Macrolide and Lincosamides

Macrolide antibiotics

- The macrolides (macrocyclic lactones) are a group of *bacteriostatic* antibiotics that structurally consist of a large lactone ring attached to deoxy sugars.

- Erythromycin is the first member discovered in the 1950s.

- Oleandomycin, troleandomycin, spiramycin, josamycin, tilmicosin, and tylosin.

- Roxithromycin, Clarithromycin and Azithromycin are the later additions.

Chemistry and source

- The macrolides or macrocyclic lactones have complex chemical structures consisting of a large lactone ring, usually 14-16 atoms, attached to deoxy sugars by glycosidic linkages.

- Each macrolide antibiotic may further consists oi a mixture of closely related agents that differs from each other with respect to some chemical substitution in the structure (e.g., erythromycin consists of erythromycins A, B, C, D, and E).

- Macrolides are mostly obtained from various species of Streptomyces soil-borne bacteria; some are prepared semi-synthetically.

Properties

- All macrolide antibiotics are weak bases.
- pKa ranging from 6 to 9.

- The basic nature of these antibiotics is due to the presence of dimethylamine group in their structures.

- Due to their basic nature, they are concentrated in acidic fluids such as milk and prostatic fluid by process of 'ion trapping'.

- They exist as colourless crystalline substances that are poorly soluble in water and soluble in polar organic solvents.

- Macrolides are often inactivated in basic (pH >10) as well as acidic (pH <4) environments.

- Maximum activity--between pH 7.8 to 8.
- They are lipid soluble but are often used in ester forms to enhance oral bioavailability and to improve oral tolerance.

Erythromycin

- It was isolated from *Streptomyces erythreus* in 1952.
- Since then it has been widely employed, mainly as alternative to penicillin.
- Water solubility of erythromycin is limited, and the solution remains stable only when kept in cold.
- It is the prototype drug of this group.

Antibacterial spectrum

- Macrolides are mainly effective against most aerobic and anaerobic Gram positive bacteria.

- In general, macrolides are narrow spectrum antibiotics and not effective against Gram negative although some strains of *Pasteurella*, *Haemophilus* and *Neisseria* spp are moderately sensitive.

- They are also active against *Mycoplasma*, *Chalmydia* and *Ricketssiaes* pp, but not against protozoa and fungi.
- Tilmicosin is a broad spectrum macrolide and has exceptionally high activity against *Pasteurella haemolytica* and *P. multocida.*

- Some of the members are also active against *Mycobacterium.*

Mechanism of action

- Erythromycin is bacteriostatic at low but cidal (for certain bacteria) at high concentrations.
- Cidal action depends on the organism concerned and its rate of multiplication.
- The action of macrolides can be divided into two processes —
  - passage of macrolides into bacterial cell and
  - interaction of macrolides with bacterial ribosomes.

Step I : Passage of macrolides into bacterial cells :

- Sensitive gram-positive bacteria accumulate erythromycin intracellularly by active transport which is responsible for their high susceptibility to this antibiotic.

- The gram-positive bacteria accumulate about 100 times more antibiotics than do gram-negative organisms.

- The non-ionised form of the macrocyclic antibiotic is considerably more permeable to bacterial cells, so the drugs show enhanced antimicrobial activity at alkaline pH.

Step II: Interaction of macrolides with bacterial ribosome:

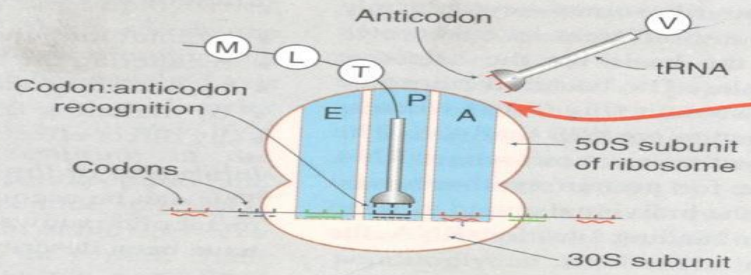
- Erythromycin acts by inhibiting bacterial protein synthesis.
- It combines with 50S ribosome subunits and interferes with 'translocation'.

- After peptide bond formation between the newly attached amino acid and the nascent peptide chain at the acceptor (A) site the elongated peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment.

- This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon.

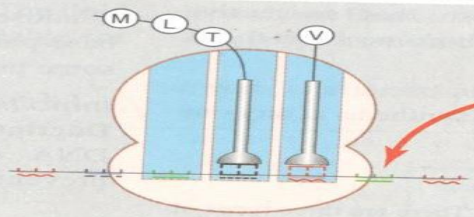
- As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is specifically suppressed.

