

Introduction

- ▶ Chloramphenicol and Tetracyclines are **bacteriostatic** antimicrobials.
- ▶ Their widespread use (or misuse) → many resistant strains of bacteria → minimized clinical usefulness.
- ▶ Paradoxically, recent surge in interest in clinical use (due to almost complete lack of use → loss of resistant bacteria from env.)

CHLORAMPHENICOL (CHLOROMYCETIN)

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- ▶ Isolated 1947; *streptomyces venezuelae*
- ▶ Synthesized 1949 ; 1st completely synthetic a/m.
- ▶ Bacterio**static**, broad spectrum aerobic and anerobic gram (+)ve and gram(-)ve .
- ▶ Rickettsiae ; not against chlamydiae
- ▶ May be **cidal** for *H. influenzae*, *N. meningitides* & bacteroides.

Mechanism of Action

Reversible binding to **50s**
inhibits peptidyl transferase

(This MOA is similar to **macrolides**.)

Resistance Mechanisms

- ▶ Ribosomal protection - decreased affinity to ribosomal binding site.
- ▶ Drug less permeable to mutants.
- ▶ Plasmid encoded enzyme acetyltransferase -inactivates the drug

Pharmacokinetics

- ▶ Rapid and complete oral absorption.
- ▶ Can be given **orally/ i.v.**
- ▶ Widely distributed in body compartments including CSF.
- ▶ **Glucuronyl conjugation** in liver → inactivation.

Pharmacokinetics

- ▶ Major excretion by urine (bile and feces also)
- ▶ Dose decreased in new born ; premature infants.

Therapeutic uses

- ▶ ***Bacterial meningitis***: alternate to beta lactams , Penicillin resistant pneumococci or meningococci
- ▶ ***Topical ear/ eye preps***: conjunctivitis, otitis externa, endophthalmitis.
- ▶ ***Serious rickettsial infs*** :Typhus, Rocky mountain spotted fever.
- ▶ ***Children <8yrs*** where Tetracyclines are contraindicated.
- ▶ Earlier used to treat typhoid fever.

Adverse reactions

- ▶ **Gastrointestinal disturbances:** Nausea, Vomiting, Diarrhoea, Oral/Vaginal candidiasis
- ▶ **Bone marrow disturbances:** idiosyncratic, dose related and reversible .Decrease in RBC production ,aplastic anemia.
- ▶ **New born infants Toxicity:** Def glucuronide conjugation dose $>50\text{mg/kg/d}$ ***gray baby syndrome*** - vomiting ,hypothermia ,gray colour,collapse.
- ▶ **Superinfection**

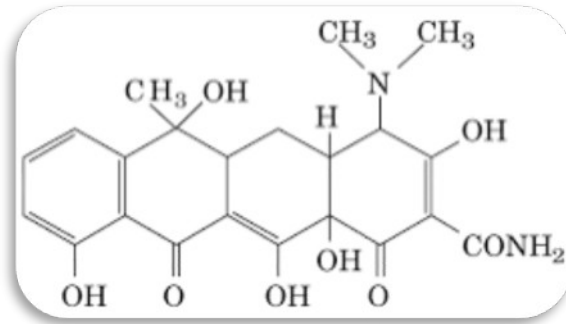
Drug Interactions

- ▶ Chloramphenicol inhibits microsomal enzymes that metabolize drugs.
- ▶ Chloramphenicol (static) antagonizes bactericidal drugs: Penicillins, Aminoglycosides.

TETRACYCLINES

TETRACYCLINES

- ▶ Have a nucleus of four (tetra) cyclic rings.



- ▶ Obtained from soil *actinomycetes*.
- ▶ Spectrum : aerobes, anaerobes, gram +ve, gram -ve, Chlamydia, Rickettsiae, Mycoplasma, Protozoa (*plasmodium*).
- ▶ Permeation into gram -ve cells : less understood, energy requiring.

Mechanism of action

- ▶ Inhibits bacterial protein synthesis.
- ▶ Binds to **30s** bacterial ribosome, prevents access of amino acyl t RNA to acceptor site on mRNA -ribosome complex.
- ▶ Prevents addition of amino-acids to growing peptide.
- ▶ High conc impairs protein synthesis in mammalian cells.

Resistance Mechanisms

1. Decrease in intracellular concentration
2. Development of ribosomal protection proteins
3. Enzymatic inactivation

Efflux pump encoded on plasmid

Transmitted by transduction / conjugation

Plasmids also encode resistance for -

Aminoglycosides, sulfonamides, chloramphenicol

Cross resistance with other tetracyclines ++

Classification

- ▶ Short acting: (6-8hrs)

Tetracycline, Chlortetracycline, Oxytetracycline

- ▶ Intermediate acting:(12 hrs)

Demeclocycline, Methacycline

- ▶ Long acting (16-18 hrs)

Minocycline, Doxycycline

- ▶ Glycylcycline: Tigecycline

Pharmacokinetics

- ▶ Orally remains in gut lumen, modifies flora
- ▶ Absorbed in upper small intestine

Impaired by food (except doxy and mino) Ca, Fe, Mg, Al in dairy products and antacids.

