Unit 2

b) Sulphonamide & Cotrimoxazole

- They are class of antibiotics which acts by inhibition / interrupting synthesis of nucleic acid
- They interfere with biosynthesis of nucleic acid. But are not genotoxic due to its target specificity

Prontosil rubrum → Sulphonamides

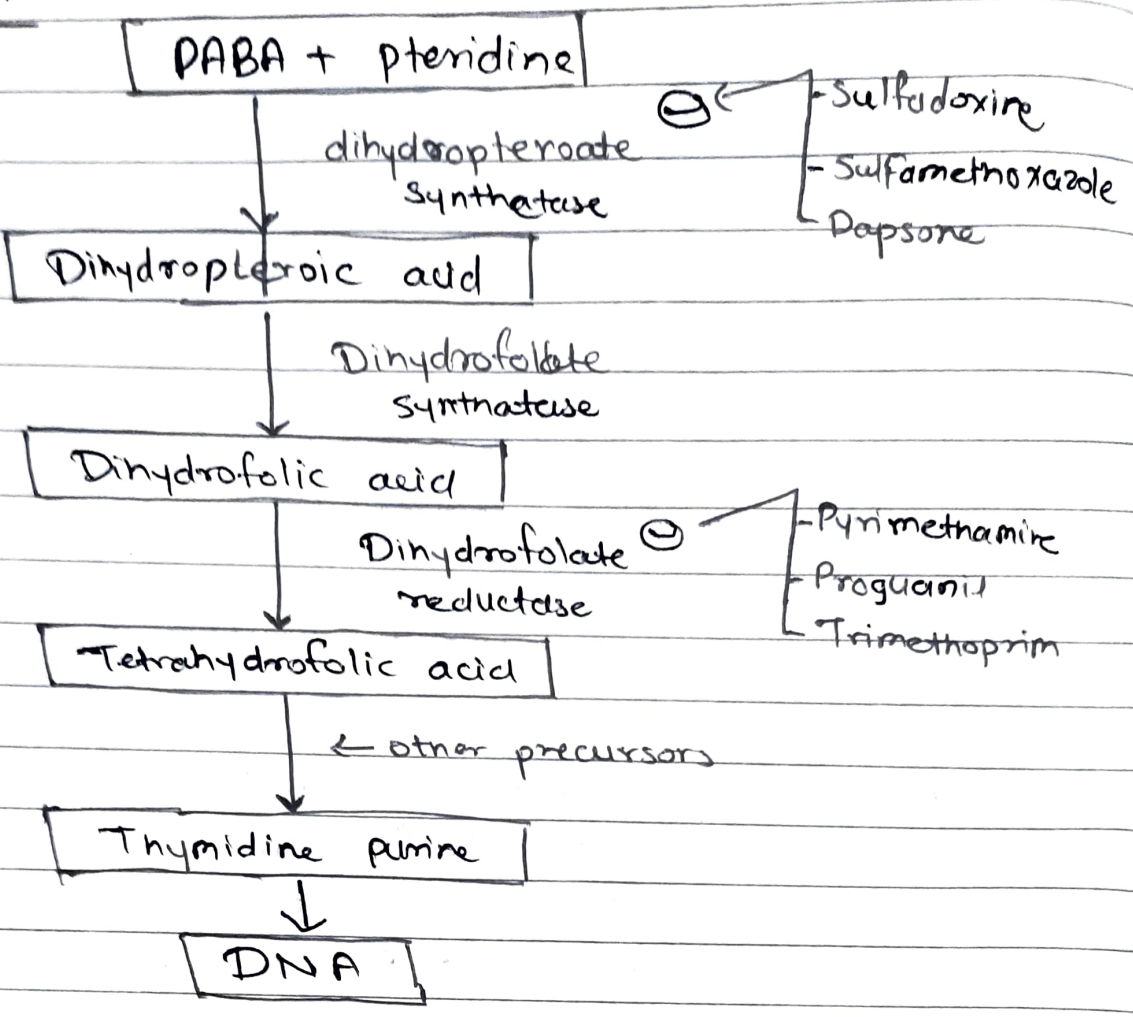
* Sulphonamides :-

Classification :-

A) Based upon duration of action :-
1. Short acting (Sulfadiazine)
2. Intermediate acting (Sulfamethaxozole)
3. Long acting (Sulfamethopyrazine)

