ANTIMICROBIAL AGENTS

1.0 INTRODUCTION

Antimicrobial agents are widely used drugs which are starling examples of modern medicine. This is because over a period of time, they have been developed to attain remarkable power and specific activity of their antimicrobial action. The recent developments target the bacterial and fungal cell wall-synthesizing enzymes, the bacterial ribosome, enzymes necessary for nucleoside synthesis and DNA replication.

Microorganisms have the capacity and ability to adapt to environmental pressures in many ways including antibiotic pressure and this results in development of resistance which occurs as a consequence of injudicious use of antibiotics especially overuse and inappropriate use of the same. This has lead to development of multi-drug resistance pathogens.

2.0 CLASSIFICATION OF ANTIMICROBIALS

Antimicrobial drugs can be classified in various ways depending on type of organisms, against which they act, chemical structure, mechanism of action, spectrum of activity, type of action and source.

Type of Antimicrobials

1. Antibiotics
2. Antiviral agents
3. Antifungal (antimycotic) agents
4. Antiparasitic agents
5. Antihelminthic agents
6. Antiprotozoal agents

Mechanism of Action

1) Inhibit cell wall synthesis
2) Cause leakage of cell membranes
3) Inhibit protein synthesis
4) Cause misreading of mRNA code
5) Inhibit DNA gyrase
6) Interfere with DNA function

Spectrum of Activity

1) Narrow spectrum
2) Broad spectrum

Type of Action

1) Bateriostatic, fungicistatic
2) Bacteriocidal, fungicidal

Source

1) Fungi
2) Bacteria
3) Actinomycetes

3.0 PROBLEMS ASSOCIATED WITH ANTIMICROBIALS

The problems associated with antimicrobial agents are resistance, superinfection and masking of infections. The mechanisms for resistance include naturally resistant strains, spontaneous mutation and transmission of genes from other organisms.

1.0 MECHANISM OF ACTION

Drugs are not the sole instruments of cure but act together with the natural body defense mechanisms. Antimicrobial agents act at different sites in the target organisms. The 4 sites are the cell wall, the cytoplasmic membrane, protein synthesis and nucleic acid metabolism

The Cell Wall

The cell wall gives the bacterium its characteristic shape and provides protection against lower osmotic pressure of the environment. Multiplication of bacteria normally involves breakdown and extension of the wall and distortion of this process makes the bacterium susceptible to effects of low osmotic pressure and hence the cell bursts. Human cells have no cell wall. Drugs that interfere with cell wall synthesis are effective only against growing cells.

Examples - penicillins, cephalosporins, vancomycin and cycloserine.

The Cytoplasmic Membrane

This is a membrane inside the cell wall and it's the site for microbial cell's biochemical activity. Drugs that act here interfere with vital biochemical activities of the microbial organisms.

Examples: - polyenes (nystatin, amphotericin), azoles (fluconazole, itraconazole,

miconazole) and polymyxins.

Protein Synthesis

Some antimicrobial agents interfere with microbial proteins synthesis at various points during the build up of peptide chains on the ribosomes.

Examples: - chloramphenicol, erythromycin, fusidic acid, tetracyclines, aminoglycosides and linezolid.

Nucleic Acid synthesis

Drugs interfere directly with the microbial DNA or its replacement or repair (examples - quinolones, metronidazole) or interfere with the RNA (example – rifampicin). The drugs may interfere indirectly with nucleic acid synthesis

Examples – sulphonamidies, trimethoprim)

ANTIBIOTICS

1.0 INTRODUCTION

Antibiotics act by interfering with vital activities of the microbes bringing about **bactericidal and bacteristatic** effects through disruptions in protein and cell wall synthesis. Bactericidal effects involve the killing of the bacteria with drugs such as penicillins, cephalosporins, aminoglycosides, isoniazid and rifampicin whereas bacteristatic effects involve arresting of bacterial multiplication by drugs such as sulphonamides, tetracyclines and chloramphenicol.

1) β-lactam antibiotics
    a. Pencillins
    b. Cephalosporins
    c. Cephamycins
    d. Monobactams
    e. β-lactamase inhibitors [clavulanic acid, sulbactam and tozabactma])
2) Carbepenems
3) Vancomycin
4) Fusfomycin
5) Bacitracin
6) Cycloserine

Antibiotics can also inhibit bacterial protein synthesis by binding to sites such as 30S, 50S and 24S of the ribosomal sub units of the bacterial cell.

2.0 MISUSES OF CHEMOTHERAPY

1. Treatment of fever(pyrexia) of unknown origin (fever is not necessarily due to infection)
2. Choice of an ineffective antibiotic
3. Inadequate or excessive doses
4. Use in such insusceptible infections as uncomplicated viral infection
5. Improper route of administration
6. Continued use after bacterial resistance has developed
7. Continued use in the presence of a serious toxic or allergic reaction
8. Failure to alter chemotherapy when superimposed infections with resistant organisms occur
9. Use of improper combinations of drugs
10. Reliance on chemotherapy or prophylaxis to the exclusion of surgical intervention e.g. drainage of localized infection

3.0 CLASSIFICATION

Classification is based on the mode of action and chemical nature of the drugs. Classification based on the mode of action falls into three main groups namely: - **cell wall synthesis inhibitors**, **protein synthesis inhibitors** and **nucleic acid synthesis inhibitors**.

I. INHIBITION OF CELL WALL SYNTHESIS

1. β Lactam Antibiotics

a. Penicillins
b. Cephalosporins
c. Monobactams
d. Beta-lactamase inhibibitors
e. Carbapenems

II. INHIBITION OF PROTEIN SYNTHESIS

1. Aminoglycosides
2. Tetracyclines
3. Macrolides
4. Chloromphenical and Derivatives

III. INHIBITION OF NUCLEIC ACID SYNTHESIS

1. Lincosamides
2. Sulphonamides
3. Trimethoprim
4. Fluoro-Quinolones (Quinolones)
5. Streoidal antibiotics - Fusidic acid
6. Nitroimidazoles
7. Azoles
8. Glycopeptides
9. Oxazolidinones
10. Polyene Antibiotics

BETA-LACTAM ANTIBIOTICS

1.0. Introduction

The β-lactam antibiotics include the penicillins, cephalosporins and cephamycins, monobactams, β-lactamase inhibitors and carbapenems. Penicillins, cephalosporins and cephamycins are called β-lactams because they contain a beta-lactam ring and hence have similar pharmacologic properties and mechanisms of action. β-lactam antibiotics are **bactericidal** in action whereby they interfere with a terminal step in bacterial cell wall synthesis and hence increase cell wall breakdown. Their spectrum of action includes both gram-positive and gram-negative organisms.

2.0. Classification

1) Penicillins
2) Cephalosporins
3) Monobactams
4) Beta-lactamase inhibitors
5) Carbapenems

PENICILLINS

1.0. Introduction

Penicillins are classified as β-lactam drugs because they have a unique four-membraned lactam ring. Penicillins are a variety of chemically related drugs derived from certain fungi called *Penicillin notatum* and *Penicillin chrysogenum*. The penicillin nucleus was first prepared chemically in 1957 and it became possible to make semi-synthetic penicillins by adding various side chains. The naturally occurring penicillins have a narrow spectrum of action mainly against the Gram positive cocci, bacilli and spirochaetes.

There are naturally accruing penicillins such as penicillin G and penicillin V and the semi-synthetic ones. The naturally occurring penicillins have a narrow spectrum of action.

2.0. Structure

Penicillins have a basic 6-aminopenicillanic acid (6-APA) nucleus with a β-lactum ring and an R-side chain (for synthetic penicillins). Penicillins are fused to a thiozolide ring.

3.0. Mechanism of Action

Penicillins are **bactericidal** and act by interfering with **bacterial cell wall synthesis** and hence they primarily affect growing cells and have minimal or no activity against intracellular microorganisms, dormant bacteria and organism lacking the cell wall (e.g. mammalian cells). They inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. The cell wall maintains the shape of the cell and prevents cell lysis from high osmotic pressure. The cell wall is composed of complex cross-linked peptidoglycan made of polysaccharides and polypeptides.

The polysaccharide has amino sugars N-acetlyglucosamine and N-acetylmuramic acid which are alternating. The N-acetylmuramic acid is linked to a five amino acid peptide which terminates in D-alanyly-D-alanine. Penicillin-binding proteins (PBPs) catalyze the *transpeptidase reaction* which removes the terminal alanine to form a cross link with a nearby peptide. This gives the cell wall its structural rigidity.

β-lactam antibiotics are **analogues of the natural D-Ala-D-ala** substrate and are covalently bound by PBPs at the active site. Attachment of the β-lactam drugs to PBPs inhibits *transpeptidation reaction* blocking formation of peptidoglycan and hence the cell dies. Penicillins interfere with the **cross linkage of mucopeptides** (between alanine and glycine) which are structural components of the bacterial cell wall and may cause release of autolysins. They inhibit cell wall synthesis and cause increased cell wall breakdown.

Cell walls of the Gram positive bacteria are largely composed of mucopeptide complexes and the Gram negative bacteria have fewer amounts of mucopeptide complexes therefore Gram positive bacteria are more sensitive to penicillins than gram negative ones that would negative one that would require larger amounts of the drug.

4.0. Pharmacokinetics

Absorption: Penicillin absorption from the GIT is variable for different penicillins. It is incomplete or erratic and occurs mainly from the duodenum and much less so from the stomach and large intestine. They are destroyed by gastric acids. Presence of food in GIT impairs absorption so to ensure maximum absorption all oral penicillins should be taken on an empty stomach (or ½ hour to 2 hours after meals). After parenteral administration, absorption of most penicillins is complete and rapid. IV administration is preferable because of irritation and local pain produced by the IM injection of large doses of penicillins. Benzathine and procaine penicillin are formulated to delay absorption resulting in prolonged blood and tissue concentrations.

Distribution: Penicillins are distributed rapidly to most body fluids and tissues after an IV or IM injection and slowly after oral administration. Penicillins are polar molecules and the concentrations within cells are less than that in extracellular fluids. Penicillin concentrations in most tissues are equal to those in serum. Concentrations are low in normal joint, ocular, pericardial, and pleural fluids and higher in the peritoneal fluid, but with inflammation penicillins penetrate well into most body fluids and spaces. Penetration into the CSF also varies but increased when the meninges are inflamed. High concentrations are found in the liver, bile, lungs, intestine and skin. Penicillins cross the blood-brain barrier well but high doses have to be given to achieve good therapeutic concentrations. Penicillin penetration into the eye, the prostate and the central nervous system is poor. Penicillins are reversibly bound to plasma protein

Excretion: Penicillin is rapidly excreted unchanged (no alteration in the liver) by the kidneys into urine. Excretion is mainly by renal tubular secretion (90%) and 10% renal secretion. Other routes of excretion include sputum, milk and bile. Renal excretion can be blocked by **probenecid**. Renal excretion is lower in neonates than adults.

5.0. Indications

Infections caused by: -

1. Pneumococci
2. Meningococci
3. Streptococcus (aerobic and anaerobic)
4. Gonococci
5. Non-penicillinase producing Staphylococci
6. Spirochetes (syphilis)
7. Clostridial infections (tetanus, gas gangrene)
8. Actinomycosis

9. Anthracis

6.0. contraindications

1. History of hypersensitivity to penicillins and cephalosporins
2. Parenteral solutions should not be injected into or near an artery or nerve

7.0. Side Effects

Hypersensitivity(causes rashes, urticaria, pruritus and anaphylaxis), diarrhoea (may cause colitis, common with broad spectrum penicillins), glossitis, stomatitis, gastritis, sore throat, dry mouth, furry tongue, anaemia, haemorrhagic manifestations, nephrotoxicity (renal failure due to tubulo-interstitial nephritis and accumulation of electrolyte because most injectable penicillins contain either sodium or potassium) and encephalopathy (due to cerebral irritation resulting from excessively high doses or in patients with renal failure).

8.0. Precautions

1. Hypersensitivity reactions may occur

9.0. Drug Interactions

1. Penicillins inactivate aminoglycosides when mixed in the same solution.
2. Bacteriostatic antibiotics such as erythromycin and tetracyclines diminish the bactericidal effects of penicillins
3. May render oral contraceptives less effective resulting in increased

Resistance

Resistance to penicillins and other β-lactams is due to four mechanisms namely: -

a) Inactivation of antibiotic by β-lactamase enzyme
b) Modification or alteration of target PBPs
c) Impaired penetration of the drug to PBPs
d) Presence of an efflux pump

Inactivation of the antibiotic: Production of β-lactamase enzyme is the main stay of development of resistance to penicillins. There are more than 300 different β-lactamases produced by *Staphylococcus aureus, Haemophilus spp* and *E. coli* (narrow spectrum as they act on penicillins only) and *Pseudomonas aeruginosa* and *Enterobacter spp* (broad spectrum acting on both penicillins and cephalosporins). Carbapenems are resistant to hydrolysis by penicillinases and cephalosporinases but are hydrolyzed by a metallo-β-lactamase

Alteration of PBPs Target: This is responsible for resistance to methicillin in staphylococcal and penicillin resistance in pneumococci and enterococci. There is production of PBPs with low affinity for binding
β-lactam antibiotics hence inhibition occurs only at relatively high concentrations which may not be clinically achievable.

Impaired Penetration of Antibiotics: Impaired penetration of antibiotics to target PBPs occurs only in Gram negative species due to the impermeability of an outer cell wall membrane present in the Gram negative microbes. β-lactam drugs enter the gram negative organisms via protein channels in the outer membrane hence there is no or great reduction in drug entry into the cell when the channels are absent. This slow process allows enzymes the time to destroy the drug

Efflux Pump: An efflux pump efficiently transports some β-lactam antibiotics from the periplasm back across the outer membrane reducing the amount of antibiotic in the cell. This is seen in Gram negative organisms.

10.0. classification

Penicillins are generally classified according to their spectrum of action into narrow spectrum and broad spectrum penicillins.

