B26 - Chemotheraputic Drugs

(a) To outline the pharmacology of antimicrobial drugs.

Anti-microbial = kill or suppress the growth of micro-organisms.

3 types

(1) anti-bacterial
(2) anti-viral
(3) anti-fungal

Anti-bacterial

(i) inhibition of cell wall synthesis

- penicillins
- cephalosporins
- vancomycin

(ii) inhibition of protein synthesis

- macrolides
- aminoglycosides
- tetracyclines
- chloramphenicol

(iii) inhibition of nucleic acid synthesis

- sulphonamides
- metronidazole
- trimethoprim
- rifampicin
- quinolones

Anti-virals

- inhibit viral DNA replication (acyclovir)
- inhibit surface proteins on viruses to stop them begin released from infected cells -> limits spread of virus in the body (tamiflu - neuraminidase inhibitor)

Anti-fungals - inhibition of cell membrane function - azoles, amphortericin B & nystatins

<u>Classification of Anti-bacterial agents</u>

See table - classification of antibiotic agents

(1) Inhibition of cell wall synthesis

Penicillins

(i) Penicillinase susceptible - pen V & G
(ii) Penicillinase resistance - methicilin, oxacillin
(iii) Peniclinase susceptible with activity agains gram negative bacilli - ampicillin, amoxil, piperocillin
(iv) Penicillins with beta-lactase inhibitors - amoxy-clavulanate

Cephalosporins

1st generation - cephazolin, cephalexin
2nd generation - cefuroxime, cefoxitin
3rd generation - cefotaxime, ceftriaxone

Glycopeptide derivatives - vancomycin

Carbopenems - imipenem

(2) Inhibition of protein synthesis

Aminoglycosides

Gentamicin
Tobramycin
Amikacin

Macrolides

Erythromycin
Clarithromycin
Azithromycin

Tetracyclines

Tetracycline
Doxycycline

Chloramphenicol

Lincomycins - clindamycin

(3) Inhibition of bacterial nucleic acid synthesis

Sulfonamides

Sulfisoxazole
Sulfamethoxazole

Metronidazole

Pyrimidine derivatives - trimethoprim

Rifampicin

Quinolones

Norfloxacin
Ciprofloxacin

Antibiotics I use a lot

Penicillin

Chemical - prototype penicillin

Uses - infections

(1) respiratory tract
(2) ENT
(3) skin, bone, soft tissues
(4) gonorrhoea
(5) meningitis
(6) SBE

Presentation

- penicillin V = tablets, 125 and 250mg
- penicillin G = injection, white powder, 0.3 to 6g

Route - PO, IV, IM, intrathecal

Dose

- PO: 125 to 250mg Q4hrly

- IV/IM: 1 to 5g/day in divided doses

PK

Absorption - bioavailability = 30-60%
Distribution - 60% protein bound, Vd = 0.75L/kg
Metabolism - penicilloic acid -> penamaldic acid -> penicillenic acid
Elimination - 80% in urine by active tubular secretion, t1/2 = 0.7hrs

PD

Main action - bacteriacidal

Bugs

- *Streptococcus*
- *Neisseria*
- *Haemophilus*
- *Corynebacterium*
- *Bacillus*
- *Clostridium*
- *Listeria*
- *Treponema*
- some sensitive staphylococci
- some oral anaerobes

Mode of action

- binds to penicillin-binding proteins in bacterial cell wall -> prevents peptidoglycan cross-linking -> decreased mechanical stability of the bacterial cell wall

Side effects

- high dose -> hypernatraemia, hypokalaemia
- N & V
- neuropathy
- nephropathy

Allergic phenomena

- anaphylaxis
- rashes
- haemolytic anaemia

Oxacillin

Chemical - penicillin with a side chain (isoxazolyl penicillin)

Uses - bacteriosidal

Bugs - Staphylococci

Presenation

- capsules: 250 & 500mg
- injection: 0.5 to 10g
- tablets:

Routes - IM, IV, PO

Dose

- 1-2g Q4hrly (adult)
- 50-100mg/kg/day (paeds)

Piperacillin

Chemical - semi-synthetic penicillin

Uses - bacteriosidal

(1) UTI & respiratory tract infection
(2) intra-abdominal & biliary tract sepsis
(3) gynaecological & obstetric infections
(4) infections of skin, soft tissue, bone & joints
(5) septicaemia
(6) meningitis
(7) peri-operative prophylaxis

