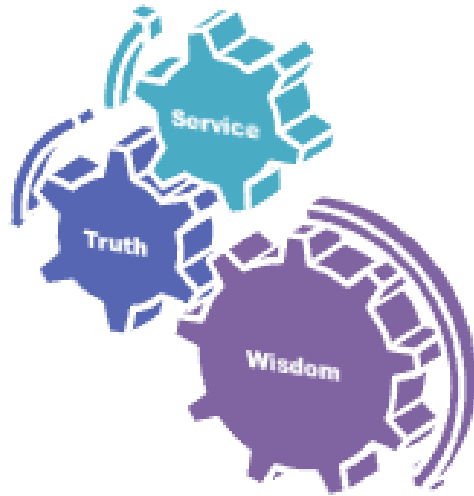


الله أكبر
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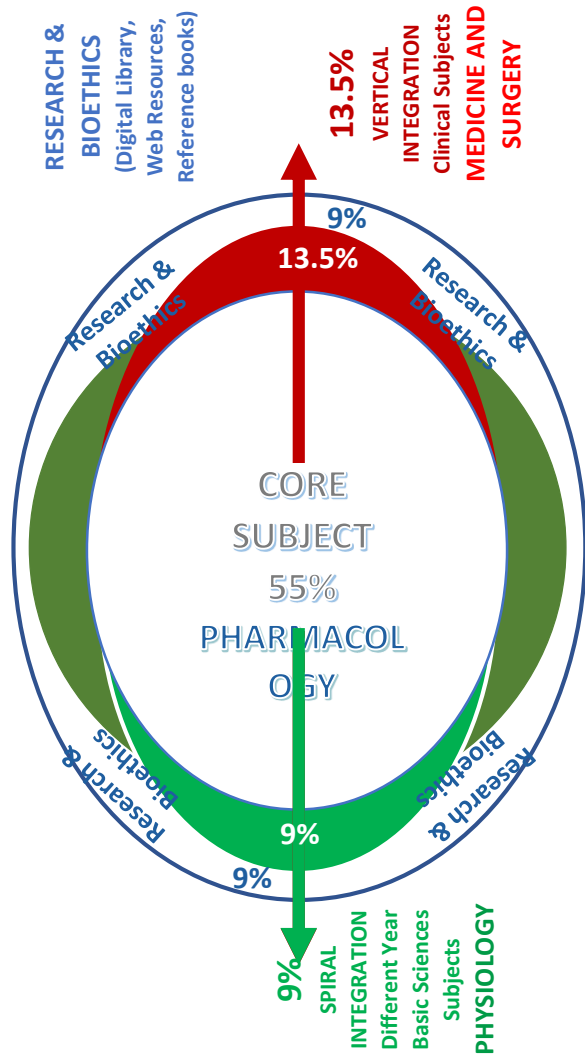
MOTTO AND VISION



- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model

For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology (34 slides)

Core Subject – 70%

Horizontal Integration – 10%

Vertical integration (Clinical Subjects)

- Medicine (15%)

Different Year Basic Sciences Subjects

Research & Bioethics 5%

AMINOGLYCOSIDES

LEARNING OBJECTIVES

At the end of the lecture, students should know:

- Classification of aminoglycosides
- Their mechanism of action, clinical uses and adverse effects
- Antibacterial spectrum and mechanism of resistance

Core subject –
Pharmacology

CLASSIFICATION

SYSTEMIC

Streptomycin
Amikacin
Gentamicin
Kanamycin
Netilmicin
Tobramycin
Sisomicin

TOPICAL

- **Neomycin**
- **Framycetin**

MECHANISM OF ACTION

- Bactericidal antibiotics
- **Described in two main steps:**
 - (a) Transport through the bacterial cell wall and cytoplasmic membrane.
 - (b) Binding to ribosome resulting in inhibition of protein synthesis.

TRANSPORT INTO BACTERIA

- A multistep process.
- They **diffuse across** through porin channels.
- Entry from the periplasmic space (**space between the inner cytoplasmic membrane and the bacterial outer membrane**) across the cytoplasmic membrane is carrier mediated.
- These processes are **inactivated under anaerobic conditions**.
- **Penetration** is also favoured by **high pH**.
- Inhibitors of bacterial cell wall (β -lactams, vancomycin) enhance entry of aminoglycosides and **exhibit synergism**.