1. Narrow spectrum
    a. Benzyl penicillin (Penicillin G)
    b. Phenoxymethyl penicillin (Penicillin V)
    c. Procaine penicillin (fortified procaine penicillin – PPF)
    d. Triplopen
    e. Seclopen
    f. Benzathine Penicillin
2. Broad spectrum penicillins
    a. Amoxicillin
    b. Ampicillin
    c. Amoxycillin + Clavulanic acid(Augumetin)
    d. Amxycillin + Fluclacillin (Suprapen)
    e. Ampiciilin + Cloxacillin (Ampiclox)

3. Penicillinase-resistant penicillins
    a. Cloxacillin
    b. Flucloxacillin
    c. Dicloxacillin
    d. Oxacillin
    e. Carbenecillin

4. Antipseudomonal penicillins
    a. Ticarcillin
    b. Timentin

5. Mecillinams - Pivmecillanam

INDIVIDUAL DRUGS

A. NARROW SPECTRUM PENICILLINS

The narrow spectrum penicillins which are naturally occurring can be further classified as: - short acting penicillins (benzyl penicillin and phenoxymethyl penicillin), long acting penicillins (procaine penicillin and fortified procaine penicillin) and depot/repository penicillin (benzathine penicillin – panadur).

1. BENZYLPENICILLIN (PENICILLIN G) – Crystalline Penicillin (Crystapen)

This is the most important and useful antibiotic but it is inactivated by bacterial β-lactamases. This is quick acting injectable penicillin dissolved in aqueous base and quickly attains desired high blood levels.

Indications

1) Throat infections
2) Otitis media
3) Streptococcal infections (including pneumococcal)
4) Gonococcal
5) Meningococcal infections
6) Anthrax
7) Diphtheria
8) Gas gangrene
9) Leptospirosis
10) Tetanus

Precautions

1) History of allergy
2) False-positive urinary glucose
3) Renal impairment

Contraindications

Penicillin hypersensitivity

Side Effects

Hypersensitivity reactions (urticaria, fever joint pains , rashes, angioedema, anaphylaxis and serum sickness like reaction), diarrhoea, severe renal impairment, haemolytic anaemia, leucopenia, thrombocytopenia, coagulation disorders and CNS toxicities

Preparation

1) Injection – 1 vial = 1 mega units (MU) or 1 000 000 IU (international units) = 600 mg; 1 mg = 1667 IU (Injection powder for reconstitution). Administered IV or IM

Dose

Adults – 2.4 – 4.8 gm daily in 4 divided doses (600 mg – 1.2 gm QID or 1 – 2 MU QID); increased dose in meningitis (2.4 gm 4 hourly or 4 MU QID); same for anthrax (in combination with other drugs). In endocarditis 7.2 gm daily in 6 divided doses

Preterm neonate and neonate- under 1 week 50 mg/kg daily in 2 divided doses (25 mg/kg BD or 250 000 IU or ¼ MU BD); 1 – 4 weeks 75 mg/kg daily in 3 divided doses (25 mg/kg TDS or 250 000 IU or ¼ MU TDS)

Child – 1 month – 12 years 100 mg/kg (50 000 IU/kg) daily in 4 divided doses (250 mg – 1.2 mg or ¼ MU – 2 MU QID)

Common Names

1) Crystapen

2. PHENOXYMETHYLPENICILLIN (Penicillin V) - PEN-V

Phenoxymethylpenicillin (Pen V) has a similar antibacterial spectrum as benzyl penicillin but is less effective. It is gastric acid stable hence suitable for oral administration. Its absorption is unpredictable and has variable plasma concentrations hence not used.

Indications

1) Streptococcal pharyngitis
2) Tonsillitis
3) Oral infections
4) Otitis media

5) Cellulites
6) Rheumatic fever and pneumococcal infection prophylaxis

Precautions

1) History of allergy
2) High dose in patients with impaired renal function

Contraindications

1) Neonates of allergic mothers
2) Penicillin and cephalosporin hypersensitivity

Side Effects

GI disturbances, allergic reactions, anaphylactic shock, super-infections, sore mouth and tongue and black hairy tongue

Preparations

1) Tablets 250 mg
2) Syrup 125 mg/5 ml

Dose

- Children < 30 kg - 250 mg BD or TID
- Adults and children over 30 kg – 500 mg BD or TID

Common names

1) Cosapen
2) Unipen

3. PROCAINE BENZYL PENICILLIN (PROCAINE PENICILLIN)

Procaine benzyl penicillin is an intermediate acting injectable penicillin in an oily base and hence has slower release form the muscles (slower absorption). It is given IM only and attains fairly high blood levels.

Indications

1) Syphilis

Preparations

1) Injection

Dose

- 600 000 IU – 1.2 MU/day or 600 mg (OD)
- Children 150 000 IU – 1.2 MU

Note 1 cc = 300 000 IU

4. BENZATHINE PENICILLIN (Panadur)

This is a long acting penicillin because the preparation is in a very oily base allowing very slow release from the muscle. It lasts 2 – 4 weeks. This gives prolonged blood levels which can be sustained for a long time.

Indications

1) Maintain a low blood level after acute infection is cleared
2) Syphilis
3) Mild streptococcal infections
4) Rheumatic fever prophylaxis

Preparation

1) Injection

Dose

- Adults 1.2 – 2.4 MU weekly or monthly
- Children 300 000 IU if < 10 kg

Combinations

1) Seclopen/Procaine penicillin fortified (PPF) = crystapen + procaine penicillin

Dose – Adults – 600 000 IU – 2.4 MU OD; Children 300 000 – 600 000 IU OD

2) Triplopen = crystapen + procaine penicillin + benzathine penicillin

Dose – Adults – 600 000 IU – 2.4 MU OD; Children 300 000 – 600 000 IU OD on alternate days

B. BROAD SPECTRUM PENICILLINS

1. AMPICILLIN

Ampicillin (α-aminobenzyl penicillin) is broad spectrum penicillin.

Indications

1) Susceptible Gram positive and Gram negative bacterial infections
2) Urinary tract infections (*E. coli* and *Proteus mirabilis*)
3) Otitis media
4) Bronchitis (*H. influenzae*)
5) Sinusitis
6) Oral infections
7) Uncomplicated community-acquired pneumonia
8) Invasive Salmonellas
9) Shigellosis

Precautions

1) History of allergy
2) Renal impairment

Contraindications

1) Penicillin and cephalosporin hypersensitivity
2) Infectious mononucleosis (increased risk of reaction)
3) During neonatal period of babies born to sensitive mothers

Drug Interactions

1) Oral contraceptives
2) Digoxin – increased levels
3) Probenecid
4) Bacteriostatic antibiotics e.g. tetracyclines decrease bactericidal activity

Side Effects

GIT disturbances (diarrhoea, nausea and vomiting), hypersensitivity/rashes and colitis

Preparation

1) Injection
2) Capsules – 250 mg and 500 mg
3) Oral suspension 125 mg/5 mls

Dose

- 250 mg – 1 gm QID; UTI – 500 mg TID; Gonorrhoea – 2 – 3 gm with probenecid
- Children – ½ the adult dose

Common names

Ampicillin, penbritin, biocillin and ampimax

2. AMOXICILLIN (Amoxil)

Amoxicillin (para-hydroxy-αaminobenzyl penicillin) is similar to ampicillin but its better absorbed from the gastrointestinal tract.

Indications

1) Susceptible non beta-lactamase producing bacterial infections

Precautions

1) Syphilis
2) Oliguria
3) Renal failure

Contraindications

1) Penicillin and cephalosporin allergy
2) Infectious monocleosis
3) Lymphatic leukaemia
4) Treatment of hyperuricaemia with allupurinol

Drug Interactions

1) Oral contraceptives fail with antibiotics
2) Increased digoxin levels

Side Effects

Allergic/anaphylactic reactions, skin rashes, urticaria, GI disturbances and super-infections

Preparation

1. Capsules – 125 mg, 250 mg and 500 mg
2. Syrup 125 mg/5 mls
3. Injection

Dose

1) Given at least 1 hour before meals or 2 hours after meals
2) Adult 250 – 500 mg TID
3) Children 125 – 250 mg TID

Common Names

Amoxil, Camox, Penamox, Elymox and Kemoxyl

AMOXICILLIN-CLAVULANIC CID (Augmentin)

Introduction

Amoxycillin and clavulanic acid combination has a broad spectrum of activity. The b-lactamase inhibitory action of clavulanate extends the spectrum of amoxicillin to embrass a wider range of organisms.

Mode of Action

Bactericidal with a wide range of organisms

Indications

1) Upper respiratory tract and ENT infections – tonsillitis, sinusitis, otitis media
2) Lower respiratory tract infections – chronic bronchitis, lobar and broncho pneuomia
3) Genitor-urinary infections – cystitis, urethritis, pyelonephritis
4) Skin and soft tissue infections – boils, abscesses, cellulites, wound infections
5) Bone and joint infections – osteomyelitis

6) Dental infections – dentoalveolar abscess
7) Others – septic abortions, pueperial sepsis, intraabdominal sepsis

Sensitive Organisms

1) Gram Positive
   a. Aerobes : *Enterococcus feacalis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Staphylococcus aureus, Corynebacterium, Bacillus anthracis*

   b. Anaerobes – *Clostridium spp*

2) Gram Negative

   a. Aerobes:*Heamophilus influenzae, E. coli, Proteus mirabilis, Proteus vulgaris, Klebsiella spp, Salonella spp, Bordetella pertusis, Brucella spp, Neisseria gonorrhoea, Neisseria meningitidis, Vibrio cholerae, Pasturella multicida*

   b. Anaerobes – *Bacteriods spp- B. fragilis*

Precautions

1) History of allergy to penicillins and cephalosporins
2) Hepatic dysfunction
3) Renal impairement

Contraindications

1) Allergy
2) Impaired renal function

Side Effects

GIT disturbances – diarrhoea, indigestion, nausea and vomiting; Candidiasis, antibiotics associated colitis and haemorrhagic colitis; Renal and urinary – rarely crystalluria; Hypersensitivity reactions – skin rash (urticarial and erythymatous), exfoliative dermatitis and rarely multiformate and Steven Johnson syndrome; Haematological – reversible leucopenia (neutropenia and agranulocytosis), reversible thrombocytopemia with prolonged bleeding time; Central nervous system - dizziness, headache, convulsions (high doses and impaired liver function); Hepatic effects – hepatitis and Cholestatic jaundice and Superficial tooth discoloration in children

Preparations

1) Syrup 156 mg/5mls, 312 mg/5ml, 228 mg/5 mls, 457 mg/5 mls
2) Tablets 375 mg (250 mg amoxicillin + 125 mg clavulanic acid), 625 mg (500 mg amoxicillin + 125 mg clavulanic acid) and 1 gm (750 mg amoxicillin + 250 mg clavulanic acid)
3) Injection

Dose

- Adults 625 mg BD (severe infections – 1 gm BD)
- Children less than 12 years 25 – 50 mg/kg/day (156 – 375 mg BD)

Common Names

Augmentin, Clavulin and Clavam

3. AMOXYCILLIN + FLUCLOXACILLIN(Suprapen)

Addition of flucloxacillin to amoxicillin increases the activity spectrum by including the activity against penicillinase producing organisms.

Preparations

1) Capsules 250 and 500 mg
2) Injection 500 mg and 1 gm
3) Syrup 250 mg/5 mls

Dose

- Adults – oral (500 mg TID) and IM/IV (500 mg – 1 gm TID)
- Children; less than 2 years (125 mg TID) and over 2 years (250 mg TID)

Common Names

Suprapen, Flamox, Flucamox and Supramox

4. AMPICILLIN + CLOXACILLIN (Ampiclox)

Cloxacillin broadens the spectrum of activity against penicillinase producing organisms

Preparations

1) Capsules 500 mg (250 mg of amoxicillin + 250 mg of cloxacillin)
2) Injection 250 mg and 500 mg per vial
3) Syrup 250 mg/5mls
4) Neonatal drops

Dose

- PO, IM or IV 500 mg – 1 gm QID
- Children 1 month – 2 years ¼ adult dose
- Children 2 – 10 years – ½ adult dose
- Neonates – oral drops (90 mg – 0.6 mls QID) or IM/IV 75 mg TID

Common Names

Ampiclox, Amiclox, Cloximed, Cosmoclox, Axylin, Broadiclox

C. PENICILLINASE-RESISTANT PENICILLINS

Introduction

Penicillanase resistant penicillins are semisynthetic penicillins indicated for infections by b-lactamase producing staphylococci (Staphylococcus aureus and Staphylococcus epidermidis) although penicillin susceptible strains of streptococci and pneumococci are also susceptible.

1. OXACILLIN

Oxacillin is a semisynthetic penicillanase resistant penicillin. It is well absorbed in the GIT (presence of food interferes with absorption) and is resistant to destruction by gastric acid. Oxacillin appears in bile, pleural fluid and amniotic fluid and human breast milk.

Indications

1) Staphylococcal infection – skin and soft tissues
2) GUT infections
3) Respiratory system infections
4) Suppurative osteomyelitis
5) Pseudomembranous enterocolitis

2. CLOXACILLIN (Orbenin)

Cloxacillin is a semisynthetic penicillanase resistant penicillin. It is well absorbed (rapid and variable) in the GIT (presence of food interferes with absorption) and is resistant to destruction by gastric acid but it is degraded to some extent. Peak serum levels are attained after 1 hour of administration of the capsule. Effective plasma levels are maintained for 4 – 6 hours after a single dose. It is distributed throughout the body with highest concentrations appearing in the kidney and liver.

Indications

1) Susceptible Gram positive and Gram negative bacterial infections
2) Urinary tract infections (*E. coli* and *Proteus mirabilis*)
3) Otitis media
4) Bronchitis (*H. influenzae*)
5) Sinusitis
6) Oral infections
7) Uncomplicated community-acquired pneumonia
8) Invasive Salmonellas
9) Shigellosis

Preparations

1) Syrup 125 mg/5 mls
2) Capsules 250 and 500 mg
3) Injection 500 mg/vial

Dose

- Adults – PO and IV; 500 mg QID, IM 250 mg QID
- Children 25 – 50 mg /kg/day

Common Names

Cloxacillin, Orbenin, Bioclox, Dawaclox and Cloxipen

3. FLUXACILLIN

As cloxacillin

Preparations

1) Injection 250 mg/vial

2) Syrup 125 mg/5ml
3) Capsules 250 mg

Dose

- Adult 250 – 500 mg QID before meals
- Children 50 mg/kg/day in divided doses

Common Names

Fluxapen, Flucloxacillin and Dawaflox

D. ANTIPSEUDOMONAL PENICILLINS

These are penicillins principally indicated for serious infections caused by Pseudomonas aeruginosa but also have activity against certain other Gram negative bacilli including Proteus spp and bacteroids fragilis. These drugs include **ticarcillin** and **timentin** (ticarcillin + clavulanic acid). They are generally used in combination with aminoglycosides because P. aeruginosa easily develops resistance to a single drug and the two groups are synergistic in action.