A The elements involved in protein synthesis are shown: a ribosome (with 3 binding sites for transfer RNA (tRNA): the P, A and E sites), messenger RNA (mRNA) and tRNA. The different mRNA codons (triplets of 3 nucleotides which code for specific amino acids) are represented by dots, dashes and straight or wavy lines and are shown in different colours. A tRNA with the growing peptide chain (consisting so far of Met–Leu–Trp: MLT) is in the P site, bound by codon:anticodon recognition (i.e. by complementary base-pairing). The incoming tRNA carries valine (V), covalently linked.



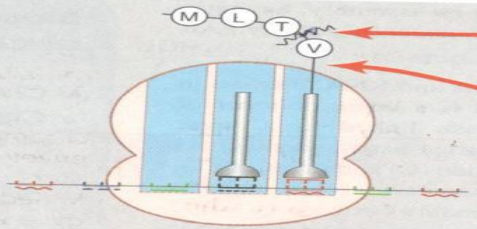
Competition with tRNA for the A site, e.g. tetracyclines; selectivity largely through selective uptake by active transport into prokaryotic cells

B The incoming tRNA binds to the A site by complementary base-pairing.



Abnormal codon:anticodon leads to misreading of the message, e.g. aminoglycosides, gentamycin, amikacin, etc.

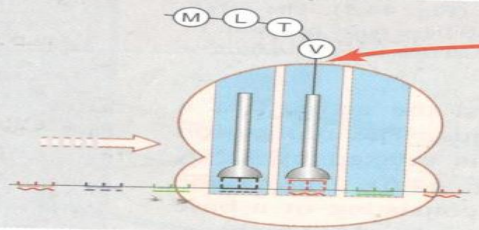
C Transpeptidation occurs, i.e. the peptide chain on the tRNA in the P site is transferred to the tRNA on the A site. The peptide chain attached to the tRNA in the A site now consists of Met–Leu–Trp–Val (MLTV). The tRNA in the P site has been 'discharged', i.e. has lost its peptide.



Inhibition of transpeptidation, e.g. chloramphenicol

Premature termination of peptide chain, e.g. puromycin, which resembles the amino acid end of tRNA (it also affects mamalian cells; used as an experimental tool)

D The discharged tRNA is now transferred from the P site to the E site; the tRNA with the growing peptide chain is translocated from the A site to the P site and the ribosome moves on one codon, relative to the messenger.



Inhibition of translocation, e.g. erythromycin (also spectinomycin, fusidic acid)

E The tRNA from which the peptide chain has been removed is ejected. A new tRNA, with amino acid (M) attached and with the relevant anticodon, now moves into the A site, and the whole process is repeated.

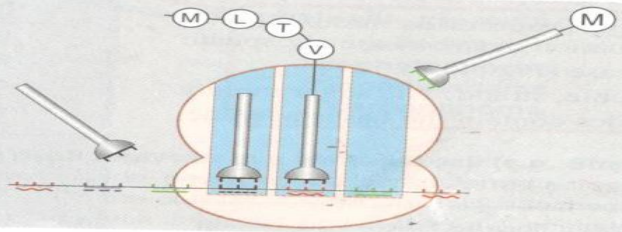


Fig. 44.4 Schematic diagram of bacterial protein synthesis [illegible]

Side Effects and Toxicity

- In general, macrolides are least toxic antibiotic but tilmicosin is comparatively toxic.
- They are irritants and may cause pain and swelling at the site of injections.
- Erythromycin estolate salt is particularly hepatotoxic and may cause cholestatic jaundice.

- Hypersensitivity reactions or skin reactions may occasionally be seen.

- High doses may cause severe GI disturbances (vomiting, diarrhea, oedema of GI mucosa etc).

- ★Horses are particularly highly sensitive and may suffer from serious and even fatal GI disturbances.

- Tylosin in dogs causes tachycardia, fibrillation and myocardial ischaemia.

- Tilmicosin is cardiotoxic and causes tachycardia and decrease the cardiac contractibility and it is contraindicated in pigs.

Uses

It is used in the treatment of

- In patient allergic to penicillin,
- Respiratory tract infections,
- Atypical pneumonia caused by Mycoplasma pneumoniae,
- Bronchopneumonia,
- Bacterial enteritis,
- Urinary tract infections,
- Bacterial pyodermatitis,
- Arthritis,
- Mastitis,
- Metritis
- CRD in poultry.

Oleandomycin and Troleandomycin

- Oleandomycin is obtained from *Streptomyes antiboticus.*
- Troleandomycin is a derivative of oleandomycin.
- Both drugs possess erythromycin like antibacterial spectrum and have special activity against Staphylococci and Streptococci.