Bugs - anaerobes & pseudomonas

- *Staphylococci aureus* (penicillin resistant)
- *Enterococcus*
- *Kelbsiella*
- *Serratia*
- *Enterobacter*
- *Pseudomonas*

Dose

- IV: 4g Q6 hrly
- reduce in renal impairment

PK

Distribution - 16% protein bound, Vd 0.3L/kg
Metabolism - none!
Elimination - 80% urine, 20% bile, t1/2 = 60min

PD

Main action - see above

Mechanism

- binds to cell wall penicillin-binding proteins -> inhibit their activity -> shape of bugs cannot be maintained

Side effects

- mild hypernatraemia
- hypokalaemia
- N & V
- LFTs disturbance
- allergy
- leucopenia
- neutropenia

Amoxycillin

- identical to ampicillin but better absorbed from the GI tract.

Bugs

- *Staphylococci aureus* (penicillin sensitive)
- *Streptococcus*
- *Enterococcus*
- *Neiserria*
- *Listeria*
- *Haemophilus*

Dose

- PO: 250 to 500mg tds
- IV: 6g over 24hrs
- decrease in renal failure

PK

Absorption -
Distribution - Vd = 0.3L/kg, protein binding = 20%
Metabolism - hepatic
Excretion - urinary 90% unchanged, bile 10%, Cl = 4mL/min/kg, t1/2 = 1hr

PD

See other penicillins

Amoxy-clavulanate

Chemical - amoxicillin + clavulanic acid (beta-lactamase inhibitor)

Bugs

- *Staphylococci*
- *Streptococcus*
- *Enterococcus*
- *Haemophilus*
- *Klebsiella*
- *Proteus*
- *Bacteriodes*

Dose (500mg amoxil + 125mg clavulanate)

- tablets: 1-2 Q8hrs
- IV: 1.2g Q6hrs
- reduce in renal failure

Cephazolin

Chemical - 1st generation cephazolin

Bugs

- *Staphylococci* (penicillin sensitive)
- *Staphylococci* (peniclin resistant)
- *Streptococcus*
- *Haemophilus*
- *E. Coli*
- *Klebsiella*

- *Serratia*
- *Proteus*

Presentation

- injection: 1g powder that needs reconstitution in H2O

Routes - IV or IM

Dose

- 1g Q8hrly (adult)
- 15mg/kg Q8hrly (paediatric)
- decrease in renal impairment

PK - t1/2 = 1.5hrs (renally excreted)

PD

Main action - bactericidal

Mechanism

- inhibit bacterial cell wall synthesis & have low intrinsic toxicity

Side effects

- hypersensitivity
- slightly nephrotoxic

Cefoxitin

Uses

(1) bowel surgery
(2) rheumatic heart disease
(3) gonorrhoea

Dose - 1-2g Q6hrly

See above for adverse effects

Ceftriaxone

Chemical - 3rd generation cephalosporin

Bugs

- *Staphylococci*
- *Streptococci*
- *Neisseria*
- *Haemophilus influenzae*
- *E coli*
- *Klebsiella*
- *Serratia*
- *Proteus*

Used in

(1) meningitis
(2) colonic surgery
(3) gonorrhoea

Dose

- 1-4g daily IV
- reduce dose in renal failure

Vancomycin

Chemical - glycopeptide derivative

Bugs

- *Staphylococci*
- *Streptococci*
- *Enterococcus*
- *Clostridium difficile*

Uses

(1) pseudomembranous colitis
(2) enterocolitis
(3) endocarditis
(4) MRSA infection
(5) cardiac & orthopaedic surgical procedures
(6) CSF shunt infections

Mechanism of action

- impaires cell wall synthesis of gram +ve bacteria

Route - PO/IV

Dose

- 10-15mg/kg over 60min
- infuse slowly -> otherwise 'red man syndrome'
- decrease dose in renal failure

PK

Elimination - renal, 90% unchanged, t1/2 = 6hrs

PD

Side effects

- histamine release -> hypotension
- ototoxic
- nephrotoxic

Imipenem

Chemical - semi-synthetic thienamycin antibiiotic in combination with cilastatin a renal peptidase inhibitor which decreases renal metabolism of imipenem.

