Penicillins

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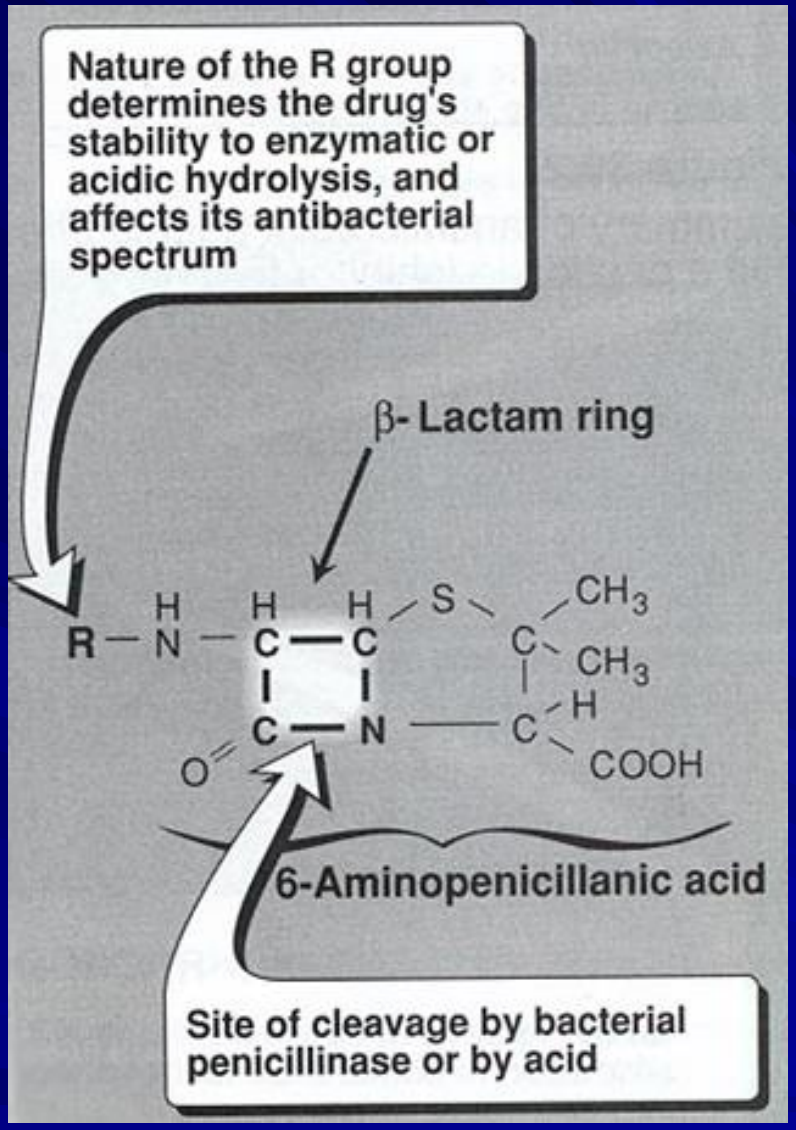
- Penicillins :are a class of beta-lactam antibiotics. Penicillin was the first antibiotic discovered from the mold Penicillium notatum in 1928 by Alexander Fleming
- The nucleus of penicillin (6-aminopencillanic acid) synthesised and become possible for attachment of different groups (R) which result in production of large number of semi synthesis compound



6-aminopencillanic acid

- Beta-lactamases (also called penicillinases) are enzymes that deactivate penicillins by destroying the beta-lactam ring via hydrolysis. Beta-lactamases allow bacteria to be resistant to penicillin.
- Enzymatic hydrolysis of the beta-lactam ring results in loss of antibacterial activity

Mechanism of Action

Beta-lactam antibiotics are bactericidal drugs. They act to inhibit cell wall synthesis by the following steps

1. Binding of the drug to specific enzymes (penicillin-binding proteins [PBPs]) located in the bacterial cytoplasmic membrane.
2. Inhibition of the transpeptidation reaction that cross-links the linear peptidoglycan chain constituents of the cell wall
3. Activation of autolytic enzymes that cause lesions in the bacterial cell wall.

Classification of Penicillins

1. Natural Penicillins:
   - Benzylpenicillin (Penicillin G)
   - Phenoxymethylpenicillin (Penicillin V)
2. Penicillinase Resistant Penicillins (antistaphylococcal)
   - Methicillin, Oxacillin, Nafcillin, Cloxacillin, and Dicloxacillin.
3. Extended Spectrum Penicillins (Aminopenicillins)
   - Ampicillin, Amoxicillin, Bacampicillin and pivampicillin
4. Anti-pseudomonal penicillins
   - Carboxypenicillins: Carbenicillin, Ticarcillin.
   - Ureidopenicillins: Piperacillin, azlocillin.

Adverse Effects of Penicillins

1. Allergy-Allergic reactions include urticaria, sever pruritus, fever, joint swelling, hemolytic anemia, nephritis, and anaphylaxis.
2. Gastrointestinal disturbances-Nausea and diarrhea may occur with oral penicillins, especially with Ampicillin.Gastrointestinal upsets may be caused by direct irritation or by overgrowth of gram-positive organisms or yeasts. Ampicillin has been implicated in pseudomembranous colitis.
3. Hematologic Reactions:
   - Hemolytic anemia.
   - Neutropenia
   - Thrombocytopenia
4. Hepatic Reactions.
5. Electrolyte Disturbances (penicillin usually administrated as Na or K salts)
6. Neurologic : Seizures.
7. Renal Reactions: nephrotoxic (Methicillin) Hemorrhagic cystitis (Methicillin).