CEPHALOSPORINS

1.0. Introduction

Cephalosporins and cephamycins have a chemical structure, mechanism of action and toxicity similar to that of penicillins. Cephalosporins are more stable than penicillins because they are innately resistant to staphylococcal penicillinases thus have a broader spectrum of activity that includes both Gram positive and Gram negative organisms.

Penicillins and cephalosporins differ primarily in that penicillins are derivatives of 6-aminopenicillic acid (6-APA) whereas cephalosporins have constituent groups

added to 7-aminocephalosporanic acid (7-ACA). The 7-ACA nucleus was initially from cephalosporin C, a fermentation product of *Cephalosporin acremonium*.

2.0. Mechanism of Action

As penicillins: - Cephalosporins are **bactericidal** and act by interfering with **bacterial cell wall synthesis** and hence they primarily affect growing cells and have minimal or no activity against intracellular microorganisms, dormant bacteria and organism lacking the cell wall (e.g. mammalian cells). They inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. The cell wall maintains the shape of the cell and prevents cell lysis from high osmotic pressure. The cell wall is composed of complex cross-linked peptidoglycan made of polysaccharides and polypeptides.

3.0. Spectrum of Activity

Spectrum of activity of cephalosporins includes both gram-positive and gram-negative organisms. They are ineffective against *Pseudomonas*, *Bordenella*, *Bacteroid fragilis* and hospital-acquired *Klebsiella*. Most species of enterococci (e.g. *Streptococcus feacalis*), enterobacter and *Listeria monocytogenes* are highly resistant.

Organisms

Staphylococcus aureus , *Streptococci, Streptococci pneumoniae, Clostridia* spp, *Escherichia coli, Proteus mirabilis*, *Neisseria gonorrhoea,* Salmonella, Shigella and *Heamophilus influenzae* and *bacteriods* – sensitivity is variable

4.0. Pharmacology

Cephalosporins are administered by various routes. Cephalosporins resistant to acid hydrolysis e.g. cephalexin and cefaclor (ceclor) can be given orally while some cephalosporins more susceptible to gatric acid destruction or are not well absorbed from the GIT should be gioven parenterally. Absorption from the GIT is variable.

After absorption they are bound to proteins to varying degrees and penetrate most tissues with the exception of penetration into the CSF even when the meninges are inflamed. Cefotaxime is a suitable cephalosporin for infections of the CNS e.g. meningitis.

Most cephalosporins are excreted unchanged by both glomerular filtration and

proximal tubular secretion (hence concurrent administration with probenecid delays excretion and prolongs the half life). Renal impairment delays excretion and dose adjustment in renal failure is advisable.

5.0. Indications

1) Septicaemia
2) Pneumonia
3) Meningitis
4) Billiary tract inefections
5) Peritonitis
6) UTI

6.0. Contraindications

- As penicillins

7.0. Side Effects

Hypersensitivity reactions - skin rash, urticaria, fever and if severe – anaphylaxis; GIT disturbances – anorexia, nausea, vomiting and diarrhoea; Blood disorders – leucopenia, thrombocytopenia, neutropenia, haemolytic anaemia (rare); Pain at the local IM injection site; Phlebitis and thrombophlebitis at IV injection site; Renal tubular necrosis (dose dependent and more often in dehydration); Hepatic dysfunction (increased SGOT and SGPT); Super-infections – 2^{nd} and 3^{rd} generation cephalosporins are in-effective against gram-positive organisms especially staphylococci and methicillin-resistant enterococci. It involves Pseudomonas and candida.

8.0. Classification

They are classified into 1^{st}, 2^{nd}, 3^{rd} and 4^{th} generations based on their spectrum of activity.

First Generation Cephalosporins: Cephalexin, Cephradine, Cefadroxil (duracef), Cefazolin, Cephalothin and Cephapirin

Second Generation Cephalosporins: Cefaclor (**Ceclor**), Cefuroxime (Zinnat/Zinacef), Cephamandole, Cefprozil, Loracarbef and Ceforanide

Third Generation Cephalosporins: Cefotaxime (Claforan), Ceftriaxone (Rocephin), Ceftazidime (Fortum), Ceftizoxime, Cefoperazone, Cefixime, Cefpodoxime proxetil and Cefditoren pivoxil

Fourth Generation Cephalosporins: Cefepime, Cefpirome

INDIVIDUAL DRUGS

A. FIRST GENERATION CEPHALOSPORINS

First generation cephalosporins are very active against gram-positive cocci including anaerobic cocci such as *pneumococci*, *streptococci*, *staphylococci*. They are also active against *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. Activity against *Pseudomonas aeruginosa*, indole-positive proteus and enterobacter is poor while *Bordetella fragilis* is resistant.

1. CEFADROXIL (Duracef)

Indications

1) Susceptible respiratory tract infections
2) UTI
3) Skin and soft tissue infections

Precautions

1) Penicillin allergy
2) Pregnancy
3) Lactation
4) Premature and neonate babies
5) Pseudomembranous colitis
6) Renal impairment

Contraindications

1) Allergy to cephalosporins

Drug Interactions

1) Probenecid inhibits renal excretion
2) Antacids should be used 1 hour before or after administration of the drug

Side Effects

Allergic reactions (rashes, pruritus, urticaria and anaphylaxis), GIT disturbances (nausea, vomiting, diarrhoea and abdominal pain), colitis, super-infections (e.g. monoliasis), hepatitis/hepatic dysfunction, headache, halluscinationsm, blood dyscrasia (leucopenia, agranulocytosis, thrombocytopenia, aplastic and haemolytic anaemia), interstitial nephritis, dizziness, confusion, hypertonia , serum (like sickness like reactions – fever, arthralgia, rashes) and toxic psychosis

Preparations

1) Capsules – 500 mg
2) Syrup – 125 mg/5 mls

Dose

- 500 mg – 1 gm BD (for Streptococcal infection give for at least 10 days)
- Children 30 mg/kg/day in divided doses (BD)

Common Names

Duracef, Cefadroxil, Neucel, Vedrox and Cefamed

2. CEPHALEXIN

Indications

1) Susceptible respiratory infections
2) UTI
3) ENT infections
4) Skin and soft tissue infections
5) Prophylaxis in dental procedures

Precautions

- As cefadroxil

Contraindications

- As cefadroxil

Drug Interactions

- As cefadroxil

Side Effects

GIT disturbances, allergic reactions and anaphylaxis, genital and anal pruritus, dizziness, fatigue, headache, toxic psychosis, convulsions and super infections – monoliasis

Preparations

1) Capsules 250 mg and 500 mg
2) Syrup 125 mg/5 mls

Dose

- Adult 250 mg QID or 500 mg BD or TID (can be given up to 1 – 1.5 gm TID or QID in severe infections)
- Children 25 mg/kg daily in divided doses (max 100 mg/kg)

Common Names

Alexin, Ceporex, Keflex, Oracef, Cefamor, Alcephin and Kelexin

3. CEPHRADINE

Indications

1) Susceptible respiratory tract infections
2) UTI
3) ENT infections
4) Skin and soft tissue infections
5) Prophylaxis in surgical procedures

Preparations

1) Capsules – 500 mg
2) Syrup – 250 mg/5 mls

Dose

- Adult – 250 – 500 mg QID or 500 mg – 1 gm BD
- Children 25 – 50 mg/kg daily in divided doses

Common Names

Intracel, Berimco

B. SECOND GENERATION CEPHALOSPORINS

Second generation cephalosporins are active against organisms affected by 1st generation cephalosporins and in addition to gram negative organisms. They are less susceptible to penicillinase inactivation then the 1st generation cephalosporins.

1. CEFACLOR(Ceclor)

Indications

1) Respiratory tract infections
2) Otitis media
3) Skin and soft tissue infections
4) Infections caused by susceptible organisms

Precautions - As Duracef

Contraindications - As Duracef

Drug Interactions

1) Probenecid inhibits renal excretion
2) Antacids should be used 1 hour before or after administration of the drug
3) Increased bleeding time with oral anticoagulants
4) Increased nephrotoxicity with aminoglycosides

Side Effects

GIT disturbances, vaginal monoliasis and vaginitis, allergic reactions, increased prothrombin time, super-infections, hepatic dysfunctions, Steven-Johnson syndrome and erythema multiforme, fever and CNS effects

Preparations

1) Tablets 375 mg and 750 mg
2) Capsules 250 mg and 500 mg
3) Syrup – 125 mg/5mls, 187 mg/5mls and 250 mg/5mls

Dose

- Adult 500 mg – 4 gm daily
- Children 20 – 40 mg/kg daily

Common Names

Ceclor, Cosclor and Halocef

2. CEFUROXIME (Zinnat, Zinacef)

Indications

1) Septicaemia
2) Meningitis in neonates and infants
3) Peri-operative infections prophylaxis
4) UTI
5) Respiratory tract infections
6) Bone infections
7) Joint infections
8) Skin and soft tissue infections
9) *Neisseria gonorrhoea*
10) *Heamophilus infleunzae*

Contraindications

1) Hypersensitivity reactions
2) Penicillin cross-sensitivity

Drug Interactions

1) Incompatible with aminoglycosides, fluconazole and vancomycin
2) Antagonistic effects with chloramphenicol

Side Effects

GIT disturbances, allergic reactions, blood dyscrasia, severe headache, glossitis, pain at the injection site, oedema, genital tract mycosis, oliguria and pseudomembranous colitis

Preparations

1) Injection 750 mg/vial
2) Tablets 250 and 500 mg
3) Syrup 125 mg/5 mls

Dose

- Orally 250 – 500 mg BD; children > 3 months 125 mg BD
- IV or IM 750 mg – 1.5 gm TID or QID
- Single dose over 750 mg is given IV only
- Children 30 – 100 mg/kg daily in 3 – 4 doses and 2 – 3 doses in neonates
- Meningitis 3 gm IV 8 hourly

Common Names

Zinacef, Zinnat, Cefogen, Zolidon, Spizef, Cefoxim and Kefotar

C. THIRD GENERATION CEPHALOSPORINS

The 3rd generation cephalosporins have expanded coverage of gram -negative organisms and some have ability to cross the blood brain barrier (BBB). However they are less active against gram positive bacteria especially Staphylococcus aurues except ceftazidime (fortum) which is active on both gram positive and gram negative organisms and pseudomonas.

1. CEFOTAXIME (Claforan)

Indications

1) Septicaemia
2) Meningitis in neonates and infants
3) Peri-operative infections prophylaxis
4) UTI
5) Respiratory tract infections

6) Bone infections
7) Joint infections
8) Skin and soft tissue infections

Precautions

1) Penicillin sensitivity
2) Pregnancy
3) Impaired renal function

Contraindications

- As cefuroxime

Drug Interactions

- As cefuroxime

Preparations

1) Injection 250 mg/vial, 500 mg/vial and 1 gm/vial

Dose

- IM or IV 1 – 2 gm TID (max 12 gm daily)
- Children 100 – 200 mg/kg in 2 – 4 divided doses
- Neonates 50 mg/kg daily in 2 – 4 divided doses

Common Names

Claforan, Cefotax, Zetaxim, Biotaxim and Oritaxim

CEFTRIAXONE (Rocephin)

Indications

Septicaemia
Meningitis in neonates and infants
Peri-operative infections prophylaxis
UTI
Respiratory tract infections

Bone infections
Joint infections
Skin and soft tissue infections

Precautions

Penicillin sensitivity
Pregnancy
Impaired renal function

Contraindications

As cefotaxime

Drug Interactions

As cefotaxime

Preparations

Injection 250 mg/vial, 500 mg/vial and 1 gm/vial

Dose

> 12 years 1 – 2 gm OD , given IM or IV (max 4 gm per day)
IV given slowly
Neonates 20 – 50 mg/kg OD
Infants and children 20 – 80 mg/kg OD

A dose of over 50 mg/kg should be given IV slowly

Common Names

Rocephin, Axone, Becef, Cefogram, Ceftiaxone, Oframax and Powercef

CEFTAZIDIME(Fortum)

Indications

Respiratory tract infections
UTI
ENT infections
Skin and soft tissue infections

GIT and biliart tract infections
Abdominal infections
Septicaemia
Bacterimia
Severe infections

Precautions

Impaired renal function
Penicillin cross-sensitivity
Lactation
Super-infections

Side Effects

Phlebitis pain at injection site, inflammation, skin rash, fever, anaphylaxis, GIT disturbances, blood dyscrasia and CNS effects

Preparations

Injection 250 mg. 500 mg and 1 gram

Dose

1 – 6 gm in 2 – 3 divided doses;
IV or IM single dose (over 1 gm give only IV)
Children < 2 months 25 – 50 mg/kg BD; 2 months – 1 year 25 – 60 mg/kg BD and > 1 year 30 – 100 mg/kg in 2 – 3 divided doses

Common Names

Fortum, Bestum and Orzid

FOURTH GENERATION CEPHALOSPORINS

CEFEPIME

Indications

UTI
Skin infections
Pneumonia
Complicated intra-abdominal infections (in combination with IV metronidazole)

Precautions

Prolonged use may result in overgrowth of nonsusceptible microorganisms
History of GI disease particularly colitis
Monitor prothrombin time in patients at risk

Contraindications

Hypersensitivity

Side Effects

Pseudomembranous colitis, diarrhoea, headache, nausea and vomiting, oral monoliasis, pruritus, urticaria and vaginitis

Preparations

Injection 1 gm or 2 gm/vial

Dose

Mild to moderate uncomplicated or complicated UTI 500 mg – 1 gm IV or IM BD for 7 – 10/7
Pyelonephritis due to E. coli, K. pneumoniae or P. mirabilis 1 – 2 gm BD
Severe uncomplicated UTI 2 gm BD x 10/7
Moderate to severe skin and skin structure infections due to Staph aurues or Strep pyogenes 2 gm BD x 10/7
Empiric therapy for febrile neutropenic patient 2 gm TID x 1/52

Common Names

Maxipime

MONOBACTAMS

Monobactams are b-lactam antibiotics with a monocyclic β-lactam ring. They are relatively resistant to β-lactams enzymes and active against gram negative rods (including *Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenzae* and *Serratia*). They have no activity against gram positive bacteria or anaerobes. Examples include **aztreonam** (**azactam**).