B) Based on chemical properties :-
1. Sulfanilamide derivatives (Sulfadiazine)
2. Sulphone (Dapsone)
3. Miscellaneous (Sulphacetamide)

MOA



P' kinetics

- better absorbed orally, also taken through IV route
- large volume of distribution, crosses all barriers
- highly protein bond
- metabolized in liver by N-acetyl transferase enzyme & excreted through kidney by urine

Resistance

- Alterations in dihydropteroate synthetase enzyme & PABA binding site
- ↑ production of PABA by bacterial strains
- ↓ cell membrane permeability of sulphonamides

ADR : Hypersensitivity reactions
Kernicterus
Steven Johnson syndrome
Haemolytic anaemia

227 Cotrimoxazole (trimethoprim - sulphamethoxazole) (1 : 5)

- Sulfamethoxazole is a close congener of sulfisoxazole.
- It is an antibacterial related to pyrimethamine
- Trimethoprim in combination with sulfamethoxazol is effective antimicrobial agents.
- Popularly this combination is various name such as cotrimoxazole, Bactrim, Septran
- trimethoprim & sulphamethoxazole have an equal $t_{1/2}$ of approx 10 hrs.

MOA

Pteridin + PABA
↓ dihydropteroate synthetase ⊖ ← Sulphonamides
Dyhydropteroic acid
glutamate → ↓ dihydrofolate synthatase
Dihydrofolic acid
NADPH → NADP ↓ dihydrofolate reductase ⊖ ← Trimethoprim
~~Trihydro~~ Tetrahydrofolic acid

Antibacterial spectrum

- trimethoprim & sulfamethoxazole have similar antibacterial spectrum
- Resistance develops when individual drug used alone.
- Synergistic interaction between the components of the preparation is apparent even when microorganism are resistant to sulphonamide with or without moderate resistance to trimethoprim activity
- Maximum degree of synergism occurs when microorganisms are sensitive to both component
- In vitro activity depends upon the medium in which it is determined

Spectrum

- G+ve :- S.pneumoniae, Staphylococcus aureus, Staphylococcus epidermis, S.pyrogens, S.viridans, MRSA
- G-ve :- E.coli, Proteus mirabilis, P.morganii, P.rettgeri, Enterobacter species.

Bacterial resistance :

- due to acquisition of a plasmid that codes for an altered DHFR enzyme

P' kinetics :-

-

- Distributed well in all body fluid, trimethoprim is distributed & concentrated rapidly in tissue & about 40% is bound to plasma protein in the presence of sulfamethoxazole. ~~65~~ %. About 66% of sulfamethoxazole is bond to plasma protein.

- Volume of distribution of trimethoprim is almost nine time sulfamethoxazole
- It is metabolized by liver
- 60% of administered trimethoprim & from 25% to 50% of administered sulfamethoxazole are excreted in urine in 24 hrs.

ADRs :-

Hypersensitivity reactions, kernicterus, Steven Johnson syndrome, Haemolytic anemia

Uses :-

- Uncomplicated lower urinary tract infections
- Bacterial respiratory tract infections
- Infection by Pneumocystis jiroveci
- In G-ve rod's infections
- Gastrointestinal infections
- MRSA infections :- Skin & soft tissue infections

Contraindication

Patient with hypersensitivity
- Sever renal or hepatic insufficiency
- Infants less than 4 weeks.
- Megaloblastic anemia pregnancy & lactating mother

* Antibiotics *

Substance produced by microorganism which have capacity to inhibit the growth or kills the other microorganism in low concentration.

