Amino glycosides

• Streptomycin, Gentamicin, Amikacin

• Physical and chemical properties
  • Water soluble, stable in solution, more active in alkaline pH

• MOA:
  • Irreversible inhibitors of protein synthesis
  • Initially passively diffuses via porin channels and then actively transported
  • Transport is enhanced by cell wall active drugs such as penicillin and vancomycin
  • Once inside the cell - binds to 30S subunits which inhibits protein synthesis by:
    • Interfering with peptide formation
    • Misreading mRNA which causes incorporation of incorrect amino acids
    • Formation of non functional monosomes
Amino glycosides

- Resistance occurs via 3 mechanisms:
  - Inactivation by phosphorylation of the amino glycoside
  - Impaired intracellular transport
  - Receptor on 30S subunit may be deleted

- Pharmacokinetics
  - A: Poor oral absorption
  - D: Highly polar compounds that do not enter cells readily, in the presence of inflammation have a higher rate of CSF penetrance
  - M:
  - E: Renal excretion, normal half life is 2 - 3 hours, rising to 24 - 48 hours in renal failure
Amino glycosides

• Pharmacodynamics
  • Concentration dependent killing - significant post antibiotic effect, meaning that the antibiotic continues to have anti bacterial activity beyond the time which measurable drug is present - ALLOWS FOR ONCE DAILY DOSING
  • Toxicity is both time and concentration dependent
    • Toxicity is unlikely to occur until a threshold concentration has been breached
    • Once this concentration is reached, time above this concentration line becomes critical
• Adverse effects:
  • All amino glycosides are OTO and RENO toxic
  • More likely to occur when dosing is continued for 5 days
  • More likely in elderly with renal insufficiency
  • Concurrent use with other nephrotoxic drugs potentiates toxicity
  • Ototoxicity results in:
    • Tinnitus and high frequency hearing loss
    • Vestibular damage: vertigo, ataxia
Amino glycosides

• Adverse effects
  • In very high doses can have a CURARE like effect and generate neuromuscular paralysis - reversible with calcium gluconate and neostigmine

• Clinical uses:
  • Gram -ve
  • Almost always used in combination with beta lactic antibiotic because of synergism
Tetracyclines

- Antimicrobial activity:
  - Broad spectrum
  - Bacteriostatic
  - gram +ve, gram -ve and protozoa (malaria)
  - Inhibitor of 30S ribosomal subunit

- Resistance:
  - Impaired influx or increased efflux
  - Production of proteins that interfere with ribosomal binding
  - Enzymatic inactivation

- Pharmacokinetics:
  - A: Well absorbed orally - agents differ in degree of PO absorption (60 - 70% for tetra, 95% for doxy)
    - A portion of administered dose remains intraluminal and alter gut flora
  - D: Distributes widely into tissues, except CSF, also cross placenta
  - M: Anticonvulsants, chronic alcohol consumption shorten the half life of doxycycline by 50% through enzyme induction
Tetracyclines

• *E*: Excreted mainly in bile and urine, 10 - 50% excreted in urine
  - Doxycycline is eliminated by non renal mechanism
• Pharmacodynamics
  - Clinical use:
    - *Mycoplasma, Chalmydiae, Rickettsiae*
    - Used in combination regimes to treat gastric and duodenal ulcers
  - Adverse reactions:
    - *Hypersensitivity* it UNCOMMON
    - *GIT*: N/V/D
    - *Bone*: binds to calcium deposited in foetal teeth leading to enamel dysplasia
    - *Liver*: Impaires hepatic function
    - *Renal*: RTA secondary to nitrogen retention
    - *Photosensitisation*
Macrolides

• Erythromycin
  • Antimicrobial activity: gram + ve (pneumococci, strep, staph), gram -ve (neisseria, bordetella, treponema)
    • Acts via protein inhibition of the 50S subunit
    • Activity is enhanced by alkaline pH
  • Pharmacokinetics:
    • A: Enteric coated as gastric acid interferes with absorption
    • D: Distributed widely except brain and CSF
    • M: Half life 1.5 hours
    • E: Excreted in bile
  • Clinical Use: Drug of choice in Corynebacterium, CAP, penicillin substitute in allergic patients
  • Adverse effects: N/V/D, Cholestatic hepatitis,
    • Drug interactions: Anticoagulants, Theophylline, Cyclosporin, Methylpred
Macrolides

• Clarithromycin: derived from erythromycin
  • Same MOI
  • Adv: Better PO Absorption, metabolised in liver - major metabolite has antimicrobial activity, lower incidence of GI intolerance
  • More active against MAC, Toxoplasma, M leparae

• Azithromycin - differs primarily in PK properties
  • Large Vd, long half-life - therefore once daily dosing, and shortened duration of treatment
Clindamycin

- Anti bacterial activity -
  - Strep, staph and pneumococci are inhibited, enterococci and gram -ve are resistant
- MOI: Binds to 50S subunit
- Pharmacokinetics:
  - A: Well absorbed PO
  - D: Well distributed, penetrates well —> except brain and CSF, penetrates well into abscess
  - M: Liver, half life around 2 - 2.5 hours
  - E: No dose adjustment in renal failure
- Clinical uses:
  - anaerobic infection caused by bactericides and mixed infections
  - Female GU tract infections
- Adverse effects:
  - N/V/D
  - Impaired LFTs + D.Diff colitis
Sulfonamides

- Sulfamethoxazole
  - Antibacterial activity: gram +ve, gram -ve, norcadia, chlamydia and some protozoa
  - Bacteriostatic alone, bactericidal with trimethoprim
  - MOA: Interferes with folate production and therefore DNA synthesis, doesn't effect mammalian cells because of exogenous folate production
  - Synergism with trimethoprim, because trimethoprim acts on sequential step of folate synthesis
  - Adverse reactions: fever, rash, dermatitis, N/V/D. Can crystalise in urine and cause obstruction, can cause granulocytopenia
Chloramphenicol

