Pharmacology Lecture 2 antibacterial drugs. Dr.Siham

AMINOGLYCOSIDES

Chemistry:- Aminoglycosides consist of two or three amino sugars joined to a hexose(aminocyclitol) by glycosidic bonds. Numerous amino groups contribute to their very polar and basic character. Sulfate salts are water soluble.

Mechanism of action.

The aminoglycosides bind to the 30S ribosomal fragment and inhibit the rate of protein synthesis and the fidelity of mRNA translation which results in the synthesis of abnormal proteins (Their uptake by bacteria includes an energy-dependent step (EDP1), which is oxygen linked and is inhibited by an anaerobic or acidic environment and by Ca^{2+} or Mg^{2+}.

They are bactericidal against Gram(–) aerobes and are synergistic with β-lactams against many Gram(+) pathogens .

Therapeutic uses:-

The aminoglycosides are used in the treatment of Gram(–) infections in all species.

1. Streptomycin and dihydrostreptomycin are the oldest members of this class of antibiotics.

Their use has declined with the advent of broader spectrum aminoglycosides such as gentamicin and amikacin.

2. Neomycin is used orally for the treatment of enteric infections and topically for treating skin, ear, and eye infections.

3. **Gentamicin and amikacin** are expanded spectrum aminoglycosides with activity against Pseudomonas, Proteus, Staphylococcus, and corynebacterium spp., as well as Gram(–) aerobes.

They are used in all species for the treatment of susceptible infections

of the skin, respiratory tract, ear, eye, urinary tract, and septicemia.

Tobramycin

is similar to gentamicin but has more potent antipseudomonal activity

and reduced nephrotoxicity.

4. **Kanamycin** has an antimicrobial spectrum similar to gentamicin except it is not effective against Pseudomonas spp. It is currently used in veterinary medicine only as an oral preparation combined with bismuth subcarbonate and aluminum magnesium silicate for the treatment of bacterial enteritis in dogs and for symptomatic relief of the associated diarrhea.

G. Adverse effects

1. The aminoglycosides are relatively more toxic than other classes of antimicrobials.

Toxicity is reversible if the treatment is stopped early. Dosage regimens must be adjusted in animals with decreased renal function and they should not be used with other ototoxic or nephrotoxic drugs such as furosemide or amphotericin B.

2. Ototoxicity is due to progressive damage to cochlear sensory cells and/or vestibular cells of the inner ear resulting in deafness and ataxia, respectively.

3. Nephrotoxicity is due to the damage of the membranes of proximal tubular cells resulting in a loss of brush border enzymes, impaired absorption, proteinuria, and decreased glomerular filtration rate.

4. Neuromuscular blockade is a relatively rare adverse effect of aminoglycosides. It is caused by prejunctional blockade of acetylcholine

(ACh) release and decreased postsynaptic sensitivity to ACh. Muscle paralysis and apnea are treated with calcium gluconate .

TETRACYCLINES

Chemistry. The tetracyclines are polycyclic compounds that are amphoteric and that fluoresce when exposed to ultraviolet light.

Most are prepared as the hydrochloride salt .

They form insoluble chelates with cations such as Ca^{2+}, Mg^{2+}, Fe^{3+}, and Al^{3+}.

They accumulate in growing teeth and bones.

Mechanism of action.

Tetracyclines reversibly inhibit bacterial protein synthesis by binding to the

30S ribosome and preventing attachment of aminoacyl tRNA to the mRNA-

ribosome complex . They block the addition of amino acids to the growing peptide chain .

They are bacteriostatic and broad spectrum. Their antimicrobial spectrum

includes Gram(+) and Gram(–) aerobes and anaerobes, Rickettsiae,

Spirochetes, Chlamydiae, Mycoplasma, and some protozoans such as Anaplasma spp. and Haemobartonella spp.

Therapeutic uses.

1. Large animals. **Tetracycline**, **chlortetracycline**, and **oxytetracycline** are used in the treatment of local and systemic bacterial, chlamydial, rickettsial, and protozoal infections in cattle ,sheep, horses, and swine and as feed additive/growth promoters in cattle and swine.

2. Small animals. **Doxycycline**, **minocycline**, and **tetracycline** are used in the treatment of respiratory and urinary tract infections in dogs and cats and

as specific therapy for Borrelia (Lyme disease), Brucella, Haemobartonella, and Ehrlichia spp. infections.

They are also effective in the treatment of psittacosis in birds.

Preslaughter withdrawal of oxytetracycline in food animals.

1. The Food Animal Residue Avoidance Databank (FARAD) recommends, in cattle, an extralabel withdrawal of 28 days for intrauterine treatment. It also recommends testing milk after intrauterine treatment, as there is inter-cow variability in the residue elimination profiles in milk.