Spiramycin

- Source: A strain of *Streptomyces ambofaciens*.
- Its antibacterial activity is also similar to erythromycin and oleandomycin.
- It attains a high concentration in body fluids (particularly pleural and peritoneal fluids); thus it is the drug of choice in the treatment of contagious bovine pleuropneumonia (@ 25 mg/kg, IM, 3 injections at 48 hr intervals).

- It is also used for the treatment of
  toxoplasmosis in ewes (100 mg/kg, orally),
  ovine rickettsial keratoconjuntivitis (20-30 mg/kg, IM),
  CRD in poultry and
  swine dysentery caused by *Treponemahyodysentriae*.

- **Tylosin:**

  Source: A strain of *Streptomyces fradiae.*

  Its antibacterial spectrum is similar to erythromycin.

- **Tilmicosin:**

  It is mainly used in the treatment of bovin respiratory diseases associated with *Pasteurella haemolytica.*

Dose, Withdrawal

Dose:

Cattle: 10mg/kg SC, single injection
(IV injection may cause fatality).

Withdrawal period for meat:
Cattle: 28 days;
Pigs: 21 days;

Milk discard time: Cattle 0 days

NEWER MACROLIDES

NEWER MACROLIDES

- To overcome the limitations of erythromycin viz.
  narrow spectrum activity,
  poor tissue penetration,
  gastric acid liability,
  low oral bioavailability and
  short half life.

- Some semisynthetic macrolides like **roxithromycin, clarithromycin and azithromycin** have been developed.

- Their antibacterial spectrum is similar to that of erythromycin and some are more active against *Mycoplasma* and *Chlamydia*.

- They are mainly used in man and small animals as an alternative to erythromycin for respiratory tract infection, pneumonia, skin, soft tissue and genital tract infections.

Lincosamides

- These antibiotics closely resemble macrolide antibiotics in their antibacterial spectrum, mechanism of action and clinical application.

- The most important members of this group are:

  lincomycin and clindamycin.

Lincomycin

- It is produced by *Streptomyces lincolnensis.*
- The drug is active against Gram positive bacteria including Penicillinase producing *Staphylococci, Streptococci, Clostridium tetani, Cl. Perfringens, Erysipelothrix, Actinomycetes, Nocrdia* and *Mycoplasma pneumonia* (certain strain).
- Its most distinctive feature is its activity against a variety of anaerobes (*Bacteroides fragelis*).
- However, aerobic Gram negative bacilli are not affected.

- Lincosamides can be administered orally, IM or IV.
- Lincomycin is readily absorbed orally and completely absorbed from IM sites.
- The drug is widely distributed in the body including skeletal and soft tissues but cannot penetrate the blood brain barrier.
- It is largely metabolized in liver and the metabolites are excreted in urine and bile.

Clinical Uses:

- Because of serious toxic effect its use is restricted in infections caused by susceptible Gram positive bacteria, particularly *Staphylococci* and *Streptococci* and for those by anerobic pathogens.

- The drug is used in respiratory, skeletal, skin, joint and adjoining tissue infections in dogs and cats.

- It is also used to treat:

  infectious arthritis in pigs (due to *Streptococci*, *Staphylococci*, *Erysipelothrix* and *Mycoplama*)

  pneumonia in pigs due to *Mycoplasma*.

Side Effects and Toxicity:

- These drugs have no serious organ toxicity.
- GI disturbances may occur.

- The major probem in man is superinfection diarrhoea and pseudomembranous colitis (treated by vancomycin) caused by a toxin produces by *Clostridium difficile.*

- Hypersensitivity reaction and skeletal muscle paralysis may also occur.
- Lincosamides are contraindicted in horses (because severe and fatal colitis may develop) and in neonates (due to limited to metabolize the drugs).

Dosage:

Dog & cat: Oral: 20mg/kg orally once or twice a day;

IM: 10mg/kg twice daily;

Cattle & pigs: IM: 10Mg/kg twice daily.

Clindamycin

- It is a semisynthetic derivative of lincomycin and differs chemically from lincomycin by substitution of a chloride atom for hydroxyl group.
- It is more potent than the parent compound.
- Its absorption is better than lincomycin and has reduced the incidence of adverse effect than lincomycin.
- The antibacterial spectrum and clinical application is similar to lincomycin.

- It has replaced lincomycin for anaerobic, skeletal, soft tissues and skin infections.
- Dose: Dogs: 5-10 mg/kg orally twice daily.

- The bacteria may develop cross resistance between macrolides, lincosamides and other antibiotic which have common mechanism of antibacterial action.

Summary

Thank You