BETA-LACTAMASE INHIBITORS

Beta lactamase inhibitors are substances that resemble β-lactam molecules but they have very weak antibacterial action. This includes **clavulanic** acid, **sulbactam** and **tozabactam**. They are potent inhibitors of β-lactamases and protect hydrolysable penicillins from inactivation by β-lactamase enzymes.

They are most active against class A β-lactamases produced by *Staphylococci, Heamophilus influenzae, Neisseria gonorrhoea, Salmonella, Shigella, Escherichia coli* and *Klebsiella pneumoniae*. They are not good inhibitors of class C β-lactamases produced by *enterococci* and *pseudomonas* and do not inhibit β-lactamases produced by *bacteroids*.

CARBAPENEMS

Carbapenems are tructurally related to b-lactam antibiotics. Examples include **emipenem**, **meropenem** and **ertapenem**. They have a wide spectrum with good activity against many gram negative rods including *Pseudomonas aeruginosa*, gram positive organisms and anaerobes.

MACROLIDES

1.0. Introduction

Macrolides are composed of large lactone rings which are attached to deoxy sugars. Macrolides are mainly used as penicillin alternatives in penicillin allergic patients. The group members include erythromycin, azithromycin, clarithromycin, miocomycin, spectinomycin, roxithromycin and ketolides (telithromycin)

2.0. Mechanism of Action

Macrolides inhibit bacterial protein synthesis (bacteriostatic) by binding to the 50S subunit of the bacterial ribosome. This inhibits the translocation step in protein synthesis. They may be bactericidal in large doses (mechanism poorly understood)

3.0. Indications

1) Skin and soft tissue infections
2) Infections in body cavities
3) *Staphylococcus aureus*
4) *Streptococcus pyogenes, Streptococcus pneumoniae and Streptococcus feacalis*
5) Gram positive bacilli – *Clostridium tetani* and *Clostridium welchii*, *Corynebacterium* and *Actinomycosis Israeli*

6) Nocardia asteroids (in combination with ampicillin)
7) Neisseria
8) Yersinia
9) Haemophilus
10) Bordetella
11) Brucella
12) Bacteroids
13) *Mycoplasma pneumoniae*
14) Trepanoma
15) Chlamydia
16) Ricketssia

4.0. Side Effects

1) Mild GIT disturbances – nausea, vomiting, ***pyrosis*** and diarrhoea
2) Mild allergic reactions – urticaria, skin rash (severe reactions with abdominal pain and fever are rare)
3) Sensorineural hearing loss (large doses)

INDIVIDUAL DRUGS

1. ERYTHROMYCIN

Introduction

Erythromycin is a mainly bacteriostatic antibiotic agent and good alternative for penicillin-allergic patients

Pharmacokinetics

Erythromycin is well absorbed orally but it is destroyed by stomach acid thus must be administered with enteric coating and food interferes with absorption. It is well distributed except to the brain and CSF. Distribution occurs within 2 – 6 hours and 20% is excreted via the kidneys and 80% is metabolized and appear in bile (high concentration in bile). It is taken up by polymorph nuclear leucocytes and macrophages and crosses the placenta reaching the foetus. Action is enhanced at alkaline pH.

Resistance

Indications

1) An alternative for penicillin
2) Intestinal amoebiasis
3) Chlamydial infections
4) Mycoplasmal infections
5) Upper and lower respiratory infections
6) Skin and soft tissue infections
7) Gonococcal male urethritis
8) Female pelvic infections
9) Long term prophylaxis of rheumatic fever
10) Early syphilis
11) Tetanus
12) Legionaires disease

Sensitive Organisms

Gram positive – pneumococci, streptococci, staphylococci and corynebacterium; Mycoplasma; Legionella; *Chlamydia trachomatis* and *pneumoniae*; Helicobacter, Listerioa, Neisseria, *Bordetella pertussis, Trepanoma pallidum,* Campylobacter and *Haemophilus infleunzae*

Precautions

1) Lactation
2) Impaired hepatic function
3) Pregnancy (mainly first trimester)
4) Do not give together with chloromphenical
5) Monitor prothrombin time (in patients on coumarins)

Contraindications

1) Impaired liver function
2) Jaundice
3) Syphilis in pregnancy
4) Terfenadine
5) Astemizole

Drug Interactions

It potentiates the effects of carbamazepine, corticosteroids, digoxin, coumarins and theophylline by inhibiting cytochrome P450 enzymes hence increase their serum concentration.

Side Effects

GIT disturbances – anorexia, nausea, vomiting, diarrhoea (due to direct stimulation of gut motility), Pseudomembranous colitis; Hepatic toxicity – acute Cholestatic hepatitis (fever, juandince) occurs as a hypersensitivity reaction; allergic reactions, reversible hearing loss, super infections, ventricular arrhythmias, agranulocytosis, pancreatitis and Steven-Johnson syndrome

Preparations

1) Tablets 250 mg
2) Capsules 250 and 500 mg
3) Syrup 125 mg/5 mls, 200 mg/5 mls

Dose

- < 2 years 125 mg QID
- 2 – 8 years 250 mg QID
- < 8 years 250 – 500 mg QID or 500 mg – 1 gm BD (max 4 gm daily)
- Early syphilis – 500 mg QID for 2/52
- Acne vulgaris – 500 mg QID for 10 – 12/52
- Intestinal amoebiasis 250 mg QID for 10 – 14/7 (children – 30 – 50 mg/kg/day)

Common Names

Erythromycin, Erythromax, Erocin, Biotrocin, Erythocin, Erythrox

2. CLARITHROMYCIN

Introduction

Clarithromycin is derived from erythromycin by adding a methyl group. This improves acid stability and oral absorption.

Indications

1) Mild to moderate upper and lower respiratory tract infections
2) Uncomplicated skin and soft tissue infections
3) Adjuvant in the treatment of duodenal ulcers by eradication of Helicobacter pylori

Precautions

1) Digoxin
2) Pregnancy
3) Lactation
4) Avoid antacids

Contraindications and drug interactions

- As erythromycin

Side Effects

GIT disturbances, elevated liver transaminases, reversible hearing loss, pseudomembranous colitis, palpitations, vaginitis, taste disturbances, Steven-Johnson syndrome and reduced neutrophils count
Preparations

1) Tablets 250 and 500 mg
2) Syrup 250 mg/5 mls

Dose

- 250 mg BD for 1/52 – 500 mg BD for 2/52 (severe infections)
- Children < 8 kg (7.5 mg/kg), 8 – 11 kg (62.5 mg), 12 – 19 kg (125 mg), 20 – 29 kg (187.5 mg) and 30 – 40 kg (250 gm) BD
- H. pylori - 500 TDS for 2/52 (with an appropriate proton pump inhibitor or H2 antagonist)

Common Names

Claithro, Zynclar, Klacid

3. AZITHROMYCIN

Introduction

Azithromycin is derived from erythromycin by adding methylated nitrogen to the lactone ring. The spectrum of activity is similar to erythromycin and clarithromycin. It is highly active against *Mycobacterium avium* and *Toxoplasma gondii*. It is slightly less active than erythromycin and clarithromycin against staphylococci and streptococci and slightly more active against *Heamophilus influenzae*. Highly

active against Chlamydia.

Pharmacokinetics

Azithromycin is rapidly absorbed orally and well tolerated. It should be administered 1 hour before or 2 hours after meals. Aluminium and magnesium antacids delay absorption and hence reduce peak serum concentrations. It does not inactivate P460 enzymes because it is a 15 member lactone ring and not 14 as the other macrolides.

Indications

1) Mild to moderate upper and lower respiratory tract infections
2) Uncomplicated skin and soft tissue infections
3) Sexually transmitted diseases

Precautions

1) Digoxin
2) Antacids
3) Pregnancy
4) Lactation

Contraindications

1) Allergy to macrolides

Side Effects

- As clarithromycin

Preparations

1) Tablets 250 mg
2) Capsules 250 and 500 mg
3) Syrup 200 mg/5mls
4) Injection

Dose

- Adults
  - Skin, soft tissue & respiratory tract infections – 500 mg stat, then 250 mg

OD x 4/7

- Community acquired pneumonia – IV 500 mg OD x 2/7, then PO 500 mg OD x 7 – 10/7
- Chlamydial infection, Chanchroid and Non-gonococcal urethritis – 1 gm stat
- Gonorrhoea – 2 gm stat
- Acute P.I.D – IV 500 mg OD x 1 – 2/7 then PO 250 mg OD x 1/52
- Mycobacterium avium in HIV patents – 1 – 2 gm weekly
- Prophylaxis of bacterial endocarditis – 500 mg stat 1 hour before surgery
- Prophylaxis in sexual assault – 1 gm stat

- Children
  - Respiratory, E.N.T and community acquired pneumonia (children > 6 months old) – 10 mg/kg stat (max daily dose 500 mg) then 5 mg/kg OD (max 250 mg) x 2 – 5/7
  - Streptococcal pharyngitis and tonsillitis (children > 2 year) - 12 mg /kg /day OD x 5/7 (max 500 mg)
  - Chlamydial (children over 8 years) – 1 gm stat
  - Chancroid – 20 mg/kg (max 1 gm) stat
  - Prophylaxis for endocarditis – 15 mg/kg stat 1 hour before the surgery

Common Names

Aziflam, Azithocin, Zithromax, Zithrox, Zocin

4. ROXITHROMYCIN

Indications

1) Mild to moderate E.N.T infections
2) Skin and soft tissue infections
3) G.U.T infections

Precautions

1) Renal insufficiency
2) Hepatic insufficiency

Contraindications

1) Concomitant administration with vasoconstrictor ergot derivatives

Drug Interactions

- Increased serum levels of theophylline

Side Effects

GIT disturbances, allergic skin reactions and increased hepatic enzymes and bilirubin

Preparations

1) Tablets 150 and 300 mg
2) Syrup 50 mg/5 mls

Dose

- Adult 150 mg BD or 300 mg OD
- Children 2 – 5 years – 5 mg/kg OD

Common names

Roxitid, Roxid

5. SPECTINOMYCIN

Introduction

Spectinomycin is an aminocyclitol antibiotic that is structurally related to aminoglycosides but it lacks amino sugars and glycosidific bonds.

Mode of Action

Inhibits protein synthesis in bacterial cell wall at the 30S ribosomal sub unit.

Indications

1) Gram positive and gram negative organisms
2) Gonorrhoea caused by penicillin-resistant bacteria or in penicillin-allergic individuals

Precautions

1) Pregnancy

Contraindications

1) Allergy to spectinomycin

Side Effects

Urticaria, dizziness, nausea, chills, fever and reduced haemoglobin

Preparations

1) Injection 2 gm/vial

Dose

- IM 2 gm stat (maximum 4 gm)
- Children > 2 years – 40 mg/kg

Common Names

Spectinomycin and Togamycin

6. KETOLIDES (TELITHROMYCIN)

TETRACYCLINES

1.0. Introduction

Tetracyclines are broad spectrum antibiotics with a wide spectrum of antibacterial activity but their clinical use has reduced due to development of resistance. They however remain the treatment of choice for infections caused by Chlamydia (trachoma, salpingitis, urethritis, lymphogranuloma venerium), ricketsia (Q fever), brucella and spirochaetes. The members include ***tetracycline, doxycycline, oxytetracycline, minocycline*** and ***lymecycline***

2.0. Mechanism of Action

Tetracyclines are **bacteriostatic** in action and act by inhibiting protein synthesis of susceptible bacteria hence preventing cell replication. Tetracyclines enter the microorganisms by passive diffusion and energy dependent active transport process. The susceptible bacterial cell wall concentrates the drug intracellularly.

Tetracyclines bind reversely to 30S sub units of the bacterial ribose and prevent tRNA from combining with mRNA thus inhibiting protein synthesis. This blocks

addition of amino acids to the growing peptide chain.

Resistance develops due to: -

a) Reduced intracellular accumulation of the drug due to impaired influx and increased efflux of the drug by active transport protein pump
b) Ribosome protection preventing binding of tetracyclines to the ribosomes
c) Enzymatic inactivation of tetracyclines

3.0. Pharmacokinetics

Tetracyclines have variable absorption and elimination after oral administration and part that remains in the gut modifies intestinal flora and is excreted in faeces. The absorption takes place mainly at the upper small intestine and is impaired by food (except doxycycline and minocycline), divalent cations such as Ca^{2+}, Mg^{2+}, Fe^{2+} and Al^{3+}, dairy products, antacids containing multivalent cations and alkaline pH. 40 – 80% is protein bound by serum proteins.

Tetracyclines are widely distributed to body tissues and fluids except the cerebral spinal fluid (CSF). Minocycline reaches very high concentrations in tears and saliva and hence it is useful for eradication of meningococcal carrier states. Tetracycline cross the placenta to reach foetus and is also excreted in milk. It chelates with calcium causing damage to growing bones and teeth.
Tetracyclines have a half life of 8 hours and are increased in renal failure. They are excreted mainly in bile and urine. Some drug in the bile (high concentrations) is reabsorbed from the intestine (enterohepatic circulation) which assists in maintaining serum levels. Doxycycline is eliminated by non-renal mechanisms hence it does not accumulate in renal failure (it is the tetracycline of choice for use in renal impairment).