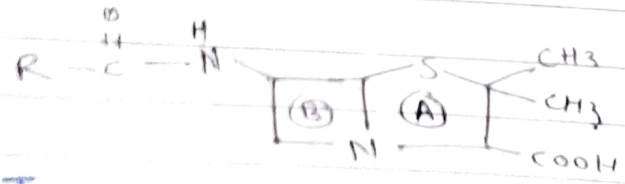
*** Penicillins

- Sir alexander fleming accidently discover of the antibacterial properties of penicillin in 1928
- In 1938, Florey & chain introduced penicillin into therapy
- The word antibiotic derived from the coord antibiosis

Chemistry :-

Basic structure consists of

1) Thiazolidine ring (A) connected to
2) β lactum ring (B)
   - (1) site of action of penicillinase
   - (2) site of action of amidase.
3) Side chain (R)



Types :-

1) Narrow spectrum penicillins
   - (1) β lactamase sensitive : Penicillin G, Penicillin V
   - (2) β lactamase resistance :
     - Oral : Cloxacillin, Flucloxacillin
     - Parenteral : Methicillin, Nafcillin

B) Broad spectrum penicillins

(1) Oral :- ~~Amino~~

Amino penicillin :- Ampicillin, Amoxycillin

(2) Parentral

Carboxy penicillin :- Carbenicillin, Ticarcillin

Ureidopenicillins :- Mezolcillin, Azolcillin

* Mechanism of action :-

→ ~~Bacterial~~ The cell walls of bacteria are essential for their normal growth & development

→ Bacterial cell wall is made up of peptide chain & sugar backbone

→ Sugar backbone contains two types of sugar NAM (~~N-acetyl~~ (N-acetyl muramic acid) & NAG (N-acetyl glucosamine)

→ They are cross-linked by peptide chain.

→ Final stage of peptidoglycan biosynthesis involves completion of the cross link accomp

→ Penicillins interfere with last step of bacterial cell wall synthesis (cross linkage) resulting in exposure of osmotically less stable membrane

→ Cell lysis (by osmotic pressure or activation of autolysins)

→ Gives bactericidal action.

→ They also inactivate protein on bacterial cell membrane which helps are helps in cell wall synthesis & maintain morphological features of bacteria.

- Penicillin V is acid stable than Penicillin G
- Penicillinase resistant penicillin have no activity against gram -ve bacteria
- Oral penicillin :- Penicillin V, amoxicillin,
- Nafcillin, dicloxacillin & oxacillin not eliminated by kindney

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* Mechanism of resistance

- Natural resistance to the penicillin is due to lack of peptidoglycan cell wall.
- Resistance is also occurs due to structural difference in penicillin binding proteins.
- Active efflux pumps serve as another mechanism of resistance removing antibiotics.
- Acquired resistance is due to plasmid transfer
- The enzyme β-lactamase present in bacteria hydrolyzes the ~~cyclic~~ cyclic amide bond of β-lactum ring, result in loss of its activity.
- Bacteria may decresed penetration of the antibiotic through out cell membrane & creeat resistance to its activity

* P'kinetics :

- Route of administration of β lactum antibiotics is determined by its gastric acid stability
- Orally ~~absorbed~~ administered penicillin ~~these~~ ~~agent~~ widely distributed throughout the body
- Therapeutic concentration attain ~~rapi~~ rapidly in tissues & in secretion
- Some antibiotic administered by iv or im (eg Ticarcillin, piperacillin, Amoxicillin + Clavulunic acid)
- ~~Oral~~ Most of penicillin incompletely absorbed after oral administration (Amoxicillin absorbed almost completely)
- Absorption of all the penicillinase resistant penicillin is decreased by food in the stomach.
- It cross placent but has no teratogenic effect.
- Metabolism of β lactum antibiotic is insignificant
- Most of antibiotics are eliminited through kidney

* **Adverse reaction :**
Hypersensitivity, Diarrhea, Nephritis, Neurotoxicity, Hematologic toxicities, Cation toxicity

β-lactamase enzyme :-

- These ~~bacteria~~ pr enzyme present in bacteria which hydrolyse cyclic amide bond in β-lactum ring.
- Different micro-organisms have no. of different β-lactamase which are also called as penicillinase or Cephalinases.
- They are grouped into 4 classes

① **Class A :-** include extended spectrum - β lactamase which degrades penicillins, some Chephalosporins & in some instance Carbapenams

② **Class B :-** They are Zn^{++} dependant enzymes that destroy all β-lactams except Aztreonam

③ **Class C :-** they are active against Cephalosporins.

④ **Class D :-** Include cloxacillin degrading enzymes.

