Inhibitors of Microbial Protein Synthesis

Aminoglycosides

Aminosugars

Highly toxic

Polar substances (Ineffective orally due to their polarity, drugs given orally should have little lipid solubility).

Include:

Streptomycin	Gentamicin	Netilmicin
Kanamycin	Tobramycin	Amikacin
Neomycin	Paromomycin	

- **Common properties:**

- Have similar structure (group of antibiotics which contain amino sugars and a cyclohexane ring)
- Differ in pharmacokinetic properties ($t_{1/2}$)
- Have similar spectrum of activity; highly effective against G-ve bacteria (some are broad spectrum but mostly used against gram-ve)

- Bactericidal (remember that whether the drug is bactericidal or bacteriostatic it has nothing to do with its mechanism of action nor its spectrum of activity)
- Ineffective orally
- Interfere with the integrity of bacterial membrane (little effects) usually these drugs enter the cell and inhibit bacterial protein synthesis (30S inhibitors) (bind irreversibly to the 30s subunit of ribosome inhibiting protein synthesis and cause misreading of mRNA)
- Do not bind plasma or tissue proteins (which is considered the major interaction for PCNs)

- Have small AVD (apparent volume of distribution 25% of lean body wt (body weight - fat), do not penetrate the BBB & eye
- - Drugs with low lipid solubility have lower AVD.
- Rapid excretion as free form (unchanged) by the kidney (no secretion or re-absorption)
- Toxic (have narrow therapeutic window, drug monitoring is essential to such antibiotics to make sure that the concentration is within therapeutic levels.)

Ototoxic (toxic to the ear), Nephrotoxic,
Curare-like effect (muscular paralysis)
Allergy

** Neomycin the most nephrotoxic used only topically and orally (using it orally is beneficial in this case because it does not get absorbed and does not cause systemic side effects, local GIT infection).

** Gentamicin the drug of choice to treat neonatal G-ve meningitis (given intrathecally).

** Streptomycin (given IM) is effective in Brucellosis & T.B (along with other antibiotics, but it causes curare-like side effects).

- Dose adjustment to aminoglycosides is necessary in:

- Children & old pts (kidneys are not functioning well yet, lower doses should be given)

- Pts with renal disease.

- Pts with hypotension.

- Pts on diuretics.

All such conditions could have high incidence of nephrotoxicity.

- **Aminoglycosides clinical uses:**

- Gentamicin, netilmicin, tobramycin, amikacin

Very potent against G-ve bacilli (E. coli, Klebsiella, Proteus, Pseudomonas…)

Synergistic with antipseudomonal PNC's

Strains resistant to gentamicin could be sensitive to amikacin and vice versa

Gentamicin is considered the drug of choice to treat neonatal G-ve bacilli meningitis

- Netilmicin

Similar to gentamicin but less ototoxic and could be effective in infections resistant to gentamicin

- Kanamycin

Same as above but has no activity against Pseudomonas

- Neomycin

Most nephrotoxic (not given systemically), used to sterilize bowel before abdominal surgeries (along with erythromycin as prophylactic agents, (to prevent development of infections)

Also used locally on skin and eye

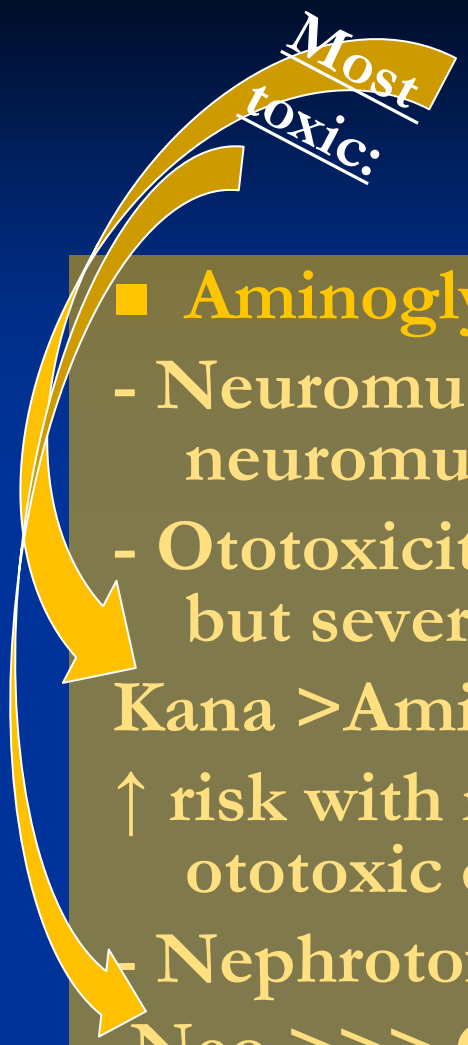
- Streptomycin

Highly effective against TB, used with PNC's to treat Strep endocarditis

Highly effective against brucellosis (Malta fever)