4.0. Indications

1) Chlamydial infection
2) Ricketssia
3) Brucellosis (in combination with streptomycin or rifampicin)
4) Spirochetes
5) Borrelia
6) Respiratory tract infections
7) Genital mycoplasma infections
8) Acne
9) Periodontal disease
10) Exacerbation of chronic bronchitis (H. influenzae)
11) Neisseria meningitidis (minocycline for meningococcal prophylaxis)

12) Oral infections

5.0. Precautions

1) Hepatic impairment
2) Myasthenia gravis (increase muscle weakness)
3) Excerbates S.L.E(systemic lupus erythematosus)
4) Antacids, Al, Ca, Fe, Zn and milk reduce absorption

6.0. Contraindications

1) Children < 12 years
2) Pregnant mothers
3) Lactating mothers
4) Renal failure (except doxycycline and minocycline)

7.0. Side Effects

GIT disturbances – nausea, anorexia, vomiting, diarrhoea, dysphagia, oesophageal irritation and antibiotic associated colitis; enterocolitis; Hepatoxicity – reduced liver function (worse in pregnancy); Boy structures and teeth – fluorescence and discolouration of teeth, enamel dysplasia and bone deformity or growth inhibition; pancreatitis, blood disorders, Photosensitivity – sunlight and ultraviolet light (more in fair-skinned persons); Hypersensitivity reactions – urticaria, angioedema, anaphylaxis and Stephen-Johnson syndrome; Vestibular reactions – dizziness, vertigo, nausea and vomiting, headache, oral and vaginal candidiasis, anal pruritus and renal toxicity

INDIVIDUAL TETRACYCLINES

1. DOXYCYCLINE

Indications

1) Respiratory infections – *Mycoplasma pneumoniae*
2) Lymphogranuloma venerium, LGV – *Chlamydia trachomatis*
3) Trachoma (*Chlamydia trachomatis)*
4) Uncomplicated urethral, endocervical, rectal infections (*Chlamydia trachomatis*)
5) Nongonococcal urethritis
6) Chancroid (*Yersinia pestis*)
7) Cholera (*Vibrio cholerae*)
8) Campylobacter (*Campylobacter fetus*)
9) Q-fever

10) Brucellosis
11) Granuloma inguinalae (LGI)
12) Prophylaxis of malaria due to P. falciparum
13) Gonorrhoea
14) Syphilis
15) Clostridia
16) Anthrax
17) Acne vulgaris
18) Chronic bronchitis
19) Intestinal amoebiasis (adjuvant to amoebicides)

Precautions

1) Renal impairment
2) Hepatic impairment
3) May aggregate Myasthenia gravis

Contraindications

1) Pregnancy
2) Lactation
3) Children < 12 years
4) S.L.E
5) Co-administration with hepatotoxic drugs

Drug Interactions

1) Antagonism with penicillins
2) Fe, Al, Ca and Mg reduce absorption
3) Reduce oral contraceptive effectiveness

Side Effects

GIT disturbances, super-infections, teeth discolouration, interfere with bone development, renal disturbances, hepatic disturbances, photosensitivity, negative nitrogen balance in elderly, increased intra-ocular pressure, nail discolouration, flushing and tinnitus

Preparations

- Capsules 100 mg

Dose

- 200 mg stat, then 100 mg OD (for severe infections 100 mg BD)
- Gonorrhoea – 300 mg stat, then 300 mg after 1 hour or 100 mg BD for 1/52
- Malaria prophylaxis – 100 mg OD
- Syphilis
  - Early syphilis 100 mg BD for 14/7
  - Latent syphilis 200 mg BD for 14/7
- Chlamydial and non-gonococcal urethritis 100 mg BD for 7/7 (14/7 in P.I.D)
- Anthrax and post exposure prophylaxis 100 mg BD for 2/52

Common Names

Doxycycline, Biodox, Doxylin, Microdox, Vibramycin, Dawadoxyn

2. TETRACYCLINE

Indications

1 Chlamydial infections (trachoma, Salpingitis, urethritis, LGV)
2 Rickectssia
3 Brucellosis
4 Acne
5 Chronic bronchitis
6 Leptospirosis
7 Mycoplasmal infections
8 Shigellosis

Preparations

1) Capsules 250 mg

Dose

- 250 – 500 mg TID or QID
- Syphilis 500 mg QID for 15/7
- Non-gonococcal urethritis 500 mg QID for 7 – 12/7

Common Names

Achromycin, Tetracycline, Biotet, Gestacycline, Recycline, Maxacycline

3. MINOCYCLINE

Indications

1) Meningococcal prophylaxis
2) Acne vulgaris

Side Effects

GIT disturbances – anorexia, dizziness, tinnitus, vertigo (worse in women), acute renal failure, pigmentation and discolouration of tears, conjunctiva and sweat

Preparations

- Capsules 50 mg

Dose

100 mg BD
Acne 50 mg DB for 6/52

Common Names

Minocin, Minocycline, Dynocin-50

AMINOGLYCOSIDES

Introduction

Aminoglycosides are **bactericidal** antibiotics originally obtained from various *Streptomyces species*. The group includes **streptomycin, neomysin, kanamycin, amikacin, gentamycin**, **tobramycin** and **netilmicin**. Aminoglycosides are widely used against gram negative enteric bacteria, endocarditis (in combination with vancomycin and penicillin) and tuberculosis treatment. They are active against some gram positive and many gram negative organisms.

Structure

Aminoglycosides have a hexose ring – streptidine (in streptomycin) or 2-deoxystreptidine(in other aminoglycosides) linked to various amino sugars by glycosidic rings. They are water soluble, stable in solution and more active at alkaline than acidic pH.

Mechanism of Action

Aminoglycosides have **bactericidal** activity. They are irreversible inhibitors of protein synthesis. The initial event is passive diffusion of the drug via porin channels across the outer membrane and then the drug is actively transported across the cell membrane into the cytoplasm by oxygen-dependent process. A proton pump is useful in maintaining an electrochemical gradient which supplies the much needed energy.

Low extracellular pH and anaerobic states inhibit ion transport by reducing the gradient. Cell wall active drugs such as penicillin and vancomycin enhance the movement. This explains the existing synergism.

On entry into the bacterial cell, aminoglycosides bind to specific 30S subunit of the risbosomal proteins where it inhibits synthesis of proteins by interfering with initiation of peptide complex formation. This induces misreading of mRNA and break-up of polysomes into non-functional monosomes.

Resistance develops by 3 mechanisms namely: -

1) Organisms produce transferase enzyme(s) that inactivate aminoglycosides
2) Impaired entry of aminoglycosides into the cell (following mutation or deletion of porin protein or transport proteins and gradient maintenance)
3) Abnormal or deleted receptor protein in the cell on 30S subunit of ribosomes

1.0. Pharmacokinetics

Aminoglycosides are absorbed very poorly from the intact GIT and the enteric dose is excreted in faeces. They are absorbed well after parenteral administration reaching peak blood level in 30 – 90 minutes. Administered in 2 – 3 divided doses for patients with normal renal function and an OD dose is advisable in renal failure.

Aminoglycosides are poorly bound to serum proteins but are widely distributed throughout the body except for the CNS and eye where penetration into the CSF and the humours of the eye may be inadequate to attain antibacterial purposes, even in the presence of inflammation because they are highly polar compounds that do not enter cells readily. Concentrations of 25 – 50% of serum levels are achieved in pleural and pericardial fluid. They cross the placenta and affect the developing foetus or newborn infant. The normal half life is 2 – 3 hours increasing to 24 – 48 hours in patients with significant renal function impairment.

Aminoglycosides are concentrated and excreted unchanged by the kidneys through glomerular filtration in direct proportion to creatinine clearance hence it changes rapidly with renal function alterations.

2.0. Indications

1) Gram negative enteric bacteria/rods – enterobacteria (Proteus) and pseudomonas
2) Gram positive organisms e.g. staphylococci
3) Gram positive rods of Bacillus and Corynebacterium
4) Serious systemic infections/sepsis caused by susceptible organisms
5) Bacterimia
6) Pulmonary infections
7) Soft tissue infections
8) Complicated UTIs

NOTE

Aminoglycosides are on many occasions used in combination with b-lactam antibiotics in order to extend the spectrum to include potential gram negative pathogens. Penicillin-aminoglycosides are used to achieve bactericidal activity in the treatment of enterococcal endocarditis and shorten duration of therapy for *Streptococcus viridans* and *Staphylococcal* endocarditis.

3.0. Precautions

1) Renal insufficiency
2) Pregnancy
3) Concomitant use with diuretics (frusemide)

4.0. Contraindications

1) Allergy
2) Pregnancy
3) Lactation
4) Myasthenia gravis

5.0. Drug interactions

1) Concomitant use with loop diuretics (ototoxic) e.g. frusemide(Lasix) increases ototoxicity
2) Concomitant use with other nephrotoxic antibiotics such as vancomycin

6.0. Side Effects

Ototoxicity – auditory damage which presents with tinnitus and high frequency hearing loss or vestibular damage which presents with vertigo, ataxia, dizziness and loss of balance. It is common if treatment is prolonged for over 5 days, given in high doses; in elderly persons and in renal insufficiency; Nephrotoxicity – increased serum creatinine levels or reduced creatinine clearance; Hypersensitivity reactions; local hypersensitivity reactions, super-infection with fungi and other organisms and rarely – neuromuscular blockade leading paralysis and potential respiratory arrest.

INDIVIDUAL DRUGS

1. GENTAMYCIN

Introduction

Gentamycin is an aminoglycoside isolated from *Micromonospora purpurea*. It is effective both gram positive and gram negative organisms. Streptococci and enterococci are restively resistant to gentamycin due to failure of the drug to penetrate into the bacterial cell. Combination with penicillin or vancomycin produces a potent bactericidal effect because of enhanced uptake of the drug that occurs after inhibition of cell wall synthesis.

Rapid emergence of resistance in staphylococcal infections occurs due to selection of permeability mutants. Gram negative organisms resistant to gentamycin are usually susceptible to amikacin which is resistant to modifying enzyme activity.

Indications

1) Sensitive UTI e.g. acute pyelonephritis
2) Respiratory tract infections
3) Systemic infections
4) Bone and soft tissue infections
5) Eye infections
6) Septicaemia
7) Neonatal sepsis
8) Biliary tract infections
9) Meningitis and other CNS infections
10) Prostatitis
11) Endocarditis
12) Ear infections `

Organisms

Enterobacter aerogene, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Neisseria, Shigella

Note: Gentamycin has limited activity against staphylococci and no action on Pneumococci, Streptococci, anaerobic bacteria (Clostridia and Bacteroids), Reckettsia, Mycobacteria, Fungi and viruses.

Precautions

1) Avoid use with potent diuretics
2) Nephrotoxic drugs
3) Neurotoxic drugs
4) Impaired renal function
5) Myasthenia gravis
6) Pregnancy
7) Infants and the elderly
8) Avoid prolonged use
9) Obesity - use deal body weight to calculate the dose

Contraindications

1) Pregnancy
2) Lactation
3) Myasthenia gravis

Drug interactions

1) Concomitant use with loop diuretics (ototoxic) e.g. frusemide(Lasix) increases ototoxicity
2) Concomitant use with other nephrotoxic antibiotics such as vancomycin, cephalosporins
3) Cross sensitivity with kanamycin and neomycin
4) Anti-emetics may mask ototoxic symptoms
5) Chloramphenicol and vitamin B complex are incompatible
6) Neuromuscular blockers may cause neuromuscular block and respiratory paralysis

Side Effects

Ototoxicity (vestibular and auditory damage) – vertigo; nephrotoxicity, nausea and vomiting, skin rash, blood dyscrasia, fever, tremors, headache, hypotension, paraesthesia, neuromuscular blockade and respiratory paralysis and neurotoxicity

Preparations

1) Injection 20 mg, 40 mg and 80 mg/ampoule
2) Ear and eye drops
3) Creams and ointments

Dose

- ***5 mg/kg TID given IV or IM for max 7 days***
- ***Children (2/52 – 3 mg/kg BD***
- ***Children (12 years 2 mg/kg BD***

Common Names

Gentamycin, Gentabulk, Dawagenta

2. AMIKACIN

Introduction

Amikacin is the first semi synthetic aminoglycoside which is water soluble acylated derivative of kanamycin. This chemical manipulation prevents inactivating bactericidal enzymes from gaining access to susceptible hydroxyl and amino groups on the drug molecule thereby making amikacin resistant to most of the enzymes that inactivate kanamycin, gentamycin and tobramycin.

Strains of multi-drug resistant *Mycobacterium tuberculosis* including Streptomycin-resistant strains are usually susceptible to amikacin. Kanamycin resistant strains may be cross-resistant to amikacin.

Pharmacology

Amikacin attains peak serum levels after 1 hour of administration with a half life of 2 hours. it is excreted unchanged in urine mainly by glomerular filtration with very limited tubular reabsorption. It does not penetrate readily into CSF in therapeutic amounts even when meninges are inflamed.

Indications

1) Serious gram negative infections resistant to gentamycin
2) Severe infections in hospitalized patients due to susceptible gram positive bacteria
3) *Mycobacterium tuberculosis*
4) Acute and chromic GUT infections – pyelonephritis
5) Respiratory infections
6) Bone and joint infections
7) Intra-abdominal infections
8) Skin and soft tissue infections

Precautions

1) Renal impairment
2) Impaired auditory-vestibualr function
3) Check serum concentrations
4) Patients under anaesthesia
5) Muscular disorders
6) Premature and neonates newborns

Contraindications

1) Pregnancy
2) Lactation
3) Myasthenia gravis

Drug Interactions

Rapid action diuretics and other neuro and nephrotoxic agents

Side Effects

Ototoxicity (vestibular and auditory damage) – vertigol; nephrotoxicity, nausea and vomiting, skin rash, blood dyscrasia, paraesthesia, neuromuscular blockade and respiratory paralysis and neurotoxicity

Preparations

1) Injection 100 gm/2ml vial; 125 mg/vial and 500 mg/2mls vial ; paediatric – 50 mg/ml

Dose

- 7.5 mg/kg BD given IM or IV
- Children 15 mg/kg in divided doses

Common Drugs

Amikacin, Amikin, Lanomycin

3. KANAMYCIN

Introduction

Kanamycin is used parenterally to treat infections caused by susceptible organisms and orally to diminish the aerobic bacterial content of the GIT pre-operatively and to treat enteritis caused by susceptible organisms. It reduces bacterial production of ammonia and may be useful in cirrhotic patients with GIT bleeding in whom hepatic coma is a threat.

Indications

1) Gram negative infections (when less toxic antibiotics are unsuitable)

Preparations

1) Injection 500 mg or 1 gm /vial

Dose

- IM or IV 250 mg QID or 500 mg BD or 15 – 30 mg/kg daily in divided doses every 8 – 12 hours

Common Names

Kanamycin, Dawacin, Kanamax

4. STREPTOMYCIN

Introduction

Streptomycin is bactericidal against a variety of aerobic gram negative bacilli and certain mycobacterium. It was isolated from a strain of *Streptomyces griseus*. Ribosomal resistance to streptomycin usually develops rapidly limiting its role as a

single dose antibacterial agent.