- Grom +ve bacteria produces & secretes a large ~~amt~~ amount of β-lactamases, mostly penicillinase
- Grom −ve bacteria β-lactamases are found in relatively small amount, they are encoded in chomosomes or in plasmids

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* Penicillin G & Penicillin V

- Antimicrobial spectrum is similar to aerobic gram positive micro-organism.
- Penicillin G is 5-10 times more active against Neisseria sp & against certain anaerobes.
- They are narrow spectrum & enzyme sensitive penicillins.
- Effective against Pneumococci, Streptococci, Meningococci non β lactamase producing gonococci & staphylococci
- Nowdays strains of Staphylococci & C.diptheria are now resistant.
- About 1/3 rd of oral dose is absorbed in favorable condition not destroyed by gastric juice
- Penicillin V is more stable in acid hence bette absorbed
- After I.M injection peack cone of penicillin G reached within 15-30 mins.
- They are eliminated rapidly from kidney but small part in bile & other routes.
- Penicillin G is effective against syphilis & actinomycosis.

* Penicillinase resistant penicillins.

- They are resistant to hydrolysis by Staphylococcal penicillinase. e.g oxacillin, cloxacillin
- ~~Pneu~~ Methicillin resistance microorganisms are resistant to all the penicillin resistant penicillins & cephalosporins.
- Hospital aquired ~~resistance~~ infection is also resistant to these penicillins.

Naficillin :- This semisynthetic penicillin is highly resistant to penicillinase & effective against infection caused by penicillinase producing strains.

Broad spectrum penicillin

Aminopenicillins:

Ampicillin & their other congeners are known as broad spectrum antibiotics

- They all are destroyed by β-lactamase
- Bactericidal for both G+ve & G-ve bacteria
- Highly active against some bacterial species (e.coli, P.mirabilis, salmonella & shigella) but now resistance is increasing
- Absorption of Amoxycillin is more & rapid than Ampicillin. & stable in acid & given orally.

Carboxypenicillins:

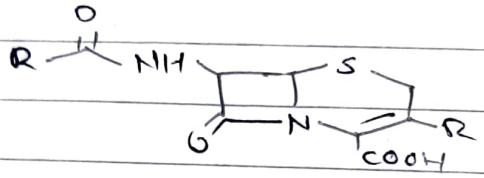
- They are active against some strains of Pseudomonas aeruginosa & certain species of Proteus.
- Hyperkalemia may occurs
- e.g. Carbenicillin, Ticarcillin.

Ureidopenicillins

- They are used against Klebsiella
- They are sensitive to destruction by β-lactamase
- e.g. Mezlocillin & piperacillin have superior activity against P. aeruginosa

** Cephalosporins

- They are β-lactum antibiotics that are closely related both structurally & functionally to the penicillins
- Mostly produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporic acid
- Nucleus consist of β-lactum ring fused to a dihydrothiazine ring



* **Mechanism of action :-**

(Same as penicillin)

* Classification :

- cephalosporins classified into different generation (1-5) based on their bacterial susceptibility pattern & resistance to β-lactamase

1) First generation :-

- They acts as penicillin G substitutes.
- Example : Cephalexin, Cefazolin, Cephalothin, Cephradrine.
- They are active against S. pneumoniae, S. pyrogens, S. aureus & S. epidermis & G+ve cocci (except MRSA)
- They also have activity against Proteus mirabilis, E. coli & klebsiella pneumoniae.
- They have minimal activity against G-ve cocci & G+ve bacilli.
- They do not cross BBB & all are sensitive to β-lactamase

2) Second generation :

- Example :- Cefuroxime, Cefoxitin, Cefaclor, Cefprozil.
- They have greater activity against three additional gram -ve organism {H. influenzae, Enterobacter aerogenes & some Neisseria species.
- Activity against gram +ve bacteria is weaker.
- Cefoxitin active against ~~H. influenzae~~ bowel anaerobes (B. fragilis)
- Cefuroxim is active against H. influenzae, S. pneumoniae.
- Cefuroxine axetil is oral form of cefuroxime
- They are used primarily ~~of~~ for respiratory tract infection
- Cefotetan ~~and~~ & cefoxitin is not preferred for treatment because of increasing prevalence of resistance amongst B. fragilis

3) 3rd -

3) Third generation :