2. FARAD recommends an extralabel preslaughter withdrawal of 28 days in sheep and goats after IM or SC oxytetracycline administration. A milk withdrawal of 96 hours is recommended for sheep and goats.

3. For swine, FARAD recommends an extralabel preslaughter period of 14 days following administration of tetracycline product in feed or water to swine.

Adverse effects.

1. The tetracyclines (except doxycycline and minocycline) are potentially nephrotoxic and should be avoided if renal function is impaired .

2. Permanent staining of unerupted teeth may occur in young animals due to the formation of a tetracycline-calcium phosphate complex in enamel and dentine.

3. Suprainfections of fungi, yeast, or resistant bacteria may occur in the GI tract with prolonged administration of broad-spectrum antibiotics such as the tetracyclines. GI adverse effects are seen frequently in cats.

Oral tetracyclines should not be used with herbivores because of serious effects on ruminant digestion.

4. Antianabolic effects are seen at high doses because of binding to mitochondrial ribosomes. This may result in an elevated blood urea nitrogen (BUN) especially with preexisting renal disease.

5. Photosensitivity and hepatotoxicity are rare side effects in animals.

MACROLIDES

Chemistry. The macrolide antibiotics include **erythromycin**, **azithromycin**, **clarithromycin**, **tulathromycin**, **tylosin**, and **tilmicosin**. They are basic, lipid-soluble compounds consisting of a lactone ring to which are attached deoxy sugars. They are prepared as sulfate salts or as esterified salts of stearate, tartrate, estolate, or lactobionate.

Mechanism of action.

Macrolides are bacteriostatic by inhibiting bacterial protein synthesis.

They bind to the 50S ribosome to prevent translocation of amino acids to the growing peptide chain .

Binding sites on the 50S ribosome overlap with binding sites of chloramphenicol and the lincosamides (especially clindamycin) and combination therapy should be avoided .

Their antimicrobial activity is primarily against Gram(+) aerobes and anaerobes and Mycoplasma spp. Tylosin and tiamulin are effective against some Gram(–) pathogens, including Pasteurella and Haemophilus spp.

Therapeutic uses

1. **Erythromycin** is an alternate to penicillin for infections caused by Gram(+) aerobes and anaerobes in dogs, cats, and horses.

It is a drug often chosen for the treatment of enteritis caused by Campylobacter jejuni in dogs and foals and for Rhodococcus equi pneumonia in foals.

2. **Tylosin** is used in cattle, sheep, and swine for the treatment of local and systemic infections caused by Mycoplasma and Gram(+) bacteria. It is also added to feed as a growth promotant in these species. **Tylosin** is used in dogs and cats for the treatment of chronic colitis.

3. **Tilmicosin** is used in cattle for the treatment of respiratory disease caused by Pasteurella spp. It has potentially fatal toxic effects in horses and humans.

4. **Azithromycin** is used in dogs, cats, and horses and is effective against Staphylococcus, Streptococcus, and Mycoplasma. It is used as an alternative for erythromycin for R. equi pneumonia in foals.

5. **Tulathromycin** is used for the treatment of bovine and swine respiratory diseases. It is effective against Mannheimia, Mycoplasma, and Haemophilus; it is concentrated in leucocytes and lung tissue.

6. **Clarithromycin** is used in dogs and cats for the treatment of mycobacterial infections including canine leproid granuloma, feline leprosy, and for Helicobacter spp. in cats and ferrets, and for R. equi in foals.

Adverse effects.

Erythromycin, tylosin, azithromycin, clarithromycin, and tulathromycin

have relatively few side effects. Mild GI upset with oral doses and pain and irritation at IM injection sites may occur.

Erythromycin is recognized to be an agonist of the motilin (a peptide that stimulates contraction of GI smooth muscle) receptor and acts on the stomach, ileum, cecum, and pelvic flexure and can produce abdominal pain and diarrhea.

Edema of the rectal mucosa with mild anal prolapse may be seen in swine following IM administration of tylosin.

Erythromycin should not be administered orally to adult ruminants or tylosin, orally or parenterally, to adult horses because of the danger of severe diarrhea. Tilmicosin produces cardiovascular toxicity in species other than

cattle by increasing myocardial Ca^{2+} concentrations. Side effects are rare for others in the group.

CHLORAMPHENICOL GROUP

Chemistry.

Chloramphenicol is an unusual natural compound because it contains dichloracetate and nitrobenzene moieties as part of its structure. Palmitate salts are water insoluble and are administered orally. Chloramphenicol sodium succinate is water soluble for parenteral use.

Florfenicol is a fluorinated derivative where the $-NO_2$ group has been replaced by $-SO_2CH_3$ to treat respiratory infections in beef cattle. It does not leave the toxic residues in meat that chloramphenicol does.

Mechanism of action.

Chloramphenicol and florfenicol bind to the bacterial 50S ribosome unit to inhibit peptide bond formation and protein synthesis .