Indications

1) Mycobacterial infections
2) Plague
3) Tularaemia
4) Brucellosis

Side Effects

Fever; Allergic reactions – skin rashes, exfoliative dermatitis, anaphylaxis, pain at the injection site, disturbed vestibular function – vertigo and loss of balance; Haemopoeitic damage – neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia; renal damage, neurologic changes, peripheral neuritis , optic nerve damage, eighth nerve damage in foetus; auditory damage – tinnitus; labyrinth dysfunction – dizziness

5. TOBRAMYCIN

Tobramycin is an aminoglycoside with antibacterial and pharmacologic properties similar to gentamycin.

Preparations

1) Injection 20 mg, 40 mg or 80 mg/vial

Dose

- Tobramycin
- Mytobrin

6. NEOMYCIN

Introduction

Neomycin has an antibacterial spectrum essentially identical to that of kanamycin. Neomycin is **too toxic for parenteral use**. Because of the toxicity, neomycin and kanamycin are limited to topical and oral use.

Pharmacology

Neomycin is not significantly absorbed from the GIT. After oral administration the intestinal flora is suppressed or modified and the drug is excreted in faeces. Any drug absorbed is excreted through the GIT into the urine.

Indications

1) Topical application to treat superficial skin infection s
2) Bowel sterilization before surgery

SULPHONAMIDES AND PYRIMIDINES (TRIMETHOPRIM)

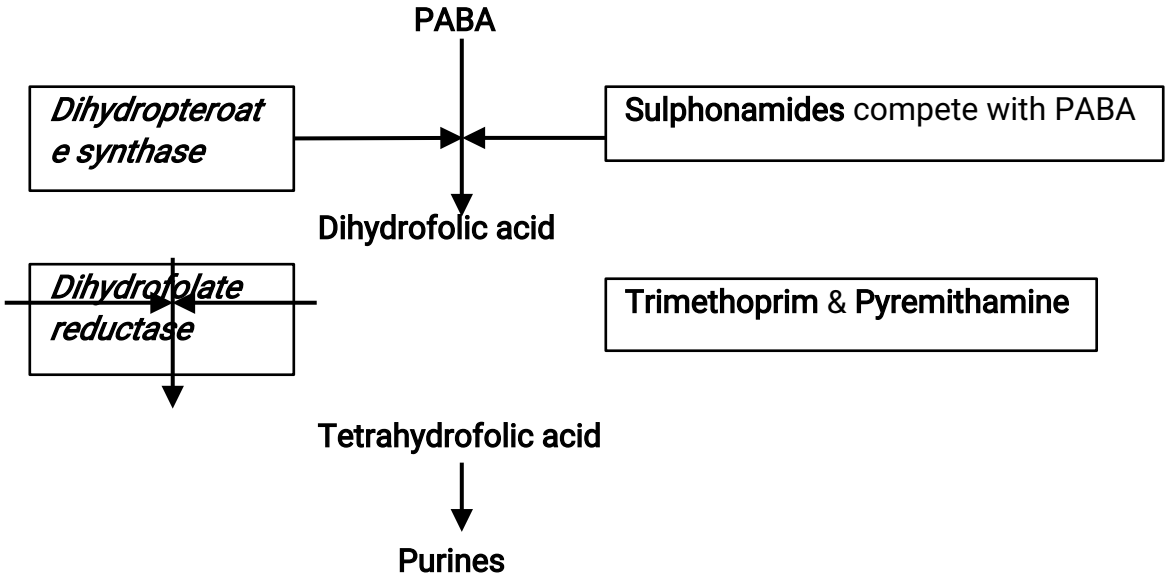
1.0. Introduction

Sulphonamides and pyrimidines (e.g. trimethoprim and pyremithamine) are antifolate drugs. Sulphonamides (sulfonamdides) are synthetic antibacterial agents with a basic benzene ring structure. They have a structural similarity to para amino-benzoic acid (PABA).

2.0. Mechanism of Action

Bacterial synthesis of purines and ultimately DNA is dependent upon the presence of folic acid derivatives. Bacterial cells are impermeable to folic acid and most of them synthesize it from PABA. Sulphonamides and trimethoprim (pyrimidines) are antifolate drugs that interfere with synthesis of folic acid by bacteria. The folic acid acts as an important precursor of DNA and RNA molecules.

Diagram 1: Mechanism of Action



DNA

Sulphonamides inhibit bacterial synthesis of dihydrofolic acid by competing with para amino-benzoic acid (PABA). This is a step in the biosynthesis of nucleic acids and proteins required by many bacteria. Many microorganisms synthesize PABA which is a necessary precursor of folic acid. The PABA reacts with another compound **pteridine** to yield **dihydrofolic acid** which is eventually converted to folic acid. Sulphonamides are structural analogues of PABA.

Trimethoprim blocks production of **tetrahydrofolic acid** from dihydrofolic acid by binding to and reversely inhibiting the enzyme ***dihydrofolate reductase***. **Pyremithamine** which is a benzyl-pyrimidine inhibits the activity of dihydrofolate reductase of protozoa because of their synergistic activity.

The end result is formation of non-functional analogues of folic acid and the bacteria cease to multiply (bacteriostatic). Organisms sensitive to sulphonamides are those that synthesize their own folic acid.

Resistance occurs as a result of mutations that cause overproduction of PABA, cause production of a folic acid synthesizing enzyme that has low affinity for sulphonamides or cause loss of permeability to the sulphonamides.

3.0. Pharmacokinetics

Most sulphonamides are rapidly absorbed from the gut (stomach and small intestine) with variation among specific drugs. They are distributed widely to tissues and body fluids including the CNS and CSF because of crossing the blood brain barrier, placenta and foetus.

They are bound to serum proteins (albumin) and displace bilirubin from plasma proteins leading to higher concentrations of free bilirubin. The free (unbound) sulphonamides diffuse freely through the serous cavity and more easily when there is inflammation. Peak blood levels are attained after 2 – 6 hours after oral administration.

Part of the absorbed drug is metabolized by acetylation or glucuronidation with acetate and glucuronic acid respectively. The process takes place in the liver. Active sulphonamides and inactivated metabolites are excreted into urine mainly by glomerular filtration (reduce the dose in renal failure).

Glucuronides and acetylated forms are less soluble than the parent drug hence

they form crystals leading to **crystalluria**. Sulphonamides are more soluble in alkaline urine. Concentration of the drug is done in the glomeruli with the concentration in urine being greater than that in the body cavities and therefore sulphonamides are good for treating urinary tract infections. The effectiveness is increased by making urine more alkaline.

Oral absorbable sulphonamides can be classified as short, intermediate and long acting sulphonamides. Short acting sulphonamides are rapidly absorbed and have a half life of 4 – 7 hours. They produce high urinary levels hence preferred for UTI treatment. Intermediate acting sulphonamides are absorbed and excreted slowly with a half life of 10 – 12 hours. Long acting sulphonamides are absorbed fairly rapidly but are excreted slowly with half lives of 17 – 40 hours.

Poorly absorbed sulphonamides are rarely used to reduce the normal bacterial flora within the gut before colonic surgery and as adjunctive treatment for ulcerative colitis. Topical sulphonamides are used on the skin and mucous membranes and the eyes.

4.0. Indications

1) *Pneumocystis jirovei* (formerly *P. carinni*)
2) Toxoplasmosis
3) Nocardiosis
4) UTI, Neisseria
5) Respiratory tract infections – otitis media, tonsillitis, pharyngitis; organisms – *H. influenzae, Strep pneumoniae*
6) Chanchroid
7) LGV

5.0. Contraindications

1) Allergy to the drug
2) Renal impairment
3) Liver impairment
4) Pregnancy
5) Neonates

6.0. Side Effects

Crystalluria, allergic reactions – rash, fever, hepatitis, agranulocytosis, purpura, exfoliative dermatitis, photosensitivity, Steven-Johnson syndrome, GIT disturbances – nausea, vomiting and diarrhoea; stomatitis, conjunctivitis, arthritis, hepatitis, haemopoeitic disturbances and cross allergy – carbonic anhydrase

inhibitors, thiazides, frusemide and sulfonyl urea hypoglycaemics

COTRIMOXAZOLE (Septrin, Bactrim)

Introduction

Sulfamethoxazole/sulphamethoxazole and **trimethoprim** are used in combination as **cotrimoxazole** because of their synergistic activity. Trimethoprim given together with a sulphonamide produces sequential blocking in the metabolic sequence resulting in marked enhancement (synergism) of the activity of both drugs. The combination is often bactericidal activity of a sulphone.

Resistance results from reduced cell permeability, overproduction of dihydrofolic reductase or production of an altered reductase with reduced drug binding capacity. Resistance may emerge by mutation but commonly it is due to plasmid-encoded trimethoprim-resistant dihydrofolic reductase.

Indications

1) Upper and lower respiratory tract infections
2) UTI
3) GIT infections
4) Skin infections
5) *Pneumocystitis jirovei* pneumonia
6) Shigellosis
7) Salmonella infections
8) Non-tuberculous mycobacterium
9) Prostatitis

Precautions

1) Regular blood counts (on prolonged use)
2) Folate impairment
3) Lactation
4) Renal impairment
5) The elderly
6) Maintain adequate fluid output
7) Allergic conditions
8) Bronchial asthma
9) Use of diuretic
10) Concomitant use with coumarins anticoagulants, methotraxate and phenytoin

Contraindications

Hepatic and renal impairment, blood disorders, pregnancy, lactation, vitamin B_{12} and folate deficiency, premature and new born infants and concomitant use with anti-convulsant medicines

Drug Interactions

1) Increase hypoglycaemic action of sulphylureas
2) Prolongs the half life of phenytoin and rifampicin
3) Disturbs anticoagulant action of courmarins
4) Antagonized by PABA
5) Diuretics increase the risk of thrombocytopenia
6) Paraldehyde increases acetylation of sulphamethoxazole thus increases formation of crystals

Side Effects

GIT disturbances – nausea, anorexia, vomiting, diarrhoea; headache, allergic reactions – skin rash, photosensitivity, erythema multiforme, dermatological necrolysis, Steven-Johnson syndrome, glossitis, stomatitis, liver damage (jaundice and liver necrosis), pancreatitis, colitis, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycaemia, blood disorders – leucopenia, thrombocytopenia, oesinophilia, megalobastic anaemia, hyperkalemia, hyponatraemia, arthralgia, myalgia and interstitial nephritis

Preparations

1) Tablets – adult 480 mg (400 mg sulphamethoxazole + 80 mg trimethoprim) and forte 960 mg (800 mg sulphamethoxazole + 160 mg trimethoprim); paediatric tablet 120 mg (100 mg sulphamethoxazole + 20 mg trimethoprim)
2) Infusion – 96mg/ml
3) Syrup 240 mg/5mls

Dose

- Adult 960 mg – 1.44 gm BD
- Children 6/52 – 5/12 120 mg BD; 6/12 – 5 years 240 mg BD and 6 – 12 years 480 mg BD
- Gonorrhoea 1.92 mg BD x 2/7 or 2.4 gm repeat after 48 hours
- Prophylaxis of UTI 480 mg nocte
- Infusion 960 every BD increased to 1.44 gm BD in severe infections
- Treatment of *Pneumocystis jiroveci* – adult and child over 4 years, 120 mg/kg daily in 2 – 4 divided doses x 14 - 21/7 (15 mg/kg/day of trimethoprim

component in 3 divided doses IV for 14 – 21/7)

- Prophylaxis of *Pneumocystis jiroveci*
  - Adult 960 mg OD (may be reduced to 480 mg) or 960 mg on alternate days (three times a week) or 960 mg BD on alternate days (three times a week)
  - Child 6/52 – 5/12 120 mg BD on three 3 consecutive days per week ; 6/12 – 5 years 240 mg BD and 6 – 12 years 480 mg BD

Common Names

Cotrimoxazole, Septrin, Bactrim, Coitreich, Biotrim, Alcotrim, Alprim, Cosatrim, Septrimed, Maxotrim, Primox

CHLORAMPHENICOL AND DERIVATIVES

1.0. Introduction

Chloramphenicol originally derived from soil actinomycete *Streptomyces venezuelae* is now produced synthetically. It is a potent broad spectrum antibiotic however it is associated with serious haematological side effects when given systemically for long durations and should therefore be reserved for life threatening infections particularly those caused by *Haemophilus influenzae*.

Chloramphenicol is a neutral stable compound soluble in alcohol but poorly soluble in water. Chloramphenicol succinate which is used for parenteral administration is highly water soluble and it is hydrolyzed easily to liberate chloramphenicol. *Haemophilus influenzae*, *Neisseria meningitidis* and some strains of bacteroids are highly susceptible (where its action is bactericidal).

2.0. Pharmacokinetics

Chloramphenicol is rapidly and completely absorbed after oral administration. After absorption chloramphenicol is widely distributed to virtually all tissues and bodily fluids including the CNS and CSF such that the concentration in the brain tissue may be equal to that in the serum.

The drug penetrates cell membranes readily. Most of the drug is inactivated either by conjugation with glucuronic acid (in the liver) or by reduction to inactive arhyl amines. It is excreted into bile or faeces. Infants less than 1 week old and premature infants clear chloramphenicol poorly and hence should not be administered on them.

3.0. Mechanism of Action

Chloramphenicol is bacteristatic in action. it binds to 50S sub unit of the bacterial ribosome and inhibits bacterial protein synthesis by preventing attachment of aminoacyl transfer RMA to its acceptor site on the ribosome. This prevents peptide bond formation by *peptidyl transferase*.

4.0. Indications

Chloramphenicol is indicated in serious infections where less potentially dangerous medicines are ineffective or contraindicated e.g. typhoid fever (salmonella), meningitis (*H. influenzae*) and whooping cough (*B. pertussis*).