INHIBITION OF PROTEIN SYNTHESIS

- Once inside the bacterial cell
- **Streptomycin binds to 30s ribosomes**
- **Other aminoglycosides** bind to 50S subunit, as well as to 30S-50S interface.
- They freeze initiation of protein synthesis
- Prevent polysome formation and promote their disaggregation to monosomes.
- Binding to 30S-50S juncture causes **distortion of mRNA codon recognition**
- Resulting in misreading of the code: one or more wrong amino acids are entered in the peptide chain and/ or **peptides of abnormal lengths** are produced.
- Different aminoglycosides cause misreading at different levels depending upon **their selective affinity for specific ribosomal proteins**.

INHIBITION OF PROTEIN SYNTHESIS

- The cidal action based on secondary changes in the integrity of bacterial cell membrane.
- After exposure to aminoglycosides, sensitive bacteria become more permeable; ions, amino acids and even proteins leak out followed by cell death.
- This probably results from incorporation of the defective proteins into the cell membrane.
- One of the consequences of aminoglycoside induced alteration of cell membrane is augmentation of the carrier-mediated entry of the antibiotic.
- This reinforces the lethal action.
- The cidal action is concentration dependent
- **Exert** a long and concentration dependent 'postantibiotic effect'.

Horizontal integration – Microbiology

Aminoglycosides

- Spectrum of activity:
 - Broad *gram negative coverage* including *Pseudomonas*, *Enterobacter*, *Serratia*, *Proteus*, *Acinetobacter*, *Klebsiella*, *others*
 - Almost always used in combination with another antibiotic such as a beta-lactam to extend coverage, provide synergy, and because may not be effective alone outside of the urinary tract (due to tissue hypoxia, WBC debris, local acidosis, etc.)

MECHANISM OF RESISTANCE

(a) Acquisition of cell membrane bound **inactivating enzymes** which phosphorylate/ adenylate or acetylate the antibiotic.

- Most **important mechanism** of development **of resistance**.
- **Susceptibility** of different aminoglycosides to these enzymes **differs**.
- Thus, cross resistance is partial or absent.

(b) **Mutation** decreasing the affinity of ribosomal proteins that normally bind the aminoglycoside.

(c) **Decreased** efficiency of **transporting mechanism**:

- Either the pores in the outer coat become less permeable or the active transport is interfered.

➤ VERTICLE
INTEGRATION
MEDICINE/
SURGERY

TOXICITIES

OTOTOXICITY

- The vestibular or the cochlear part affected.
- Concentrated in the labyrinthine fluid
 - Slowly removed from it when the plasma concentration falls.
- The vestibular/cochlear sensory cells and hairs undergo conc. dependent destructive changes.
- Aminoglycoside ear drops can cause ototoxicity when instilled in patients with perforated eardrum; contraindicated in them.

COCHLEAR DAMAGE

- It starts from the **base** and spreads **to the apex**
- Hearing loss affects the **high frequency sound first**.
- **No regeneration of sensory cells**
- **Auditory nerve degenerate permanently.**
- Older patients and those with pre existing hearing defect are more susceptible.
- Tinnitus then appears, followed by progressive hearing loss.

VESTIBULAR DAMAGE

- **Headache** is usually first to appear followed by **nausea, vomiting, dizziness, nystagmus , vertigo and ataxia** (the loss of full control of bodily movements).

2. NEPHROTOXICITY

- It manifests as **tubular damage**
 - Resulting in loss of urinary concentrating power, low G.F.R., nitrogen retention, albuminuria .
- More in the elderly and in those with preexisting kidney disease.
- Drug **interfere with the production of PGs** in the kidney causes the reduced g.f.r.
- **Reduced clearance** of the antibiotic ultimately higher blood levels leads to **enhanced ototoxicity**.