- ▶ Distributed in body tissues and fluids, except CSF

Pharmacokinetics

- ▶ Cross placenta, **excreted in milk**, chelate with Ca and affect bone and teeth
- ▶ Carbamazepine, phenytoin, barbiturates are enzyme inducers → hepatic enzymes are induced, half life reduced.
- ▶ Enterohepatic circulation
- ▶ 10-50% ✓ excreted in urine
- ▶ 10-40% excreted in feaces
- ▶ Doxycycline - **non renal excretion**

| | <i>Tetracycline (T)</i> <i>Oxytetracycline (OxyT)</i> | <i>Demeclocycline</i> | <i>Doxycycline (Doxy)</i> <i>Minocycline (Mino)</i> |
|-----------------------------------|--|--|--|
| 1. Source | Oxy T: <i>S. rimosus</i> T: semisynthetic | <i>S. aureofaciens</i> (mutant) | Doxy: semisynthetic Mino: semisynthetic |
| 2. Potency | Low | Intermediate | High (Doxy < Mino) |
| 3. Intestinal absorption | T: Moderate Oxy T: Moderate | Moderate | Complete, no interference by food |
| 4. Plasma protein binding | Oxy T: Low T: Moderate | High | High |
| 5. Elimination | T: Rapid renal excretion Oxy T: Rapid renal excretion | Partial metabolism, slower renal excretion | Doxy: Primarily excreted in faeces as conjugate Mino: Primarily metabolized, excreted in urine and bile |
| 6. Plasma t _{1/2} | 6-10 hr. | 16-18 hr. | 18-24 hr. |
| 7. Dosage | 250-500 mg QID or TDS | 300 mg BD | 200 mg initially, then 100-200 mg OD |
| 8. Alteration of intestinal flora | Marked | Moderate | Least |
| 9. Incidence of diarrhoea | High | Intermediate | Low |
| 10. Phototoxicity | Low | Highest | Doxy: High |
| 11. Specific toxicity | Oxy T: less tooth discolouration | More phototoxic, diabetes insipidus | Doxy: Low renal toxicity. Mino: Vestibular toxicity, less superinfections |

Therapeutic uses

▶ **Rickettsial infections**

▶ **Mycoplasma** infections - pneumonia

▶ **Chlamydial** infections -

Lymphogranuloma Venereum - Doxy 100mg bd × 21 d

Atypical Pneumonia, bronchitis 10-14 d

Trachoma - Doxy 100mg bd × 14 d or

Tetra 250mg qid × 14 d

(Azithromycin single dose preferred)

Non specific urethritis - Doxy 100 mg BD x 7d

(Azithromycin single dose preferred)

► ***Sexually transmitted diseases***

Uncomplicated gonococcal infections

C. trachomatis - Doxy 100mg bd ×7 d .

Pelvic inflamm diseases : C trachomatis

Doxy 100 mg iv 12hrly × 48 hrs Followed by oral therapy -14d

Non pregnant ; penicillin allergic patients

Prim /sec/ latent syphilis (2nd line agents)

Doxycycline 100mg bd ×2 wks ,not to be used in neurosyphilis.

- ▶ **Brucellosis**
- ▶ **Tularemia**
- ▶ **Plague**
- ▶ **Cholera** - Doxy 300mg single dose
- ▶ **Acne** (*propionibacteria*) -Tetra : 250 mg bd
doxycycline 100mg od

Minocycline last resort (fears of hepatitis /
pneumonitis/ pigmentation) +cost factor

Adverse effects

- **Gastrointestinal** : epigastric burning, distress, nausea, vomiting, abd discomfort (with meals)
avoid with dairy products, diarrhoea
Pseudomemb. enterocolitis : Cl difficile : life threatening
- **Photo toxicity** : Demeclo, Doxy : lesser extent, severe with others, nail pigmentation

- **Hepatotoxicity** : jaundice, more in pregnancy, oxytetra and tetra - least among group
- **Renal toxicity** : aggravate uremia in pts with renal disease.
- **Fanconi syndrome** - nausea, vomiting, proteinuria, polydipsia, acidosis, glycosuria, gross aminoaciduria **due to outdated preps**

- **Teeth** : brown discoloration - permanent



- **Diabetes Insipidus** - by antagonism of ADH action.
- Increased Intracranial pressure
- Vestibular Toxicity
- Hypersensitivity Reactions

Contraindications

- ▶ Pregnancy
- ▶ Children before attainment of puberty

Glycylcycline: Tigecycline

- ▶ First member of new class of synthetic tetracycline analogues. Introduced in 2005.
- ▶ Derivative of Minocycline.
- ▶ Active against bacteria resistant to classical tetracyclines.
- ▶ Apart from usual tetracycline spectrum, also active against MRSA, VRSA, VRE.

Lack of cross resistance b/w Tetracyclines and Tigecycline because **efflux pumps are unable to pump it out.**

Ribosomal protection is also less effective against Tigecycline.

- ▶ Only given by slow **i.v.** infusion.
- ▶ Approved only for **serious pneumonia, complicated skin infections, complicated intra-abdominal infections.**
- ▶ **A/E** - Nausea, vomiting, epigastric distress, diarrhea, skin reactions, photosensitivity, superinfections, pancreatitis.
- ▶ Contraindicated in children, pregnancy.