been reported. Skin reactions, including serious forms, are also possible.

Interactions

- Flucytosine: Toxicity of flucytosine is increased and allows a lower dose of amphotericin B. Amphotericin B may also facilitate entry of flucystosine into the fungal cell by interfering with the permeability of the fungal cell membrane.
- Diuretics or cisplatin: Increased renal toxicity and increased risk of hypokalemia
- Corticosteroids: Increased risk of hypokalemia
- Cytostatic drugs: Increased risk of kidney damage, hypotension and bronchospasms
- Other nephrotoxic drugs (like Aminoglycosides) : Increased risk of serious renal damage, monitor kidney function closely
- Foscarnet, ganciclovir, tenofovir, adefovir: Risk of hematological and renal side-effects of amphotericin B are increased.
- Transfusion of leukocytes : Risk of pulmonal (lung) damage occurs. Space the intervals between the application of amphotericin B and the transfusion, and monitor pulmonary function.