- Example : Ceftriaxone, Cefotoxime, Cefixime, Ceftazidime
- They have important role in treatment of infectious disease
- Highly active against G-ve cocci, bacilli & anaerobes.
- Ceftriaxone & cefotaxime have become agent of choice for treatment of meningitis.
- Ceftazidine has activity against P. aeruginosa.
- Ceftriaxone has long ~~hlo~~ half life & not used in neonates
- Cefotaxime preferred in neonates
- Third generation cephalosporins must be used with caution, as they are associated with "collateral damage"
- They can penetrate BBB (except :- Cefoperazone & Cefixime)

4) fourth generation :-

- Example : Cefepime, Cefirome.
- must be administered parentrally
- Cefepime has wide antibacterial spectrum & active against streptococci & staphylococci
- Cefepime is also effective against aerobic gram -ve organism
- They are more resistance to some β lactamase & not active against ~~anero~~ anaerobes

5) fifth generation

- Example :- Ceftaroline
- They inhibit cell wall synthesis by bind to & inhibit ~~PBP~~ PBP-2 produced by MRSA & penicillin resistant S. pneumoniae. which is not inhibited by many antibiotics
- Also active against Enterococcus & G-ve bacilli
- Used for ~~commonly~~ community acquired bacterial Pneumonia & acute bacterial skin infection include MRSA

* Cha Cephalexin administered orally

* Resistance

- Resistance to cephalosporins may be related to inability of antibiotic to reach site of action or alteration in PBPs that are targets of the cephalosporins such that ~~antibacterial~~ antibiotic binds to bacterial enzyme (β-lactamase) than can hydrolyse β-lactum ring & inactivates the cephalosporins.

* P'kinetics :

- Many cephalosporins must be administereed IV or IM due to their poor oral absorption (except Ceplalexin)
- Cephalosporins distribute very well into body fluids.
- several of the cephalosporins penetrates CSF in sufficient conc. to be useful in meningitis.
- Cephalosporins crosses the placenta & also found in high conc. in synovial & pericardial fluid.
- Cephalosporins are excreted primarily by kidney
- Ceftriaxone is excreted through bile into the feces
- ~~feces~~ & Cefotaxime is deacetylated in vivo & half excreted in kidney & half in bile

* Adverse effects:

- Hypersensitivity reaction (eg anaphylaxis, bronchospasm)
- Cross reactivity between penicillins & cephalosporins due to structural similarity
- Superinfection by 3rd, 4th & 5th generation
- Nephrotoxicity (cephaloridine & cephalothin)
- Diarrhea (cephoperazone)
- Bleeding related to hypoprothrombinemia (cefotetan)

* **Theropeutic uses :-**

① First generation
- Skin & soft tissue infection
- Colorectal surgery
- Prophylaxis for intracellular anaerobes

② Second generation
- Active for URTI, for penicillin resistant S-pneumoniae infections.
- otitis media
- Diabetic foot infection

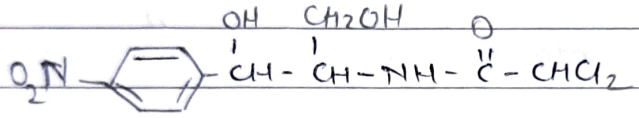
③ Third generation :-
- With or without aminoglycosides are drug of choise for serious infection caused by klebsiella, enterobacter, Proteus, Serratia.
- Ceftriaxon is drug of choice for gonorrheal & lyme disease & also for typhoid fever.
- Pseudomonas meningitis (Ceftazidine + aminoglycosides)
- Community acquired pneumonia

④ Fourth generation
- Nosocomial infections where antibiotics resistance owing to extented spectrum β lactamase

*** Clorampheniçol

*** Chloramphenicol

- Isolated from streptomyces venezuelae in 1947.
- It is active against wide range of gram positive & gram negative organisms.
- It is now synthesized chemically & is commercially available as synthetic product.
- Because of its toxicity, its use is restricted to life-threatening infection for which no alternative exist.



* Mechanism of action:

- It inhibits protein synthesis by interfering with transfer of peptide chain to newly attached aminoacyl-tRNA at Ribosome mRNA complex
- Drug binds to bacterial ~~505~~ 50s ribosomal subunit.
- Inhibit protein synthesis at peptidyl transferase reaction.
- Thus may hinder the access of aminoacyl tRNA to acceptor site for amino acid incorporation.
- High chloramphenicol level may also inhibit mitochondrial protein synthesis.