They are bacteriostatic and broad spectrum and are effective against most anaerobic bacteria.

Therapeutic uses.

Chloramphenicol is not allowed for use in food-producing animals because the potential danger of residue-induced toxicity in humans .It is used in dogs, cats, horses, and birds for local and systemic infections, inducing respiratory, CNS, and ocular infections, and infections caused by anaerobes and Salmonella spp. Florfenicol is approved for use only in cattle for the treatment of bovine respiratory disease (BRD) caused by Pasteurella spp. and Haemophilus somnus. It is used in dogs and cats for treating susceptible infections when the myelotoxic potential of chloramphenicol must be avoided.

D. Pharmacokinetics

1. Chloramphenicol is rapidly absorbed from the GI tract and widely distributed to all tissues including the CNS and eye. Hepatic metabolism by glucuronide conjugation occurs slowly for 75% of the administered drug in cats, but faster to 90% in dogs.

The elimination t 1/2 is 1–1.5 hours for dogs and horses and 4–5 hours in cats.

2. Florfenicol is absorbed orally in dogs and cats and from IM sites in cattle. It is widely distributed, including the CNS, similar to chloramphenicol. The serum t 1/2 is 18 hours in cattle and 4–6 hours in dogs and cats. In cattle, two-thirds of a dose is excreted as the parent drug in the urine and one-third is metabolized by the liver.

E. Administration.

Chloramphenicol is administered orally, IM, IV, or SC every 6–8 hours

to dogs, birds, or horses and every 12 hours to cats. Florfenicol is administered IM in cattle and repeated 48 hours later for a total of two doses of the slow-release preparation.

It is administered IM or SC every 8 hours in dogs and every 12 hours in cats.

F. Resistance.

Resistant bacteria inactivate chloramphenicol by production of an acetyltransferase and other metabolizing enzymes. Similar inactivation is expected with florfenicol.

G. Adverse effects

1. Anemia, which is dose-related, may occur in animals and humans. Chloramphenicol may inhibit the uptake of iron by erythrocytes and their rate of maturation in bone marrow .

A second type of anemia may occur in humans treated with chloramphenicol. It is non-dose-related and rare but the resulting aplastic

anemia is often fatal and this is the reason for the drug's ban in food-producing animals.

2. Anorexia and diarrhea may occur especially in cats with high or prolonged dosage.

3. Florfenicol is not known to produce aplastic anemia and its use is permitted in beef cattle.

LINCOSAMIDES

A. Chemistry. Lincomycin, clindamycin, and **pirlimycin** are derivatives of a sulfurcontaining octose with an amino acid-like side chain and are highly lipid soluble.

They are prepared as HCl or phosphate salts, which are water soluble, or clindamycin palmitate for oral administration.

B. Mechanism of action. The lincosamides bind to the bacterial 50S ribosome to inhibit protein synthesis

Since this is the same binding site of chloramphenicol and the macrolides, combined therapy should be avoided. Lincomycin and clindamycin

are bacteriostatic and are active against Gram(+) aerobes and obligate anaerobes, Toxoplasma spp. Neospora canis, and Mycoplasma spp. The antibacterial activity of clindamycin is greater than that of lincomycin, especially against anaerobes.

C. Therapeutic uses. Lincomycin is used in swine for the control and treatment of swine dysentery, and the treatment of staphylococcal, streptococcal, and mycoplasmal infections.

Clindamycin is used in dogs and cats for periodontal disease, osteomyelitis,

dermatitis, and deep soft tissue infections caused by Gram(+) organisms. It is used for treating toxoplasmosis in dogs and cats and neosporosis in dogs. Pirlimycin is prepared and used for the treatment of bovine mastitis.

D. **Pharmacokinetics.** Oral absorption is 50% for lincomycin and 90% for clindamycin. Distribution is wide with excellent penetration of bone and soft tissues, including tendon sheaths. CNS levels are low unless the meninges are inflamed.

Lincosamides are metabolized by the hepatic microsomal enzymes into sulfoxide and other metabolites(60%, lincomycin; 90%, clindamycin). Parent drug and metabolites are excreted inurine, bile, and feces. The elimination t 1/2 is 3–5 hours in dogs and cats. No information

is available for other species.

E. Administration. Lincomycin is administered IM to swine once a day or added to the drinking water.

Clindamycin is administered orally or IM twice a day to dogs and cats. Pirlimycin is given by intramammary infusion.

F. Resistance. Altered drug binding by bacterial ribosomes is the usual form of resistance. Cross-resistance between lincosamides and macrolides is common.

G. **Adverse effects.** Lincosamides are contraindicated in horses, rabbits, hamsters, and guinea pigs because they may produce a severe, often fatal, diarrhea due to altered GI flora. Side effects are rare in dogs, cats, cattle, and swine except for neuromuscular blockade at high doses or when used with anesthetics.