5.0. Precautions

1) Routine blood counts
2) Change parenteral administration to oral therapy as soon as possible
3) Impaired liver function
4) Impaired renal function
5) Do not use for treatment of trivial infections
6) Avoid repeated and prolonged courses

6.0. Contraindications

1) Pregnancy and lactation
2) During active immunization
3) Porphyria
4) Infants (only in life threatening infections)
5) Preterns and neonates

7.0. Drug Interactions

1) Inhibits metabolism of chlopropamide, cyclophosphamide
2) Elevated levels occur during concomitant administration of paracetamol

8.0. Side Effects

Bone marrow depression, blood dyscrasia (especially aplastic anaemia), Grey baby syndrome in premature and new born babies – cyanosis, abdominal distention, circulatory collapse and hypothermia, optic neuritis, peripheral neuritis, GIT

disturbances – nausea, vomiting, diarrhoea, super-infections, hypersensitivity reactions – urticaria, erythema multiforme, headache, stomatitis, glossitis and dry mouth

9.0. Preparations

1) Injection 1 gm/vial
2) Capsules 250 mg
3) Syrup 125 mg/5 mls

10.0. Dose

- Adult 50 mg/kg daily in 4 divided doses (500 mg – 1 gm QID)
- Children over 2 weeks 50 mg/kg in 4 divided doses
- Children less than 2 weeks 25 mg/kg in 4 divided doses

11.0. Common Names

Chloramphenicol, Biomphenicol, Elycetin, Gestomicol, Oramnicol, Maxamycetin

LINCOSAMIDES

1.0. Introduction

The lincosamide group of antibacterial agents include **clindamycin** and **lincomycin**. They are used in treatment of serious anaerobic infections. Lincomycin is an antibacterial agent produced by *Streptomyces lincolnensis* and its semi synthetic derivate clindamycin have a spectrum of activity similar to erythromycin. The spectrum of activity includes common gram positive pathogens such as staphylococci and streptococci and anaerobic organisms such as bacteroids, clostridia, actinomycosis and nocardia.

2.0. Mechanism of Action

Lincosamides are **bacteriostatic** in action as they bind to the 50S subunit of bacterial ribosome. This inhibits translocation step in protein synthesis.

3.0. Side Effects

1) Colitis, G.I.T disturbances – nausea, vomiting, anorexia and diarrhoea
2) Weight loss
3) Pain at the injection site
4) Sterile abscess or induration at the injection site
5) Thrombophlebitis at IV injection sites (rapid IV – cardiac arrest)

6) Hypotension
7) Hypersensitivity reactions
8) Blood disorders

1. CLINDAMYCIN

Introduction

Clindamycin is a chlorinated derivative of lincomycin and its use is limited due to serious side effects. It is active against gram positive cocci including penicillin-resistant staphylococci and many anaerobes especially *Bacteroides fragilis*. Both gram negative and positive organisms are usually susceptible. Enterococci, gram negative anaerobes and *Clostridium difficile* are resistant.

Resistance to clindamycin generally confers cross resistance to macrolides because both bind at 50S subunit of bacterial ribosome and is usually due to mutation of risbosomal receptor site, modification of the receptor by a constitutively exposed *methylase* enzyme and enzymatic inactivation of clindamycin. Gram negative aerobic organisms are intrinsically resistant because of poor permeability of the outer membrane.

Pharmacokinetics

Administered IV or orally. Clindamyicn is 90% bound to serum proteins and metabolized in the liver. Clindamycin is well concentrated in bone and penetrates well into most tissues with the exception of the brain and CSF. It penetrates well into abscesses and it is actively taken and concentrated by phagocytic cells. Clindamycin has a half life of 2½ hours (increased to 6 hours in patients with renal failure) and the active drug and metabolites are excreted in urine and bile.

Indications

1) Upper and lower respiratory tract infections especially pneumonia
2) Skin and soft tissue infections
3) Bone infections e.g. osteomyelitis
4) Joint infections
5) Bacteraemia
6) Intra-abdominal sepsis e.g. penetrating wounds (with aminoglycosides), septic abortions, pelvic abscess
7) Prophylaxis of endocarditis in patients allergic penicillin
8) With pyrithemine for AIDS related toxoplasmosis of the brain and PCP in AIDS patients

Precautions

1) Atopic patients
2) Renal impairment
3) Hepatic impairment
4) Reserved for serious infections
5) Other medicines with neuromuscular blocking properties

Contraindications

1) Meningitis
2) Lincomycin and doxorubin sensitive patients
3) GIT disturbances (especially history of colitis)
4) Pregnancy
5) Lactation
6) Infants
7) Concomitant administration with erythromycin

Drug Interactions

1) Enhance action of neuromuscular blocking agents
2) Incompatible with aminophylline, ampicillin, barbiturates, solutions containing B complex, calcium gluconate and magnesium sulphate

Side Effects

Pseudomembranous colitis, abdominal cramps, taste disorders, nausea, diarrhoea, hypersensitivity reactions, blood dyscrasia e.g. neutropenia, thrombophlebitis, super-infections and impaired liver functions

Preparations

1) Capsules – 150 and 300 mg
2) Injection 150 mg/vial
3) Syrup 75 mg/5 mls

Dose

- Adults 150 – 450 mg TID or QID 1 hour before meals – given orally, IV and deep IM
- Children 3 – 6 mg/kg TID/QID

Common Names

Clindamycin, Dalacin C, Clinder B, Clindacin

2. **LINCOMYCIN**

As clindamycin

Preparations

1) Capsules 500 mg
2) Syrup 250 mg/5mls
3) Injection 600 mg/2 mls

Dose

- Adult 500 mg TID
- Children 30 – 60 mg/kg/day in divided doses

Common Names

Lincomycin, Lincocin, Lincar B

OXAZOLIDINONES

Introduction

Oxazolidinones is a new class of synthetic antimicrobials active against gram positive organisms including Staphylococci, Streptococci, Enterococci, gram positive anaerobic cocci and gram positive rods such as corynebacteria and *Listeria monocytogenes*. They are active against methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci. They are not sufficiently active against gram negative organisms. **Linezolid** is a class member.

Mechanisms of Action

Linezolid is primarily bacteriostatic save for streptococci for which it is bactericidal. Has modest activity against *Mycobacterium tuberculosis*. It inhibits protein synthesis by preventing formation of the ribsome complex which is meant

to initiate protein synthesis. This is achieved by binding on the 23S ribosomal RNA of the 50S subunit hence no cross resistance with drugs of other classes.

Indications

1) Community acquired pneumonia
2) Nosochomial pneumonia
3) Complicated skin and skin structure infections
4) Vancomycin resistant *Enterococcus faecium*
5) Febrile neutropenia
6) Septicaemia
7) Endocarditis
8) Osteomyelitis
9) Surgical prophylaxis

Precautions

1) May promote over growth of non-susceptible organisms
2) Full blood counts weekly

Contraindications

1) Hypertension
2) Phaeochrocytoma
3) Schizophrenia
4) Thyrotoxicosis
5) Acute confusional states
6) Breast feeding
7) Renal impairment
8) Hepatic impairment

Drug Interactions

1) Reversible non-selective inhibition of MAO hence it has potential to interact with adrenergic or serotonergic agents.

Side Effects

GIT disturbances – nausea and vomiting, antibiotic associated colitis and diarrhoea, taste disturbances, headache, fever, dizziness, oral and vaginal monoliasis, hypertension, dyspepsia, pruritus/ rash, insomnia, abdominal pain, tongue discoloration, fatigue, neuropathy, blurred vision, blood disorders – anaemia, leucopoenia, thrombocytopenia, and renal failure

Preparations

1) Injection 200 mg/100 mls, 600 mg/300 mls
2) Tablets 600 mg
3) Syrup 100 mg/5 mls

Dose

- 600 mg BD

Common Names

1) Linolial

STEROIDAL ANTIBIOTICS

Introduction

Steroidal antibiotics such as fusidic acid are narrow spectrum antibiotics used for treatment of infections caused by penicillin resistant staphylococci especially osteomyelitis because they are well concentrated in bone. A 2nd anti-staphylococci antibiotic is necessary to prevent emergence of resistance.

Mechanism of Action

Steroidal antibiotics such as fusidic acid inhibit protein synthesis by inhibiting the factor necessary for translocation of peptide subunits and elongation of the peptide chain.

Indications

1) Staphylococcal infections
    a. Penicillin resistant staphylococcal infections including osteomyelitis
    b. Staphylococcal endocarditis (in combination with other antibiotics)

Precautions

1) Monitor liver function especially with high doses and prolonged use
2) Hepatic impairment
3) Elimination is reduced in hepatic impairment
4) Pregnancy

Contraindications

1) Hypersensitivity
2) Pregnancy
3) Hepatic impairment

Drug Interactions

1) Lincomycin and rifampicin (both excreted via biliary pathways)
2) Incompatible with dextrose 40%, 50% and whole blood

Side Effects

GIT disturbances – nausea and vomiting, hepatotoxicity (high dose, rapid dissemination), jaundice, thrombophlebitis, acute renal failure, blood disorders and hypersensitivity reactions

Preparations

1) Tablets 250 mg
2) Syrup 250mg/5mls
3) Infusion

Dose

- Adults 500 mg TID (with meals)
- Severe and chronic infections combine with Penicillins

Common Names

1) Fusidin

GLYCOPEPTIDE ANTIBIOTICS

Introduction

The glycopeptide antibiotics such as **vancomycin** and **teicoplanin** have bactericidal activity against aerobic and anaerobic gram positive bacteria including resistant staphylococci.

VANCOMYCIN

Mechanism of Action

Glycopeptide antibiotics inhibt cell wall synthesis, alter cell membrane permeability and RNA synthesis. They bind firmly to the terminal of a forming polypeptide chain preventing further elongation of peptidoglycan and cross-linking. This produces a weakened peptidoglycan and the cell becomes susceptible to lysis. Damage to the bacterial cell membrane contributes to the antibacterial effect. Resistance ensues from modification of the drug binding sites.

Pharmacokinetics

Vancomycin is poorly absorbed from the intestinal tract hence it is administered orally only for treatment of antibiotic associated enterocolitis caused by *Clostridium difficile*. Parenteral doses must be administered IV. It is widely distributed in the body and CSF levels increase when the meninges are inflamed. 90% is excreted by glomerular filtration.

Indications

1) Severe staphylococcal infections
2) Antibiotic associated pseudomembranous colitis
3) Endocarditis
4) Osteomyelitis
5) Pneumonia
6) Soft tissue infections
7) Enterocolitis
8) Peritonitis

Precautions

1) Hearing loss
2) Renal insufficiency
3) Concomitant administration with other neurotoxic and nephrotoxic drugs

Side Effects

Nephrotoxicity, ototoxicity, vertigo, dizziness, tinnitus, superinfections, anaphylaxis,

reversible, neutropenia, thrombocytopenia, oesinophilia, nausea, fever, chills and rashes

Preparations

1) Injection 500 mg/vial

Dose

- IV infusion 500 mg QID (over 1 hour) or 1 gm BD (over 100 minutes)
- Children 10 mg/kg after 6 – 12 hours

Common Names

Vancomycin, Vancocin

QUINOLONES

Introduction

Quinolones are important antibiotics which are active against a variety of gram positive and gram negative organisms. This group of antibiotics include nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, lomefloxacin, moxifloxacin, pefloxacin, galifloxacin and sparfloxacin. Nalidixc acid was fluorinated to produce 4 flouroquinolones.

Mechanism of Action

Quinolones interfere with the enzyme *DNA gyrase* which is essential for the synthesis of bacterial DNA. Quinolones block synthesis of bacterial DNA by inhibiting *bacterial topoisomerase II (DNA gyrase)* required for normal transcription and replication of the bacteria and *topoisomerase IV* needed for separation of DNA strands top form daughter cells during cell divison.

Antibacterial Spectrum

Quinolones have an excellent activity against gram negative aerobic bacteria. Older ones have limited activity against gram positive organism while the newer quinolones have improved activity against gram positive cocci. Norfloxacin is least active against both gram negative and gram positive organisms. Ciprofloxacin, levofloxacin, ofloxacin and pefloxacin have excellent activity against gram negative and moderate to good activity against gram positive bacteria. Methicillin-susceptible strains of *Staphylococcus aureus* are susceptible to quinolones but

resistant strains are not. Streptococci and enterococci are less susceptible than staphylococci. Resistance emerges among staphylococci and pseudomonas due to mutation at binding sites or change in wall permeability of the bacteria.

Pharmacokinetics

They are well absorbed after oral administration and are widely distributed in body fluids and tissues with a bioavailability of 80 – 90%. The serum half life ranges from 3 hiours (norfloxacin and ciprofloxacin) to 10 hours (pefloxacin) or longer for sparfloxacin. Oral absorption is reduced by divalent cations and antacids. Concentrations in the prostate, kidney, neutrophils,macrophages exceed serum concentrations. Excretion is by renal mechanisms of tubular secretion or glomerular filtration. You need to adjust the dose in renal failure.

Indications

1) UTI
2) Shigella
3) Salmonella
4) Bone and joint infections
5) Intra-abdominal infection s
6) RTI(respiratory tract infection)

Side Effects

GIT disturbances – nausea, vomiting, diarrhoea, headache, dizziness, insomnia, skin rash, abnormal liver function tests and photosensitivity

1. NALIDIXIC ACID

Nalidixic acid is the fisrt quinoline introduced ibn 1963. it is not fluorinated and is excreted rapidly to be used for systemic infections.