* Antimicrobial spectrum:

- Broad spectrum antibiotics
  Primarily bacteriostatic & bactericidal at high conc.
- It has excellent activity against anaerobes
- less active against gram +ve bacteria
  Highly active against Salmonella including S. typhi

Resistance:

- Resistance is mainly due to presence of R factor encoded for acetyl transferase enzyme which inactivates chloramphenicol.
- It also developed by inability of ~~microorganism~~ to antibiotics to penetrate the organism.
- This change is may be basis of multidrug resistance

P' kinetics:

- Administered by either I.V or orally.
- Rapidly & completely absorbed from GIT.
- Widely distributed throughout the body, freely passes BBB crosses placenta & secreted in bile & milk.
- 50 - 60% bond to plasma protein
- Primarily conjugated with glucoronic acid in liver & excreted mainly in urine
- $t_{1/2}$ is 3-5 hrs.

* Adverse effects:

Bone marrow depression, GI upset, Anemia, Gray baby syndrome, Super infection

* Interaction:

- Inhibit metabolism of Warfarin, phenytoin, tolbutamide
- Phenobarbitone, rifampin inhance its metabolism.
- It can antagonize the cidal action of β-lactams or aminoglycosides.

* Uses:

1) Enteric fever
2) ~~Anthrax~~ Pyogenic meningitis
3) Intraocular infections
4) Topically for conjuctivitis.

*** # Macrolides

- It was isolated from Streptomyces erythreus in 1952.
- Macrolides are group of antibiotics with macrocyclic lactone structure to which one or more deoxy sugar are attached.
- Erythromycin is the first member discovered in 1950.
- Telithromycin, a semisynthetic derivative of erythromycin is first "ketolide" antimicrobial agent
- Ketolide & macrolides have similar antibiotic activity but
- Ketolides are active against many macrolide resistance gram positive strains.

Mechanism of action:

- They act by inhibiting bacterial protein synthesis
- Bind irreversibly to site on 50s subunit of bacterial ribosome
- Inhibit translocation step of protein synthesis
- It also interfere at other steps, such as transpeptidation
- ~~Generally~~ Thus process of shifting m RNA is affected.
- Generally they are bacteriostatic, but they may be bactericidal at higher doses.

Antibacterial spectrum:

- Antibacterial spectrum between penicillin G & tetracyclines
- Narrow spectrum of activity
- Highly active against St. Pyrogens, & St. pneumonia, N. gonorrhea clostridia, C. diphtheriea, H. influenza Enterobacteriacae, other gram negative bacilli & B. fragilis are not inhibited

* Newer macrolide: Azithromycin

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Resistance:

- Inability of organism to take up the antibiotic or presence of efflux pump create resistance.
- Alteration in the ribosomal binding site for erythromycin by plasmid encoded methylase enzyme.
- Resistant Enterobacteriaceae found to produce to esterase.
- Cross resistance occurs between the group & also between clindamycin & chloramphenicol.

P'kinetics:

- ~~Administ~~ Taken in form of enteric coated tablet or esterified form.
- food interferes with absorption of erythromycin & azithromycin
- Widely distributed in body, enters cells & absesses, cross placenta but does not penetrate the CNS.
- 70-80% plasma protein bond.
- metabolized in bile in active form & excreted through urine
- $t_{1/2}$ is 1.5 hrs

Adverse effects:

GI disturbance, Cholestatic jaundice, ototoxicity, hypersensitivity.

Interaction:

- Inhibit hepatic metabolism of no. of drugs leads to their toxic accumulation

Use:

1) As an alternative to penicillins
2) First choice of drug for M. pneumonicae, whooping cough.

* demethyltetracycline → demeclocycline.

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*** **Tetracyclines**

- It consists of four fused rings with a system of conjugated double bond
- Chlortetracycline is first member, derived from soil organism Streptomyces aureofaciens.
- It was introduced by Benjamin M. Duggar in 1948.
- Drugs :- Tetracycline, Oxytetracycline, Doxycycline, Minocycline

Mechanism of action

- Entry of tetracycline in bacteria is mediated both by passive diffusion & by energy dependant transport protein mechanism unique to the bacterial inner cytoplasmic membrane.
- Nonresistant strains concentrate the tetracyclines intracellularly.