3. NEUROMUSCULAR BLOCKADE

- All aminoglycosides **reduce ACH release**
- Interfere with mobilization of synaptic vesicles to fuse with the terminal membrane (probably by antagonizing Ca^{2+}) as well as decrease the sensitivity of the muscle endplates to ACh.
- Apnoea and fatalities have occurred.
- **Rapid absorption from the peritoneum/ pleura** produces high blood levels and adds to the action of the neuromuscular blocker.

- **High risk :-**
 - Neomycin and streptomycin
- **Low risk :-**
 - kanamycin, gentamicin or amikacin; tobramycin .
- The neuromuscular **block antagonized by** i.v. injection of a **calcium salt.**
- **Neuromuscular blockers** should be **used cautiously** in patients receiving aminoglycosides.

PRECAUTIONS AND INTERACTIONS

1. Avoid during pregnancy: **risk of foetal ototoxicity.**
2. **Avoid concurrent** use of other **ototoxic drugs**
 - e.g. high ceiling diuretics, minocycline.
3. **Avoid** concurrent use of **other nephrotoxic drugs**
 - e.g. amphotericin B, vancomycin, cyclosporine and cisplatin.
4. **Cautious use in patients** past middle age and in those **with kidney damage.**
5. **Cautious use of muscle relaxants** in patients receiving an aminoglycoside.

STREPTOMYCIN

- Obtained from *Streptomyces griseus*
- Less potent
- Gentamicin or one of the newer aminoglycosides is now preferred due to low potency
- Widespread resistance

ANTIMICROBIAL SPECTRUM:-

- Narrow spectrum
- Low Sensitive organisms:-
 - aerobic gram-negative bacilli.
- Sensitive organisms are-
 - *H. ducreyi*, *Brucella*, *Yersinia pestis*, *Francisella tularensis*, *Nocardia*, *Calym. Granulomatis*, *M. tuberculosis*.
- At high conc.: -
 - Only few strains of *E. coli*, *H. influenzae*, *V. cholerae*, *Shigella*, *Klebsiella*, enterococci and some gram-positive cocci
- All other organisms including *Pseudomonas* are unaffected.

USES:-

- 1 . Tuberculosis
2. Subacute bacterial endocarditis (SABE)
- 3 . Plague
4. Tularemia (characterized by ulcers at the site of infection, fever, and loss of weight)

ADVERSE EFFECTS:-

- Vestibular disturbances.
- Auditory disturbances – less.
- lowest nephrotoxicity than other
- Hypersensitivity reactions are rare
- Pain at injection site is common.
- Occasionally:- Paraesthesias (an abnormal sensation) and scotoma (a partial loss of vision)

GENTAMICIN

- Obtained from *Micromonospora purpurea*
- Properties same as streptomycin
- **But following Differences:**
 - (a) **More potent**
 - (b) **A broader spectrum of action:**
 - effective against *Ps. aeruginosa* and most strains of *Proteus*, *E. coli*, *Klebsiella*, *Enterobacter*, *Serratia*.
 - (c) **Ineffective against**
 - *M. tuberculosis*, *Strep. pyogenes* and *Strep. pneumoniae*, but **inhibits** many *Strep. faecalis* and some *Staph. aureus*.
 - (d) **More nephrotoxic.**

USES:-

- Cheapest & First line antibiotic.
1. For preventing and treating respiratory infections in critically ill patients.
 2. *Pseudomonas*, *Proteus* or *Klebsiella* infections:
 - Burns, urinary tract infection, pneumonia, lung abscesses, osteomyelitis (inflammation of bone or bone marrow), middle ear infection, septicaemia, etc.
 3. Meningitis caused by gram-negative bacilli
 4. SABA

TOBRAMYCIN

- Obtained from *s. tenebrarius* in 1970s.
- The antibacterial and pharmacokinetic properties, as well as dosage are almost identical to gentamicin.
- But 2-4 times more active against *Pseudomonas* and *Proteus*, including those resistant to gentamicin.
- Used only as a reserve alternative to gentamicin.
- Serious infections caused by *Pseudomonas* and *Proteus* are its major indications.
- Ototoxicity and nephrotoxicity is lower than gentamicin.