Indications

1) Uncomplicated UTI

Precautions

1) Porphyria
2) History of convulsive disorder
3) Strong sunlight

4) Monitor blood counts
5) Monitor renal and hepatic function if treatment is > 2/52

Side Effects

Toxic psychosis, increased ICP, metabolic acidosis, cholestasis, cranial nerve palsy, paraesthesia and weakness

Preparations

1) Tablets 500 mg

Dose

- Adult 0.5 gm – 1 gm QID x 1/52
- Children 3/12 – 12 years 55 mg/kg/day in 4 divided doses

Common Names

Nalidixic acid, Dawaseptic

2. CIPROFLOXACIN (Ciproxin)

Indications

1) ENT infections
2) UTI
3) RTI
4) Skin and soft tissue infection s
5) Bone and joint infections
6) GIT infection s
7) Intra-abdominal infections
8) Pelvic infections
9) Severe infections
10) Gonorrhoea

Precautions

1) Convulsive disorder
2) Dehydration
3) Alkaline urine
4) Impaired renal function
5) Impaired hepatic function

6) Administer 1 – 2 hours before or 4 hours after Fe preparations

Contraindications

1) Children < 18 years (used only when other tried drugs have FAILED)
2) Pregnancy
3) Lactation

Drug Interactions

1) Metochlopramide increases absorption
2) Probenecid increases its serum concentrations
3) Intensify action of warfarin
4) Februfen increases the risk of CNS stimulation and convulsive seizures
5) Antacids and sucralfate reduce absorption
6) Reduce theophylline metabolism

Side Effects

Local irritation at injection site, GIT disturbances, dizziness, headache/migraines, tremors, confusion, convulsions, skin rashes, blurred vision, psychotic reactions, disturbed smell and taste, Steven-Johnson syndrome , hot flashes and photosensitivity

Preparations

1) Tablets 250 mg, 500 mg
2) Infusion 2 mg/ml

Dose

- Bone and joint infections
  - ✓ Mild – moderate infection – 500 mg BD x 4 – 6/52
  - ✓ Severe/complicated infections - 750 mg BD x 4 – 6/52
- Infectious diarrhoea – 500 mg BD x 5 – 7/7
- Gonorrhoea (urethral and endocervical) – 500 mg stat
- Intra-abdominal infections – 500 mg BD x 2/52 + oral metronidazole
- Lower respiratory tract infections
  - ✓ Mild – moderate 500 mg BD x 7 – 14/7
  - ✓ Complicated/severe – 750 mg BD x 1- 2/52
- Meningococcal carriers – 750 mg stat
- Chronic prostatitis 500 mg BD x 1/52
- Typhoid fever and Sinusitis – 500 mg BD x 10/7

- Skin and soft tissue infections 500 mg – 750 mg BD x 1-2/52
- UTI – 100 – 500 mg BD x 3 – 14/7
- Infusion – over 30 – 60 minutes (400 mg over 60 minutes) 200 – 400 mg BD

Common Names

Ciprofloxacin, Ciproxin, Ciprox, Cifin, Ciprobiotic, Ciprointa, Cipromax, Neofloxin, Recipro, Roxin

3. NORFLOXACIN

Indications

1) UTI
2) Gonorrhoea
3) RTI. Pharyngitis
4) Prostatitis
5) Cervicitis
6) Typhoid fever

Precautions

1) Convulsions
2) Adequate fluid intake
3) Excessive sunlight
4) Pregnancy
5) Lactation
6) Children

Contraindications

1) Pre-puberty children
2) Hypersensitivity to quinolones

Drug Interactions

1) Increase serum levels of nitrofurantoin and theophylline
2) Enhance effects of oral anticoagulants
3) Antacids , Zinc and Fe reduce absorption

Side Effects

GIT disturbances, neuropsychiatric disturbances, skin rashes and hypersensitivity

Preparations

1) Tablets 400 mg

Dose

- UTI – 400 mg BD x 7 – 10/7
- Uncomplicated acute cystitis – 400 mg BD x 3 – 7/7
- Chronic relapsing UTI – 400 mg BD up to 12/52
- Acute gonorrhoea – 800 mg stat
- Typhoid fever 400 mg TID x 14/7

Common Names

Norfloxacin, Normax, Norfen, Zeflox, Norilet, Norfocin, Noroxin, Tamflox, Uniflox, Noflox

4. SPARFLOXACIN

Indications

1) ENT infection s
2) UTI
3) RTI
4) Skin and soft tissue infections
5) Bone and joint infections
6) GIT infections
7) Intrabdominal infections
8) Pelvic infections
9) Severe infections
10) Gonorrhoea

Precautions

1) Convulsive disorder
2) Dehydration
3) Alkaline urine
4) Impaired renal function
5) Impaired hepatic function
6) Administer 1 – 2 hours before or 4 hours after Fe preparations

Contraindications

1) Children under 18 years
2) Pregnancy
3) Lactation
4) Hepatic disorders
5) Hypersensitivity to quinolones

Drug Interactions

1) Antacids reduce absorption
2) Reduce metabolism of theophylline

Side Effects

- As ciproflaxin

Preparations

1) Tablets 200 mg

Dose

- 200 mg OD

Common Names

Sparfloxacin, Sparflox, Sparflo, Sparta, Sparx

5. OFLOXACIN

Indications

1) UTI
2) LRTI
3) Gonorrhoea
4) Skin infections
5) Prostatitis

Precautions

1) Impaired renal function
2) Impaired hepatic function
3) Elderly
4) Strong sunlight

5) Pseudomembranous colitis

Contraindications

1) Pregnancy
2) Lactation
3) Cerebral convulsive disorder
4) Children

Drug Interactions

1) Antacids and Fe preparations reduce absorption

Side Effects

Allergic reactions, GIT disturbances, muscular and joint pains, blood dyscrasia, CNS effects(muscular coordination disturbances, neuropathy, unsteady gait, visual and sensory disturbances, hallucinations, convulsions), psychiatric reactions, anxiety, and for injection – reduce blood pressure after rapid infusion/thrombophlebitis

Preparations

1) Tablets 200 mg
2) Infusion 2mg/ml

Dose

- Uncomplicated UTI 200 mg BD x 3/7
- Complicated UTI 200 mg BD x 10/7
- Mild – moderate skin infectuions – 400 mg BD x 10/7
- LTRI 400 mg BD x 10/7
- Prostatitis – 300 mg BD x 6/52
- Acute uncomplicated gonorrhoea 400 mg stat
- Cervicitis, urethritis 300 mg BD x 1/52

Common Names

Kiroll, Tarivid, Oflamoc

NITROIMIDAZOLES

Introduction

Nitroimidazoles are imidazole derivatives of the azole group of drugs. Nitroimidazoles is a large group of drugs that exhibit a wide spectrum of activity against gram positive and gram negative bacteria, protozoa, a few helminths and certain types of cancer. They are selectively toxic to anaerobes alone. Nitroimidazoles have a spectrum of activity that transcends many taxonomic boundaries. **Metronidazole** discovered in 1959 is a key member of the group. Others members include **aminosidine**, **tinidazole**, **secnidazole**, **ornidazole**, **nimorazole** and **satranidazole**.

METRONIDAZOLE (Flagyl)

Introduction

Metronidazole is a nitroimidazole antiprotozoal drug with potent antibacterial activity against anaerobes including bacteroids and clostridium species. Metronidazole has a broad spectrum cidal activity against protozoa including *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis*, and many anaerobic bacteria such as *Bacteroid fragilis*, *Fusobacterium*, *Clostridium perfringes*, *Clostridium difficile*, *Helicobacter pylori* and aerobic *Streptococci*. It does not affect aerobic bacteria.

Mechanism of Action

Metronidazole enters the cell by diffusion and its nitro group is reduced by redox proteins which only operate in anaerobic microbes. The highly reactive nitro radical exerts cytotoxicity by damaging DNA and critical biomolecules. This result in destabilization of the DNA helix leading to breakage of the strands. An aerobic environment attenuates cytotoxicity of metronidazole by inhibiting its reductive activation. Metronidazole inhibits cell mediated immunity and induces mutagenesis and cause radiosensitivity. Metronidazole is a potent *in vitro* amoebicide and is effective in both intestinal and extra-intestinal amoebiasis.

Pharmacokinetics

Metronidazole is well absorbed from the small intestine after oral administration. The little unabsorbed drug reaches the colon. It is widely distributed in body tissues attaining therapeutic concentrations in vaginal secretions, semen, saliva and CSF. It penetrates all tissues by simple diffusion. Can be given IV or by rectal suppositories. It is metabolized in the liver primarily by oxidation and glucuronide conjugation hence may accumulate in hepatic insufficiency. it has a plasma t½ of

8 hours and is excreted in urine. Metronidazole is less effective than many luminal amoebicides in eradicating amoebic cysts from the colon because it is almost completely absorbed in the upper bowel.

Indications

1. Mixed intra-abdominal infections (*E. histolytica*)
2. Amoebias (invasive intestinal)
3. Giardiasis (*Girdia lamblia*)
4. *Trichomonas vaginalis*
5. Anaerobic bacterial infections – occur after colorectal orpelvic surgery, appendicitis
6. Brain abscess
7. Endocarditis
8. Pseudomonas enterocolitis due to *Clostridium difficile* generally associated with use of antibiotics
9. Surgical prophylaxis
10. Acute dental infections/ulcerative gingivitis
11. Helicobacter pylori
12. Surgical/gynaecological sepsis
13. Leg ulcer and pressure sores,
14. Bacterial vaginosis

Contraindications

Neurological disease, blood dyscrasias, pregnancy (first trimester) – risk of mutagenesis but no reported teratogenesis, chronic alcoholism and lactation*

Precautions

Avoid alcohol, pseudomembranous colitis, hepatic impairment, hepatic encephalopathy and concurrent administration of anti-hypertensives

Drug Interactions

1. Intolerance to alcohol
2. Enzyme inducers such as phenobarbitone and rifampicin may reduce its therapeutic effect
3. Enhances action of oral anticoagulants – warfarin
4. Cimetidine reduces metabolism of metronidazole
5. Reduces renal elimination of lithium

Side Effects

GIT disturbances (anorexia, nausea, vomiting, abdominal cramps and loose stools), unpleasant metallic taste, dry mouth, furred tongue/glossitis, headache, dizziness, skin rashes, transient neutropenia, vertigo, thrombophlebitis at the site of IV injection (solution poorly prepared), prolonged use causes peripheral neuropathy, CNS effects such as depression and insomnia and seizures.

Preparations

1) Tablets 200mg, 400mg
2) Infusion 5mg/ml
3) Syrup 200mg/5mls
4) Rectal suppositories 500mg

Dose

1) Invasive intestinal/dysentery/liver abscess
   - ✓ 800mg TDS x 5/7
   - ✓ Children 30 – 50 mg/kg/day TDS x 5/7
   - ✓ Serious cases of liver abscess 1 gm slow infusion, then 0.5 gm every 12 hours till oral therapy is started
2) Giardiasis
   - ✓ 200mg TDS x 7/7 or 2 gm OD x 2/7
   - ✓ Children, 1 – 3 years 500mg OD, 3 – 7 years 600 – 800mg OD and 7 – 10 years 1gm OD x 2/7
3) Trichomonas vaginalis
   - ✓ 200 - 400mg TDS x 7/7
   - ✓ 800 mg morn and 1200 mg nocte x 2/7
   - ✓ 2gm stat
4) Pseudomonas colitis – 800mg TDS
5) Acute dental infections – 200 – 400mg TDS x 5/7

Common Names

Metronidazole, flagyl, elogyl, eflaron, flagimed, gestazole, megyl, metrogyl, zagole, trogyl, tricozole and amebazole.

TINIDAZOLE (Fasigyn)

Introduction

Tinidazole is an analogue of metronidazole thus it has similar properties with metronidazole only that it has a longer duration of action. It has a plasma t½ of 12 hours with slow metabolism

Indications

1. *Trichomonas vaginalis*
2. Amoebiasis
3. Giardiasis
4. Anaerobic infections

Precautions

Avoid alcohol during the course and at least 72 hours after the course.

Contraindications

1. Pregnancy (first trimester)
2. Organic CNS disorders
3. Hypersensitivity

Drug interactions

Alcohol preparations

Side Effects

GIT disturbances (nausea, anorexia, diarrhoea), metallic taste, abdominal pains, hypersensitivity (rash), neurological disturbances (dizziness, vertigo, ataxia, peripheral neuropathy, convulsions), leucopenia, headache, furry tongue and tiredness.

Preparations

1. Tablets 500mg
2. Syrup 150mg/5mls

Dose

1) Amoebiasis
   - ✓ Adults - 2gm OD x 3/7,
   - ✓ Children – 30 – 50mg/kg/day or 0.6 gm BD x 5/7
2) Trichomoniasis

- ✓ Adult – 2gm stat
- ✓ Children 50 – 75 mg/kg stat

3) *Helicobacter pylori* – 500mg BD x 1-2/52
4) Giardiasis and Trichomoniasis – 2 gm stat or 0.6gm OD x 7/7
5) Anaerobic infections
   - ✓ Prophylactic 2 gm stat
   - ✓ Therapeutic 2 gm stat then 0.5 gm BD x 5/7

Common Names

Tinodazole, fasigyn, amtiba, tinibulk, quadran and tricogyn

AMINOSIDINE (Gabboral)

Aminosidine (paromomycin) is an amoebicide that is also useful in the treatment of *leishmaniasis*.

Indications

1. Intestinal amoebiasis
2. Giardiasis
3. Trichomoniasis
4. Prophylactic sterilization in GIT surgery
5. Prophylactic treatment in coma hepaticum

Side Effects

Have minimal side effects as it is primarily not absorbed from the gut.

Preparations

1. Tablets 250mg
2. Syrup 125mg/5mls

Dose

1) Adult 1 gm OD, children 20 – 30 mg/kg/day
2) Intestinal amoebiasis, giardiasis and trichomoniasis
   - ✓ 500mg OD x 6/7
   - ✓ Children 15mg/kg/day OD x 6/7
3) Prophylactic sterilization in GIT surgery
   - ✓ 2 gm OD x 3/7
   - ✓ Children 50mg/kg/day OD x 3/7

4) Prophylactic treatment of coma hepaticum
   - ✓ 2 gm stat
   - ✓ Children 50mg/kg/day

SECNIDAZOLE

Secnidazole is a nitroimidazole with a longer half life. Has the same spectrum of action and potency as metronidazole. It is rapidly and well absorbed after oral administration. Metabolism is slower resulting in a plasma t½ of 17 – 29 hours.

Indications

1. *Trichomonas vaginalis*
2. Amoebiasis
3. Anaerobic infections
4. Giardiasis

Precautions

1. Avoid alcohol during the course and at least 72 hours after the course

Contraindications

1. Allergy to imidazole derivatives
2. Pregnancy (first trimester)
3. Breast feeding
4. Blood dyscrasia
5. Psychotic disorders

Drug Interactions

As metronidazole

Side Effects

Metallic taste, gastralgia, nausea, vomiting, stomatitis, vertigo and moderate neurological disorders.

Dose

1) *Trichomonas vaginalis*
   - ✓ 2 gm stat
2) Amoebiasis (acute)
   - ✓ Symptomatic 2 mg stat/children 30 mg/kg stat
   - ✓ Asymptomatic 2 mg OD x 3/7, Children 30 mg/kg OD x 3/7

3) Hepatic amoebiasis
   - ✓ 1.5 gm in one dose or divided doses x 5/7
   - ✓ Children 30mg/kg

***Take at the beginning of the meal

Common Names

Secnida, cipazol and flagentyl

COMBINATIONS – Metronidazole + Diloxamide

Diloxamide furoate is active agsints the cystic form of amoeba.

Preparations

1. Tablets 200mg/250mg
2. Suspension 100mg/125 mg/5mls

Dose

1) 2 tablets TID x 5/7 (10/7 in refractory cases)
2) Children 5 – 12 years ½ tablets or 10 mls TID x 5/7; less than 5 years 5 mls TDS

Common Names

Dyrade-M, Trogyl plus, entamizole, dirazole, dilazole