"Pharmacology"

Lecture (4)
Protein synthesis inhibitors:

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. 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 may cause toxic effects as a result of interaction with mitochondrial ribosomes.

Protein synthesis inhibitors include:

1. Tetracyclines
2. Aminoglycosides
3. Macrolides
4. Chloramphenicol
5. Clindamycin
6. Quinupristin / dalfopristin
7. Linezolid

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.

Mechanism of action:

Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport.

Susceptible cells concentrate the drug intracellularly. Once inside the cell, tetracyclines bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. This prevents addition of amino acids to the growing peptide.

Classification:
Tetracyclines are classified as short action (chlortetracycline and tetracycline), intermediate acting (demeclocycline), or long acting (doxycycline and minocycline) based on serum ½ lives.

Antibacterial spectrum:

Tetracyclines are broad spectrum bacteriostatic antibiotics that inhibit protein synthesis. They are active against many gram +ve and gram –ve bacteria, including anaerobes, spirochetes, mycoplasma, chlamydiae and rickettsiae; and against some protozoa. The antibacterial activities of most tetracyclines are similar except that tetracycline-resistant strains may remain susceptible to doxycycline or minocycline.

Resistance:

Three mechanisms of resistance to tetracycline have been described:

1. Inability of the organism to accumulate the drug. This is accomplished by Mg-dependent active efflux of the drug.
2. Enzymatic inactivation of the drug.
3. The production of bacterial proteins that prevent tetracyclines from binding to the ribosome.

Pharmacokinetics:

1. Absorption: All tetracyclines are adequately but incompletely absorbed after oral ingestion. However, taking these drugs concomitantly with dairy foods decreases absorption due to the formation of non-absorbable chelates with calcium ions. Non-absorbable chelates are also formed with other divalent and trivalent cations (e.g., those found in magnesium and aluminum antacids and in iron preparations). Doxycycline and minocycline are almost totally absorbed on oral administration.
2. Distribution:
   Tetracyclines are distributed widely to tissues and body fluids. They bind to tissues undergoing calcification e.g., teeth and bones. Although all
tetracyclines enter the CSF, levels are insufficient for therapeutic efficacy, except for minocycline. Minocycline enters the brain in the absence of inflammation and also appear in tears and saliva. Although useful in eradicating the meningococcal carrier state, minocycline is ineffective for CNS infections. All tetracyclines cross the placental barrier, and concentrate in fetal bones and dentition.

3. Fate:
   All the tetracyclines are metabolized in the liver 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. 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. Tetracyclines are also excreted in breast milk.

Clinical uses:
1. A tetracycline is the drug of choice in infections with mycoplasma pneumonia, chlamydiae and rickettsiae.
2. They are used in combination regimens to treat gastric and duodenal ulcer disease caused by helicobacter pylori.
3. Tetracyclines rapidly stop the shedding of vibrios in cholera, but tetracycline resistance has appeared during epidemics.
4. A tetracycline usually in combination with an aminoglycosides is indicated for plague, tularemia, and brucellosis.
5. A tetracycline is indicated in the treatment of some spirochetes as lyme disease and leptospirosis.
6. Tetracyclines are sometimes employed in the treatment of protozoal infections e.g those due to Entamoeba histolytica or Plasmodium falciparum.
7. Minocycline can eradicate the meningococcal carrier state.
8. Demeclocycline inhibits the action of ADH in the renal tubule and has been used in the treatment of inappropriate secretion of ADH.
9. They may be employed in serious gram +ve and gram –ve infections.

Adverse effects:

1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for non-compliance in patients treated with these drugs.
2. Effects on calcified tissue: Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporarily 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, doxycycline, and demeclocycline.
5. Vestibular problems: Dizziness, nausea and vomiting occur particularly with minocycline which concentrates in the endolymph of the ear. Doxycycline may also cause vestibular effects.
6. Pseudotumor cerebri: Intracranial hypertension characterized by headache and blurred vision may also cause vestibular effects.
7. Superinfections: Overgrowth of candida in the vagina or resistant staphylococci in the intestine may occur. Pseudomembranous colitis due to 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 tetracycline may aggravate preexisting azotemia by interfering with protein synthesis, thus promoting amino acid degradation. The tetracyclines should not be employed in pregnant or breast feeding woman or in children under 8 years of age.
Aminoglycosides:

Aminoglycosides antibiotics had been the mainstays for treatment of serious infections due to aerobic gram –ve bacilli. The group includes streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, netilmicin. Neomycin and kanamycin are now largely limited to tropical or oral use. All members of this family are believed to inhibit bacterial protein synthesis.

