

CHLORAMPHENICOL

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CHLORAMPHENICOL

- Broad spectrum antibiotic isolated from *Streptomyces venezuelae*
- Anti-bacterial spectrum similar to tetracycline
- Effective against *Gm +ve*, *Gm -ve*, *Rickettesia*, *Mycoplasma* and *Chlamydia*
- **Bacteriostatic**, but bacteriocidal to *H. Influenzae*.
- **Inhibits** bacterial protein synthesis by binding **at 50S ribosomal subunits**
- It also **inhibits mammalian mitochondrial protein synthesis** by **inhibiting 70S ribosomes** → Exerts associated host toxicity

CHLORAMPHENICOL

- **Resistance** to chloramphenicol **develops** to :-
 - i) **H. influenzae, Salmonella Typhii** etc
 - li) **Decreased permeability** to the drug
 - lii) **Decreased affinity** for the drug to bind to ribosomal binding site
 - Iv) **Production of acetyl-transferase enzyme** that metabolites chloramphenicol to an inactive form

CHLORAMPHENICOL

- Antimicrobial **spectrum :-**
- i) **Gm -ve Bacteria :-** Salmonella typhii, H. influenzae, N. Meningitidis
- ii) **G +ve bacteria:-** Streptococcus pneumoniae,
- iii) **Anaerobic bacteria :-** B. Fragillis
- **Iv) Atypical micro-organisms :-** Spirochetes, rickettesiae, mycoplasma, chlamydia

CHLORAMPHENICOL- MOA

Chloramphenicol



Actively taken up by susceptible bacteria



Binds reversibly to 50 S ribosomal subunit



Prevent access of aminoacyl tRNA to the mRNA- Ribosome complex at 50S ribosomal subunits



Prevent the addition of amino acid to the growing peptide chain



Inhibit Protein Synthesis (Bacteriostatic)

Also inhibit mammalian Mitochondrial 70 S - ribosomal subunit

CHLORAMPHENICOL- PK/s

- Available as **oral, parenteral , suspension form**
- **Complete, rapid oral absorption – good bioavailability**
- **Chloramphenicol palmitate** → for oral suspension → Degraded into chloramphenicol by pancreatic lipase juice in duodenum
- **Distributed widely in the body, CSF**
- **Metabolized** in liver by glucuronyl Transferase enzyme by **Glucuronyl conjugation**
- Excreted in urine
- Plasma **t_{1/2}** is **3-5 hrs**

CHLORAMPHENICOL - USES

- 1) **Bacterial meningitis** due to *H. Influenzae*; *Meningococcal* & *Neisseria Meningitidis* (Bactericidal) along with Ampicillin.(50 -75mg / kg/ day) in children & cephalosporin allergic Pts.
- 2) **Anaerobic infections :-** *B. Fragilis* → *intra-abdominal/pelvic abscess, brain abscess, wound infections etc...*– Alternative to Metronidazole / Clindamycin or in combination
- 3) **Typhoid (Enteric) Fever** – *Till 1980s* used as 1st line → now, resistant developed to *S.typhii* → not used → Bacteriostatic → ↑ Relapse rate , **not effective in carrier state**

CHLORAMPHENICOL - USES

- 4) Rickettsial infections :- *Rocky mountain spotted fever, typhus, Q fever* in young children & pregnant women where tetracyclines are **contraindicated**.
- 5) *Gm +ve ocular infection, Trachoma, conjunctivitis, chronic otorrhoea due to Gm-ve microbes .Topical chloramphenicol effective*
- 6) *Cholera, Lymphogranuloma inguinale, cellulitis due to H. Influenzae*

CHLORAMPHENICOL- ADVERSE EFFECTS

- **1) Haematological Toxicity :-**
- **A) Bone Marrow depression :-** aplastic anaemia; agranulocytosis; thrombocytopenia & Pancytopenia occur
- **i) Idiosyncratic – Non-Dose dependent reaction :-** Genetic predisposition, serious, fatal and unpredictable reaction with repeated doses.
- Causes fatal aplastic anaemia.
- Leukaemias develop in survived pts.
- **ii) Dose / Duration related Myelosuppression :-**
- Effect direct & predictable but reversible
- Occurs due to mammalian mitochondrial synthesis inhibition I RBCs
- Prone in Liver & kidney disease pts

CHLORAMPHENICOL- ADVERSE EFFECTS

- *II) Gray Baby Syndrome* in premature new born baby
- *III) Superinfection*
- *IV) Hypersensitivity reactions à Fever, rashes, angioedema and glossitis*

CHLORAMPHENICOL – DRUG INTERACTIONS

- **I) It irreversibly inhibit microsomal enzyme P450, thus increases blood levels of :-**
 - * Tolbutamide, chlorpropamide– causing Hypoglycaemia
 - * Phenytoin – causing phenytoin toxicity
 - * Warfarin – causing Bleeding
- **II) Drugs like Phenobarbitone, Rifampicin induces microsomal enzyme metabolism of Chloramphenicol resulting into treatment failure**

What is Gray – Baby Syndrome? Which drug produces it?

- It is a **fatal chloramphenicol toxicity** in premature neonates / babies who are exposed to high doses (> 100 mg / kg /day) of chloramphenicol. **It occurs due to :-**
- *i) Failure of the drug to undergo glucoronide conjugation* due to **inadequate activity of glucuronyl transferase** in the liver of the new born babies.
- *ii) **Inadequate renal excretion of the unconjugated drug*** in the newborn
- *iii) **Blocking of electron transport*** in the liver, myocardium **and** skeletal muscle **by** chloramphenicol

CHLORAMPHENICOL- GRAY BABY SYNDROME

- **Clinical Manifestations** :-*Vomiting, refusal to suck & feed*, irregular & rapid respiration, abdominal distension, cyanosis and **passage of loose green stools**. **Later**, there is **flaccidity**, ashen grey colour, **lactic acidosis**. **Death** occur on 5th day.
- Those who recover exhibit no sequelae.

CHLORAMPHENICOL

- **Clinical Points :-**

- 1) *Is not a DOC for all systemic infections*
- 2) *Never use for minor infections or those treated by other safer drugs*
- 3) *Avoid repeated administration*
- 4) *Do not exceed daily dose > 2-3Gm & duration >2 weeks*
- 5) *Routine blood check to rule out bone marrow toxicity*
- 6) *Combination with bacteriocidal drug not permitted*
- 7) *Do not give high doses in premature neonates or pregnant women, in pts with liver and kidney diseases*
- 8) *Resistance has developed to S. typhii and others microbes*
- 9) *Can be used if blood culture and drug sensitivity tests are favourable*