Uses - infection treatment

(1) urinary
(2) respiratory
(3) intra-abdominal sepsis
(4) bone
(5) joint
(6) bacteraemia

Bugs

- gram +ve & -ve aerobes & anaerobes + staphylococci
- *Pseudomonas aruginosa*
- *Haemophilus influenzae*
- *Neisseria gonorrhoea*
- *Escherichia coli*
- *Proteus*

- *Klebsiella*
- *Salmonella*
- *Shigella*

Presentation

- vials
- 500mg of imipenem monohydrate
- 500mg of cilastatin sodium

Route - IV

Dose

- 1 to 2g/24hrs in 3 to 4 divided doses
- 50mg/kg/day
- reduce dose in renal failure

PK

Distribution - 20% bound, Vd = 0.25L/kg
Metabolism - partial post-excretory metabolism in renal proximal tubules
Elimination - 70% unchanged in urine, Cl = 3mL/min/kg, t1/2 = 60min

PD

Main action - see above

Mechanism

- inhibition of cell wall synthesis

Side effects

- hypotension
- rashes
- eosinophilia
- abnormal LFTs
- seizures (2%)
- irritant to veins

Gentamicin

Chemical - an aminoglycoside

Uses

(1) UTI
(2) severe respiratory tract infections
(3) severe neonatal infection
(4) septacaemia

Bugs - gram -ve & +ve

- Escherichia coli
- Klebsiella
- Proteus
- Pseudomonas aruginosa
- Staphylococci

Presentation

- clear solution for injection
- 10 to 40mg/mL
- also available for topical treatment, bone cement, beads & for intrathecal administration.

Route - IV, TOP, intrathecal

Dose

- loading dose based on renal function (5mg/kg)
- then subsequent dosing on clearance

PK

Distribution - <10% bound, Vd = 0.14 to 0.7L/kg
Metabolism - NONE!
Elimination - dependent on GFR, Cl = 1.2mL/min/kg, t1/2 = 2hrs

PD

Main action - see above

Mechanism

- irreversible binding to bacterial ribosomal proteins -> inhibits protein synthesis

Side effects

- ototoxicity
- nephrotoxicity

- headaches
- nausea & vomiting
- rashes
- abnormal LFTs

Azithromycin

Chemical - macrolide

Uses

(1) chronic infections in HIV
(2) respiratory tract infections
(3) anti-tuberculous drugs

Dose - 500mg OD PO

Side effects

- N & V
- hepatic impairment
- phlebitis
- Stevens-Johnson syndrome
- prolongation of QT interval

Metronidazole

Chemical - synthetic imidazole derivative

Uses

(1) anaerobic infections (treatment & prophylaxis)
(2) protozoal infections - amoebiasis, giardiasis & trichomoniasis
(3) dental infections
(4) pseudomembranous colitis

Presentation

- tablets: 200 to 500mg
- suppositories: 500mg or 1g
- injection: clear, colourless, 0.5% solution

Routes - IV, PO, PR

Dose

- PO: 200 to 800mg
- PR: 1g Q8hrly
- IV: 500mg Q8hrly

PK

Absorption - bioavailability PO = 80%, PR = 75%
Distribution - 10% protein bound, Vd = 0.75L/kg
Metabolism - oxidation & glucuronidation in liver
Elimination - 60% unchanged in urine, Cl = 1mL/kg/min, t1/2 = 8hrs

PD

Main action - antimicrobial

Mechanism

- reacts with bacterial DNA -> resultant DNA complex can not longer function as an effective primer for DNA & RNA polymerases -> all nucleic acid synthesis is effectively terminated.