Mechanism of action:

Susceptible gram –ve 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 cell membrane. The antibiotic then binds to the 30S ribosomal subunit and distorts its structure, thus interfering with the initiation of protein synthesis. It also allows misreading of the mRNA, causing mutations or premature chain termination. Polysomes become depleted.

Resistance: resistance can be caused by:

1. Decreased uptake of the drug when the oxygen dependent transport system or porin channels are absent.
2. An altered 30S ribosomal subunit aminoglycoside-binding site that has a decreased affinity for the drug.
3. Plasmid associated synthesis of enzymes (e.g. acetyltransferase, nucleotidyltransferase, phosphotransferase) that modify and inactivates aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross resistance is not an invariable rule. Amikacin is less vulnerable to these enzymes.

Antibacterial spectrum:
The aminoglycosides are effective in the empirical treatments of infections suspected of being due to aerobic gram–ve bacilli including Pseudomonas aeuroginosa. To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactom, or vancomycin, or a drug active against anaerobic bacteria. The aminoglycosides synergize with β-lactom antibiotics, because the latter’s action on cell wall synthesis, which enhances diffusion of the aminoglycosides in the bacterium. All aminoglycosides are bactericidal, some therapeutic applications of four commonly used aminoglycosides – amikacin, gentamicin, tobramycin and streptomycin are listed below:

1. Enterococcus species: gentamicin or streptomycin plus vancomycin or a β-lactom, such as penicillin-G
2. Pseudomonas aeuroginosa: infections in immunocompromised patients and in burn victims: tobramycin in combination with an anti-pseudomonal penicillin, such as piperacillin or ticarcillin.
3. Klebsiella species: an aminoglycoside e.g. gentamicin plus an anti-pseudomonal penicillin.
4. Yersinia pestis, Francisella tularensis, and brucella species: gentamicin or streptomycin plus doxycycline.

Pharmacokinetics:

The highly polar structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except neomycin) must be given parenterally to achieve adequate serum levels. 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 aminoglycosides 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 post antibiotic effect. Because of these properties, once-daily dosing can be employed. The exceptions are pregnancy,
neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hrs.

Aminoglycoside levels achieved in most tissues are low, and concentrations in the 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.

All aminoglycosides are rapidly excreted into the urine, predominantly by glomerular filtration. Accumulation occurs in patients with renal failure and requires dose modification.

Adverse effects:

It is important to monitor plasma levels of aminoglycosides to avoid concentrations that cause dose related toxicities. When drugs are administrated 2-3 times daily, both peak (1/2 – 1 hrs. after infusion) and trough (before the next dose) levels are measured. When once-daily dosing is employed, only trough concentrations are monitored. All aminoglycosides are ototoxic and nephrotoxic. Ototoxicity and nephrotoxicity are more likely to be encountered when therapy is continued for more than 5 days, at higher doses, in the elderly, and in the setting of renal insufficiency:

1. Ototoxicity: ototoxicity can manifest itself either as auditory damage (mostly with neomycin, kanamycin, and amikacin), or as vestibular damage (mostly with streptomycin and gentamicin). Ototoxicity is directly related to high peak plasma levels and the duration of treatment. Patients simultaneously receiving another ototoxic drug, such as loop diuretics or cisplatin are particularly at risk. Deafness may be irreversible, and has been known to affect fetuses in utero.
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, renal impairment to severe, acute tubular necrosis, which can be irreversible. Neomycin, tobramycin, and gentamicin are the most nephrotoxic. Concomitant use with loop diuretics, vancomycin, or amphotericin can potentiate nephrotoxicity.

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 Ach from prejunctional nerve endings and the sensitivity of the post-synaptic site. Patients with myasthenia gravis are particularly at risk.

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