• Antibacterial activity: Bacteriostatic, broad spectrum Abx
  • H. influenzae, N meningitidis and some bactericides

• Pharmacokinetics
  • A: Rapidly absorbed orally
  • D: Widely distributed to virtually all tissues including CSF
  • M: Most of the drug is inactivated by conjugation
  • E: Renally excreted - need not be dose reduced in renal failure, but needs to be altered in hepatic failure
Chloramphenicol

- Adverse Reactions:
  - GI - N/V/D
  - Bone marrow - Dose related reversible red cell suppression, aplastic anaemia
  - New born toxicity - Gray - Baby Syndrome
  - Interactions - inhibits microsomal enzymes - increased serum concentrations for
    - Phenytoin, Warfarin
Quinolones

- Antibacterial effect: gram +ve, -ve and pseudomonas
- MOA: Block bacterial DNA synthesis by inhibiting topoisomerase 2 (DNA gyrase)
- Pharmacokinetics:
  - A: Good PO bioavailability 80 - 95%
  - D: Large Vd
  - M: T1/2 3 - 10 hours
  - E: Renally excreted
- Adverse Reactions: N/V/D, QT prolongation, damages growing cartilage therefore not for use in under 18 year olds.
Metronidazole

• Inhibits nucleic acid synthesis
• Good for anaerobes and protozoa esp C Diff
• AE: N/D, Abdo pain, metallic taste, disulfram effect when taken with alcohol
Disinfectants

- Disinfectant - strong chemical agents that inhibit or kill microorganisms
- Antiseptics - are disinfecting agents with sufficiently low toxicity for host cells and so can be used on skin (Alcohol)
Anti - protozoal agents

- Treatment of malaria
  - Four species of plasmodium cause human malaria
    - Falciparum
    - Vivax
    - Malariae
    - Ovale
  - Falciparum is responsible for nearly all serious complications
- Chloroquine is used for prophylaxis only in areas known to be infested by sensitive parasites
  - Doxycycline for areas with very high prevalence of multi drug resistant malaria
- Sensitive Falciparum malaria and non falciparum first line —> if from sensitive are —> Chloroquine
- Falciparum malaria —> non sensitive —> PO Quinine + Doxycycline
- Vivax and ovale —> Primaquine after Chloroquine
Chloroquine

- Utility against falciparum species has been seriously compromised by resistance
- Mechanism of action: controversial - blood schizontocide
  - rapidly ceases fever and clears parasite load in 48 - 72 hours
- Pharmacokinetics
  - A: Rapid and complete
  - D: Rapid and widespread - very large Vd
  - M:
    - E: Urine over 3 - 5 days
- Clinical uses:
  - Choice in non falciparum and sensitive falciparum cases
- Adverse effects: well tolerated generally
  - G6PD - haemolysis
  - Puritis
  - N/V/D/Abdominal pain
Quinine

• First line for falciparum species especially in severe disease
• MOA: Blood schizontocide - not active against liver stage parasites
• Clinical use: Falciparum malaria + severe infections
• Pharmacokinetics:
  • A: Rapid
  • D: Widely distributed
  • M: Liver
  • E: Kidney
• Adverse effects:
  • Cinchonism - Tinnitus, headahce, nausea, dizziness, flushing
  • Haematological - haemolysis, leukopenia
  • Can cause hypoglycaemia
  • Can stimulate contractions in late pregnancy (still use)
Primaquine

- Drug of choice for elimination of dormant liver forms of vivax and ovale
- Antimalarial actions: gametocidal, active against dormant hypnozoite

Pharmacokinetics:
- A: Well absorbed orally
- D: Widely distributed into tissues
- M: Rapidly metabolised in liver
- E: Urine

Adverse effects:
- Generally well tolerated
- GI upset more common at higher doses
Antivirals

• Viral replication takes several steps -
  • Attachment, entry through cell membrane, uncaring of nucleic acid, synthesis of regulatory proteins, synthesis of late proteins, assembly of viral particles, release
  • Antivirals interfere with these steps
Acyclovir

- Guanosine derivative - active against HSV 1, 2, and VZV

- Three steps before drug activation -
  - Converted into monophosphate derivative by viral cell specific thymidine kinase
  - Competes for DNA polymerase
  - Causes DNA chain termination

- Pharmacokinetics
  - A: 15 - 20% PO bioavailability
  - D: Well distributed, CSF concentrations are 50% of serum
  - M:
    - E: Renally excreted through filtration and tubular excretion

- Long term suppression of genital herpes, reduced symptoms by 2 days, reduced viral shedding, IV for HSV encephalitis
Principles of HIV therapy

- Start treatment if CD4 count is < 200 or verifier high or opportunistic infection
- Use multiple agents to avoid resistance
- Neucleotide RTI
  - Competitively inhibit HIV 1 reverse transcriptase
  - E.g. Lamivudine - cytosine analog when incorporated it results in premature termination of the DNA chain
- Non nucleoside RTI
  - Bind directly to HIV1 reverse transcriptase and inhibits
  - Delavirdine
- Protease inhibitor
  - Results in immature, non infectious viral particles
- Entry inhibitor
  - gp120 binding, prevents viral entry into cell
  - E.g. enfuvitide
Principles of HIV therapy

• Integrase inhibitor
  • Inhibits transfer of reverse transcribed HIV DNA into chromosomes of host cells

• M2 proton pump inhibitor and inhibition of uncoating of viral RNA
  • Amantadine