Side effects

- decreases cholesterol content of bile
- unpleasant taste
- nausea & vomiting
- rashes
- darkening of urine (reddish, brown)
- chronic use -> leucopenia, neuropathy

Drug interactions

- warfarin -> increase anticoagulation
- alcohol -> delirium
- NDNMBD -> prolongation of block

Trimethoprim

Chemical - pyrimidine derivative

Uses

(1) UTI
(2) prophylaxis in COPD

Bugs

- Escherichia coli
- Klebiella
- Serratia
- Proteus

Mechanism

- inhibition of nucleic acid synthesis

Dose

- PO: 200mg bd
- IV: 150 to 250mg bd
- decrease dose in renal impairment

Side effects

- N & V
- pruritis
- folate deficiency -> marrow suppression

Ciprofloxacin

Chemical - quinolone

Uses

(1) UTI
(2) respiratory
(3) GI
(4) bone, joint
(5) skin
(6) eyes
(7) ENT
(8) pelvic & intra-abdominal
(9) gonorrhoea
(10) septicaemia

Bugs - wide variety of gram +ve & -ve & anaerobes

- *Escherichia coli*
- *Salmonella*

- *Shigella*
- *Klebsiella*
- *Proteus*
- *Haemophillus*
- *Psedomonas*
- *Neiserria*
- *Staphylococci*
- *Clostridium*
- *Bacteroides*
- *Brucella*

Presentation

- tablets: 250 to 750mg
- suspension: 50mg/mL
- injection: clear, pale yellow, 2mg/mL

Routes - PO, IV

Dose

- PO: 250 to 750mg in divided doses
- IV: 200 to 400mg daily

PK

Absorption - bioavailability = 70%
Distribution - 30% protein bound, Vd = 2L/kg
Metabolism - active metabolites
Elimination - urine & faeces, Cl = 500mLmin, t1/2 = 5hr

PD

Main action - bacteriacidal

Mechanism - inhbition of DNA gyrase -> DNA unable to form supercoils

Side effects

- N & V
- anxiety
- insomnia
- seizures
- hallucinations
- allergy -> photosensitivity
- abnormal LFT's

(b) To outline the interactions between anti-microbial & drugs used peri-operatively.

NDNMBD's

Aminoglycosides, tetracyclines, linomycin and clindamycin, metronidazole -> potentiate the effects of NDNMBD (inhibition of pre-synaptic release of Ach & stabilisation of post-synaptic membrane)

Penicillin G, tetracyclins & cephalosporins -> no effect on NDNMBD's.

Benzodiazepines

Erythromycin -> potentiates the action of midazolam.

(c) To explain the principles of antibiotic prophylaxis.

Antibiotic prophylaxis = to prevent infection at the surgical site where risk of wound infection is high.

Basic priniciples

1. Give when high bacterial innoculum likely
2. Artificial device inserted
3. Patient immune deficient
4. Give antibiotics IV
5. Complete injection or infusion before the incision is made
6. First generation cephalosporin (cephazolin) most cost effective -> cover skin & genitourinary tract pathogens.
7. Colorectal & abdominal operations - prominance of anerobes -> metronidazole, cefoxitin, cefotetan or cefmetazole.
8. Vancomycin -> cardiovascular, joint prostheses & MRSA.
9. Give another dose at 3hrs (risk of contamination highest at incision and closure)

Gynae - C/S & hysterectomy
Ortho - arthroplasty, ORIF, open #'s
General - cholecytectomy, colon surgery, appendx, gastric resection, penetrating abdominal trauma
Urological
Oropharyngeal
Cardiothoracic - CABG, valves, pacemaker insertion, thorocotomy
Vascular - AAA, PVD
Neuro - shunt, craniotomy

Common pathogens

- *staph aureus*
- *coagulase-negative staph*

- *aerogic gram-negative organi*sms

- illogical to continue prophylactic A/B's until surgical drains come out.

(c) To outline the pharmacology of antiseptics & disinfectants.

Antiseptic = an agent capable of preventing infection by inhibiting growth of infectious agents.

Disinfectants = an agent capable of destroying pathogenic micro-organisms or inhibit their growth.

Types of disinfectants

Alcohols - isopropanol, ethanol
Aldehydes - glutaraldehyde, formaldehyde
Chlorhexidine
Sodium hypochlorite
Hexachlorophene
Povidone, iodine
Quaternary ammonium compounds
Strong oxidizing agents

Alcohols

- rapidly active
- kill vegetative bacteria, fungi & inactivate lipophilic viruses.
- act by denaturing proteins.
- must be left to evaporate before cautery or laser surgery.

Chlorexidine

- cationic biguanide
- low H2O solubility
- active against vegetative bacteria, fungi, mycobacteria & viruses.
- absorbed by the membrane of organism -> leakage of small molecules & preciptation of cytoplasmic proteins.