KANAMYCIN

- Obtained from *S. kanamyceticus* (in 1957)
- Second systemically used aminoglycoside
- Similar to streptomycin in all respects including efficacy against *M. tuberculosis* and lack of activity on *Pseudomonas*.
- More toxic, both to the cochlea and to kidney
- Hearing loss is more common than vestibular disturbance.
- Because of toxicity and narrow spectrum of action it has been largely replaced by other aminoglycosides in treatment of gram-negative bacillary infections.
- It is occasionally used as a second line drug in resistant tuberculosis.

NEOMYCIN

- Obtained from *S. fradiae*
- Wide-spectrum
- Active against most gram negative bacilli and some gram-positive cocci.
- Pseudomonas and Strep. pyogenes are not sensitive.
- Highly toxic to the internal ear and to kidney.
- Not used systemically.
- Oral and topical administration does not ordinarily cause systemic toxicity.

USE:-

1. Topically (often in combination with polymyxin, bacitracin, etc.)
 - For infected wound, ulcers, burn, external ear infections, conjunctivitis.
2. Orally for:
 - (a) Preparation of bowel (cleansing of the intestines from fecal matter and secretions) before surgery
 - (b) Hepatic coma

ADVERSE EFFECTS

- Rashes .
- Oral neomycin has a damaging effect on intestinal villi-prolonged treatment can induce malabsorption syndrome with diarrhoea and steatorrhoea.
- Decrease the absorption of digoxin and many other drugs, as well as bile acids.
- Due to marked suppression of gut flora, superinfection can occur.
- In patients with renal insufficiency-cause further kidney damage and ototoxicity.
- Neomycin is contraindicated if renal function is impaired.

FRAMYCETIN

- Obtained from *S. Lavendulae*.
- It is very similar to neomycin.
- It is too toxic for systemic administration and is used topically on skin, eye, ear in the same manner as neomycin.

AMIKACIN

- A semisynthetic derivative of kanamycin
- Resembles in pharmacokinetics, dose and toxicity.
- Outstanding feature is resistance to bacterial inactivating enzymes.
- Thus widest spectrum of activity, including many organisms resistant to other aminoglycosides.
- However, relatively higher doses are needed for Pseudomonas, Proteus and Staph. infections.
- Used are the same as for gentamicin.
- Recommended as a reserve drug for hospital acquired gram-negative bacillary infection where gentamicin/ tobramycin resistance is high.
- Effective in tuberculosis, but rarely used.
- More hearing loss than vestibular disturbance occurs in toxicity.

SISOMICIN

- Natural aminoglycoside-1980s - from *Micromonospora inyoensis*
- Chemically and pharmacokinetically similar to gentamicin
- More potent on *Pseudomonas*, a few other gram-negative bacilli and haemolytic *Streptococci*.
- Moderately active on faecal *s. treptococci*--can be combined with penicillin for SABE.
- Susceptible to aminoglycoside inactivating enzymes
- Ototoxicity and nephrotoxicity.
- Used interchangeably with gentamicin for the same purposes in the same doses.

NETILMICIN

- Semisynthetic derivative of sisomicin
- A broader spectrum of activity than gentamicin.
- Resistant to aminoglycoside inactivating enzymes
- Effective against many gentamicin-resistant strains.
- More active against *Klebsiella*, *Enterobacter* and *Staphylococci*, but less active against *Ps. aeruginosa*.
- Pharmacokinetic characteristics and dosage of netilmicin are similar to gentamicin.
- Less ototoxic than gentamicin and tobramycin but hearing loss occurs
- Preferable in critically ill and neutropenic patients, and in hospitals where gentamicin resistance has spread.

Q #1. The drug has characteristics almost identical to gentamicin but has much less activity in combination with ampicillin against enterococci

- Amikacin
- Netilmycin
- Spectinomycin
- Tobramycin
- Doxycycline

- Q# 2. A pregnant women was hospitalized and catheterized. She developed UTI caused by pseudomonas and was treated with gentamicin. Which of the following is a risk for fetus while women is on gentamicin
- Hearing loss
- Blindness
- Teratogenesis
- Skeletal deformity
- Mental retardation

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 6. Journals and Researches will appear
 7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

RESEARCH ARTICLES

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4817740>
- <https://www.mdpi.com/1999-4923/13/12/2085>



THANK YOU