Natural Penicillins

Penicillin G:

- Destroyed by gastric acid and thus its given parentally
- Easily destroy by Beta-lactamase.
- High activity against gram positive organisms and gram negative cocci.
- Low activity against gram negative Bacilli.

Clinical Uses of Penicillin G

- Streptococcal Infections.
- Gram Positive Rods (Clostridia-anaerobic infections and Bacillus species) including: Tetanus, Gas gangrene and Anthrax.
- Syphilis due to Treponema pallidum.
- Primary syphilis: Single dose of Benzathine Penicillin G.
- Secondary syphilis: Procain Penicillin.
- Neurosyphilis: High dose of Penicillin G
- Benzylpenicillin is the drug of choice for infections due to Neisseria meningitis (meningococcal meningitis and septicaemia)
- Neisseria gonorrhoeae
- Corynebacterium diphtheriae (diphtheria)
- Leptospira spp. (leptospirosis)
- Actinomyces israelii (actinomycosis).
- It is also the drug of choice for Borrelia burgdorferi (Lyme disease) in children

Natural Penicillins

Penicillin V (Phenoxymethyl Penicillin):

- Same antibacterial spectrum of penicillin G but its less active against Neisseria meningitis Neisseria gonorrhea, so its mainly used for upper and lower RTI, sinusitis
- It is resistant to gastric acid (given orally) and so reaches the small intestine intact

Penicillinase Resistant penicillin

(Methicillin, Cloxacillin, dicloxacillin, oxacillin, fluxocillin)

- They posses acyl side chain which , protect the B-lactam bond by prevent B-lactamase (penicillinase) from binding to penicillin and prevent hydrolyze the beta-lactam ring and prevent termination the antibacterial activity of these penicillins
- Their primary use is in the treatment staphylococcal infections Skin infections (impetigo), abscesses, Pneumonias, Prosthetic joint, endocarditis, meningitis and bone infections
- Methicillin-resistant staphylococci [MRSA] are resistant to all penicillins and are often resistant to multiple antimicrobial drugs.

Extended Spectum Penicillins (Amino Penicillins)

- The activity of these semisynthetic penicillins extends beyond the Gram-positive and Gram-negative cocci which are susceptible to benzylpenicillin, and includes many Gram-negative bacilli.
- Against Enterococcus faecalis
- Many strains of Haemophilus influenzae.

Extended Spectum Penicillins
(Amino Penicillins)
Ampicillin:

- Not completely absorbed(the absorption affected by presence of food,
- It be given orally IM,IV orally 4 time daily
- High incidence of diarrhea.

Amoxicillin is a structural analogue of Ampicillin

- Better absorbed from the gut
- Diarrhea is less frequent with amoxicillin than with Ampicillin. The oral Dose 3 times daily is preferred because
- Greater bioavailability
- Fewer adverse effects.

Extended Spectum Penicillins (Amino Penicillins)

- Bacampicillin and Pivampicillin: (Ester salts of Ampicillin) metabolized in the intestinal cell or liver releasing Ampicillin.
- Characterize by :
  1. Better absorption from the GIT.
  2. Low incidence of diarrhea.
  3. Absorption is not effected by food.

Antipseudomonal Penicillins

- Same antibacterial spectrum as Ampicillin (and are susceptible to (B-lactamases), but have the additional capacity to destroy Pseudomonas aeruginosa and indole-positive

Antipseudomonal Penicillins are divided into 2 groups:

- Carboxy Penicillins, including: Carbenicillin and Ticarcillin.
- Ureidopenicillins, including: Azlocillin and Piperacillin.

Antipseudomonal Penicillins
Carboxypenicillin

- Ticarcillin and carbinicillin are administered as disodium salt each 1g of Ticarcillin delivers about 5.4 mmol of Na, which should be borne in mind when treating patients with impaired cardiac or renal function

Antipseudomonal Penicillins

Ureidopenicillins:

- Administered parenterally and are eliminated mainly in the urine

  Ureidopenicillins major advantages over the Carboxypenicillins are:

  1. Higher efficacy against Pseudomonas aeruginosa
  2. They administrated as monosodium salts and deliver about 2 mmol of sodium per gram of (safer in renal or cardiac disorder)
  3. These agent produce less accumulation in patient with renal impairment because about 25% of the dose excreted by a bile

Antipseudomonal Penicillins

Ureidopenicillins

Piperacillin has the same or slightly greater activity as azlocillin against Pseudomonas aeruginosa but is more effective against the common Gram-negative organisms.

Clinical Uses of Antipseudomonal Penicillins

1. Serious P. Aeruginosa infections .
2. Mixed infections
3. Complicated UTIs.
4. Prostatitis.
5. Surgical prophylaxis.

B-lactamase inhibitors

- Clavulanic acid, Sulbactam and Tazobactam. They bind with B-lactamase enzyme(inhibit the enzyme irreversibly), protect the penicillin from action of these enzyme and promote the activity of penicillin against B-lactamase producing bacteria

B-lactamase inhibitors Combinations:

- They are used for the treatment of infections due to B-lactamases producing bacteria (resistant infections) such as: H.influanzae, staphylococcus aureous, E.coli, Klebsiella species and Proteus mirabilis.
- **Note :** clavulinic acid may cause collestatic jaundice duo to obstruction of billiary tract

B-lactamase inhibitors Combinations:

- Amoxicillin-Clavulanic acid (Augmentin)
- Ampicillin-Sulbactam
- Ticarcillin-Clavulanic acid (Timentin)
- Piperacillin-Tazobactam.

Clinical Uses

1. The diseases treated include:
2. Respiratory tract infections.
3. Skin and soft tissue infections.
4. Endocarditis.
5. Bone and joint infections.
6. UTIs.
7. Intra-abdominal infections.
8. Septicemia.