→ The drug binds reversibly to the 30s subunit of the bacterial ribosome.

→ Blocks the binding of aminoacyl tRNA to the A site on mRNA ribosome complex

→ Addition of further amino acid to the nascent peptide is ~~preve~~ stopped.

→ Bacterial protein synthesis get inhibited

Antibacterial spectrum :

- Broad spectrum bacteriostatic antibiotics
- Effective against gram negative & gram positive bacteria, as well as against organism other than bacteria (Rickettsia, Traponema, pallidum, mycoplasmas etc.

- Only minocycline provide therapeutic conc. in CSF
- Doxycycline excreted via bile to faces
- Tetracycline also excreted in breast milk
- Renally impaired person - Doxycycline.

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Resistance:

- Resistance develops in graded manner.
- Bacteria acquire capacity to pump out the tetracycline out ~~for~~ of the cell.
- Enzymatic inactivation of the drug & production of bacterial proteins prevent tetracyclin from binding.
- Nearly complete cross resistance is seen among different members of tetracycline
- organism resistant to one tetracycline is resistant to all.

P'kinetics:

- They are usually given orally. Old tetracyclines have incomplete absorption due to low solubility. Newer agent is completely absorbed (Doxycycline, minocycline)
- They widely distributed in body. Concentrated in liver, kidney, spleen & skin, enters in CSF.
- They are partly metabolized with some ~~drug~~ degree of enterohepatic circulation, excreted by glomerular filtration

Adverse effects:

GI disturbance, liver damage, kidney damage. phototoxicity, deposition of drug in teeth & bones. Superinfection, nausea, vomitting

Contraindication:

- Not used in pregnancy, lactation & in children
- Avoid in patients on diuretics
- Use cautionly in renal & hepatic insufficiency.
- Do not mix with penicillin inactivation occurs.
- Do not inject intrathecally

Use

- Empirical therapy
- 1st choice drug in Cholera, Plague, Atypical pneumonia
- 2nd choise drug in tetanus, anthrax, lasteria
- UTI, lyme disease, Amoebiasis, prophylactic use in COPD.

** Aminoglycosides

- It is group of natural or semisynthetic antibiotics
- They have polybasic amino groups linked glycosidically to two or more amino sugar like sterptidine, 2-deoxystreptamine, glucosamine.
- Aminoglycosides that are derived from Streptomyces ~~have~~ named with suffix -mycin.
- Aminoglycoside which are derived from Micromonospora are named with suffix -micin.
- Streptomycin is oldest aminoglycoside obtained from Streptomyces griseus.

Mechanism of action:

→ Amioglycosides enters in gram -ve bacteria by diffuse through porin channels in their outer membrane
→ The drug is transported across cytoplasmic membrane through oxygen dependant transport system.
→ Then it binds to the (16S RNA of) 30S ribosomal subunit
→ Disort its structure & interfere with initiation of protein synthesis
→ They also causes misreading of mRNA, blocks further translation & ~~diets~~ elicits premature termination of or mutation.
→ Incorporation of incorrect amino acids results in production of abnormal or nonfunctional proteins.

Antibacterial spectrum

- Effective in combination for empirical treatment of infection ~~suspected of being~~ due to gram -ve bacilli including Pseudomonas aeruginosa.
- Combined with β-lactam antibiotics gives synergistic effect
- Also used against M. tuberculosis.
- few strains of E.coli, ~~V. Cholo~~ V. Cholerae, H. influenzae, Enterococci etc. sensitive at higher concentration.

Resistance:

Resistance can be caused by

- decreased uptake of drug when the oxygen dependant transport system for aminoglycosides is absent
- Plasmid associated synthesis of enzymes that modify & inactive aminoglycoside
- Decrese in affinity of antibiotic due to mutation
- Corss resistance is partial & unidirectional streptomycin & other aminoglycoside

P'kinetics:

- They are highly polar & neither absorbed nor destroyed in GIT
- All aminoglycosides (except neomycin) given by parentral route
- Distributed on extracellularly, All aminoglycoside crosses placental barrier
- ~~Mete~~ It does not metabolised & ~~are~~ excreted unchanged in urine by glomerular filtration

Adverse effects:

Ototoxicity, Nephrotoxicity, Neuromuscular paralysis, allergic skin reactions

Use

- Aerobic gram -ve bacteria, H. influenzae, M. catarrhalis & shigella species
- Often used in combination with β-lactams

Gonorrhoea (Spectinomycin, IM), TB (streptomycin, IM)

Classification of aminoglycosides

1) Systemic aminoglycosides:

Streptomycin (Str. griseus)
Gentamicin (Micromonospora purpurea)
Kanamycin (Str. kanamyceticus)
Tobramycin (Str. tenebrarius)
Amikacin (semi synthetic derivative of kanamycin)
Sisomicin (Microspora inyoensis)
Netilmicin (semisynthetic derivative of sisomicin)

2) Topical aminoglycosides:

Neomycin (Str. fradiae)
Framycetin (Str. lavendulae)

*** # Quinolones

- Synthetic antimicrobials
- Bactericidal
- Primarily used against gram -ve bacteria
- First member : Nalixidic acid :-

Spectrum :

- Used against Gram negative bacteria especially coliforms,
  E.coli, Proteus, Kleibseilla, Enterobacter
- It is bactericidal antibiotic.

P'kinetics :

- Concentration of free drug in plasma & most tissue is non-therapeutic for systemic infections.
- Therapeutic concentration attained in urine & gut lumen are lethal to common urinary patnogens & diarrhoea causing coliforms.

Therapeutic use :

- As urinary antiseptic & UTI
- Diarrhoea caused by coliforms

It has narrow spectrum & low potency & rapid development of bacterial resistance So no longer used.

Fluroquinolones :-

- Florination of quinolone structure at position 6 & piperazin substitution at position 7 resulted in derivatives called Fluoroquinolones

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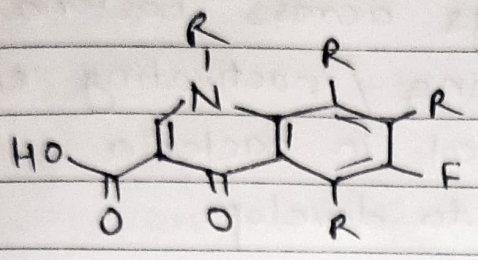

Classification :

(a) First generation :- Norfloxacin, Ciprofloxacin, ofloxacin, Pefloxacin

(b) Second generation :- Levofloxacin, Lomefloxacin, Sparfloxacin, Gemifloxacin

Mechanism of action :

- Drug enters the bacteria by passive diffusion through porin channels
- They interfere with action of DNA gyrase ~~(Top II)~~ (topoisomerase III) & topoisomerase IV.
- Drug bind to both enzymes & DNA forms ternary complex.
- They inhibit DNA replication of bacterial DNA by inducing cleavage of DNA res causes cell death.
- Mammalian cells topoisomerase II shows less affinity for Fluoroquinolones, but they are inhibited by quinolones only at much high concentration.

Resistance

- Chromosomal mutation
- Bacteria produce DNA Gyrase / Topoisomerase IV with reduced affinity for flouroquinolones
- Efflux of these drugs across bacterial membrane
- No quinolone modifying / inactivating enzymes have been ~~id~~ identified in bacteria
- Resistance is slow to develop.

Antibacterial spectrum

- Potent bactericidal against gram negative bacteria E. coli, Salmonella, Shigella, Enterobacter.
- Ciprofloxacin is more active against Pseudomonas aeruginosa
- They ~~a~~ have also good activity against S. aureus but not against methicillin resistant strains
- Intracellular bacteria are also inhibited

P'kinetics:

- Rapid oral absorption
- High tissue permeability
- Concentrated in lung, sputum, muscle, bone & phagocytes exceeds than in plasma
- CSF & aqueous levels are low.
- Excreted in urin
- Urinary & bilary

Adverse effects :

- Nausea, vomiting, abdominal discomform,
- Headache, dizziness, delirium
- Hypersensitivity

Interaction :

- NSAIDs may enhance CNS toxicity of fQ's
- Antacids, sucralfate, Iron salts reduces absorption of fQ's

Therapeutic use :

- UTI, sexually transmit disease, GI infection
- Active against gram -ve bacilli
- Active against gram +ve bacteria & anaerobes
- Administered for 4-6 weeks
-