Iodine

- 1:20,000 solution
- takes 1 minute to kill bacteria
- kills spores in 15 min
- can cause hypersensitivity reactions

Povidone

- same activity as iodine.
- less irritating than iodine

Quaternary ammonium compounds

- cationic surface-active detergents
- have atleast one long water repellent hydrocarbon chain -> molecules form layer on surface of solutions
- works by inactivation of energy-producing enzymes, denaturing proteins & disruption of cell membrane
- act on all organisms
- used for sanitation of noncritical surfaces

Aldehydes

- used for sterilization of instruments (fiberoptic endoscopes, respiratory therapy equipment, haemodylzers, dental hand peices)
- have broad spectrum of activity
- they alkylate chemical groups in proteins & nucleic acids.

(e) To outline the pharmacology of antiviral agents

- difficult to make agents as viruses are intracellular parasites that use host cell mechanisms.
- thus is hard to kill viruses without harming host.

Agents

Idoxurdine

- halogenated pryimidine -> incorporated into both viral & mammalian DNA
- works agains herpes simplex keratitis on skin, conjunctiva, & mucous membranes.

Amantadine

- synthetic tricyclic amine
- inhibits replication of influenze A virus.

Vidarabine

- analogue of adenosine
- effective in the treatment of herpes simplex encephalitis & keratoconjunctivitis
- inhibits viral DNA polymerase

Zanamivir

- sialic acid analogue
- potent inhibitor of influenza virus neuraminidase

- enzyme is essential for replication, cleaves terminal sialic acid residues, allows the release of virus from infected cells, prevents the aggregation of virus.

Acyclovir

- limited action against herpes viruses

Ganciclovir

- nucleoside analogue of guanosine
- treatment of CMV
- inhibits viral DNA polymerase
- administer with granulocyte stimulating factor -> prevent granulocytopenia

Inteferon

- general term used for designated glycoproteins produced in response to viral infection.
- bind to specific receptors on cell membranes -> degradation of viral RNA
- also inhibits cell proliferation and enhances the tumouricidal activities of macrophages.

(f) To outline the pharmacology of antifungal agents.

Agents

Nystatin

- polyene antifungal
- increases permeability of membranes -> small particles can escape
- primarily used to treat *Candida* infection

Amphortericin B

- a polyene antifunga
- most effective anti-fungal drug
- must administer IV
- doesn't penetrate CSF -> intrathecal injection may be needed
- dose reduction in renal impairment
- horrible side effects: fever, chills, dyspnoea, hypotension

(g) To outline the pharmacology of cancer chemotheraputic agents with particular reference to problems in the perioperative period.

Thrombocytopaenia -> metrotrexate, bleomycin, cisplatin & busulfan.

Cardiomyopathy -> danunorubicin, doxorubicin & bleomycin

Renal toxicity -> buslphan, cisplatin & methotrexate.

Hepatic toxicity -> buslphan & methotrexate

Plasma cholinesterase inhibition -> larethamine & cyclophosphamide

Anaemia -> buslfan, methotrexate, bleomycin & cisplatin.

Methotrexate

- poorly lipid solube
- folate analogue
- antimetabolite
- inhibits enzyme involved in the synthesis of new pyrimidines & purines.
- used in lymphoblastic leukaemias, choriocarcinoma, psoriasis, RA

Cisplatin

- platinum atom, 2 amines & 2 chlorides
- DNA alkylating drug
- used in treatment of non-haematologic malignancies

Busulphan

- alkyl sulfonate
- used in CML

Cyclophosphamide

- used in a wide variety of cancers & inflammatory conditions
- Hodgkins disease, lymphosarcoma, Burkitt lymphoma, ALL, breast cancer, Wegeners granulomatosis, RA

Bleomycin

- water soluble glycopeptides
- in the prescence of O2, Fe or Cu -> free radical that create DNA breaks
- used for: testicular carcinoma, palliative treatment of SCC's
- minimise O2 (FiO2 < 30%) & crystalloid administration

Danunorubicin & Doxorubicin

- anthracycline antibiotics
- produced from soil fungi

- bind to DNA and inhibit the template activity of nucleic acids
- used to treat: acute leukaemias, solid tumours

Cyclosporin

- least toxic
- but nephro & neurotoxic