- Paromomycin

Effective only to treat tape worm infestation and intestinal amoebiasis



- **Aminoglycosides toxicity:**

- Neuromuscular blockade, acts on the neuromuscular junction (curare-like effect)

- Ototoxicity (toxic to 8th cranial nerve), reversible but severe toxicity could lead to deafness

Kana >Amikacin >> Genta=Tobra

↑ risk with renal failure or concomitant use of other ototoxic drugs

- Nephrotoxicity

Neo >>> Genta=Amikacin > Tobra

They lead to acute tubular necrosis; more in pts with renal disease or with concomitant use of other nephrotoxic drugs

Macrolide antibiotics

Static, contain lactone ring + sugars (12-22 carbon lactone ring linked to sugars)

Include:

Erythromycin; Clarithromycin; Azithromycin

Oleandomycin; Telithromycin; Roxithromycin; Spiramycin…etc

Erythro. has high activity against G+ve bacteria, little effect against G-ve bacteria

- Clarithromycin and Azithromycin are more active than erythromycin against several gram negative bacteria as well as Mycoplasma pneumonia, Helicobacter pylori (causes peptic ulcer, that is treated with antibiotics combination and proton pump inhibitors along with other agents, resulting in rapid healing of ulcers),Toxoplasma gondii, cryptosporidia and several atypical mycobacteria
- Macrolides differ in their pharmacokinetic properties ($t_{1/2}$)

You are not required to memorize the following details.

- Erythromycin is available in 250 and 500 mg tab. and 125mg, 200mg, 400mg/5ml susp. and topical gels and solutions. (dose 250mg x 4 daily or 500mg x 2 for 10-14 days)
- Azithromycin is available in 250 & 500 mg tablet & 100 & 200mg/5ml suspension dosage forms
- Total dose of azithromycin=1.5-2.5g (3days therapy or 5 days therapy)

Macrolides are considered drugs of choice to treat Corynbacteria diphtheria and mycoplasma pneumonia (along with tetracyclines)

- **Macrolides mechanism of action:**

Reversibly bind 23S rRNA of the 50S subunit of the ribosome inhibiting translocation during protein synthesis (inhibition of protein synthesis simply).

Considered alternatives to PNC's (particularly erythromycin) (second line drugs) to treat Strep. and Staph. infections e.g. tonsillitis in patients with penicillin allergy

Considered 2nd line therapy to PNC's for Rx of dental infections (never 1st line because they are static; resistance develops easily to them, less effective than PNC's in orodental infections and more toxic)

Given orally; distribute well but cross well inflamed meninges

- **Side effects to macrolide antibiotics:**

- GIT irritation (major & most frequent, nausea, vomiting, and diarrhea.)
- Allergy
- Cholestatic hepatitis (direct toxic effect or hypersensitivy reaction; reversible; more common in adults; more common with estolate form of erythromycin=the gastric acid resistant form of erythromycin)

Chloramphenicol (not related to Macrolides nor Aminoglycosides).

Bacteriostatic

Protein synthesis inhibitor

Broad spectrum (G+ve & -ve bacteria and anaerobes)

The drug of choice to treat H. influenza meningitis and epiglotitis, brain abscesses and Salmonella infections (typhoid and paratyphoid fever) (recent restriction due to toxicity)

- **Chloramphenicol mechanism of action:**

Binds to rRNA of 50S subunit of the ribosome inhibiting transpeptidation during protein synthesis

Highly lipid soluble, orally effective and widely used locally on eye (eye drops).

Never used parentally (locally or orally).

The best antibiotic that crosses BBB

Metabolized to inactive metabolites by conjugation (glucuronide)

- **Cholramphenicol side effects:**

- Reversible dose-related bone marrow depression

- Aplasic anemia (allergic in nature; fatal; none dose-related)

- Gray-baby syndrome (fatal toxic reaction; abdominal distension, severe vomiting, cyanosis, hypothermia, collapse)

- Optic neuritis, nausea, vomiting, diarrhea

Spectinomycin (protein synthesis inhibitor).

- Bacteriostatic
- Chemically related to aminoglycoside
- It binds to the 30S subunit of the bacterial ribosome and inhibits protein synthesis
- Alternative to PNC's and cephalosporins to treat uncomoplicated gonococcal infection in pts allergic to PNC's and cephalosporins
- A single injection is adequate