Medicinal Chemistry II

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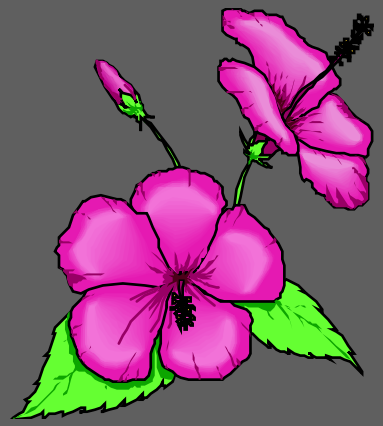
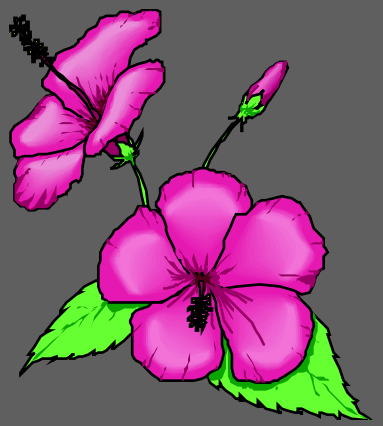




Antibiotics

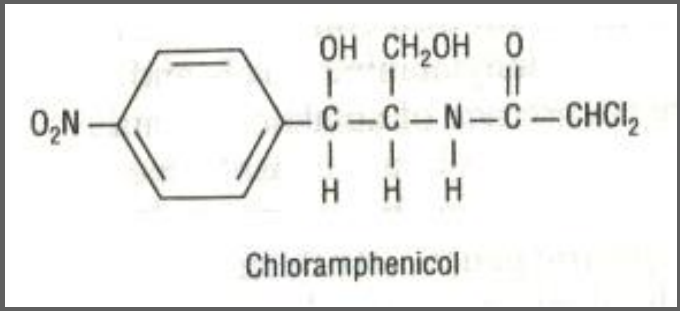
Chloramphenicol & Tetracyclines

I- Chloramphenicol:

- **Chloramphenicol was first isolated from cultures of *Streptomyces Venezuelae* in 1946 and was synthesized in 1949, the first completely synthetic antibiotic of importance to be produced commercially. It is the only available representative of its chemical type.**

Chloramphenicol:

- **Chemistry:** **Crystalline chloramphenicol is a neutral, stable compound with the following structure:**



Chloramphenicol

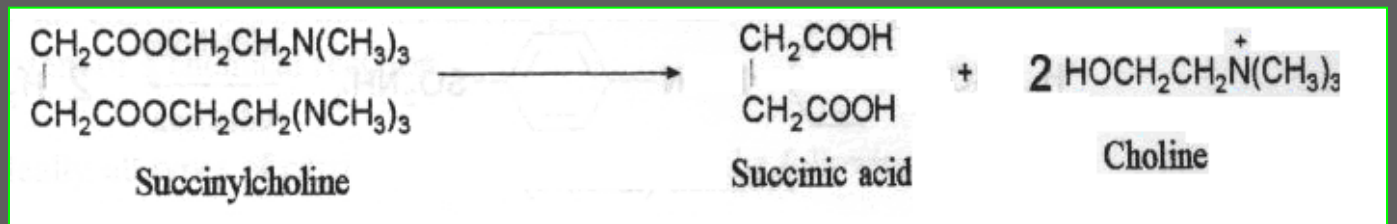
- **chloramphenicol consists of colorless crystals with an intensely bitter taste. It is highly soluble in alcohol and poorly soluble in water. Saturated aqueous solutions (0.25%) keep their activity for many months at refrigerator or room temperature if protected from light.**

Chloramphenicol:

- Chloramphenicol succinate is highly soluble in water and is hydrolyzed in tissues, with liberation of free chloramphenicol; It is used for parenteral administration.

Antimicrobial Activity:

- Chloramphenicol is a potent inhibitor of microbial protein synthesis and has little effect on other microbial metabolic functions.
- Chloramphenicol binds reversibly to a receptor site on the 50S subunit of the bacterial ribosome. There it interferes markedly with the incorporation of amino acids into newly formed peptides by blocking the action of peptidyl transferase.
- Chloramphenicol also inhibits mitochondrial protein synthesis in mammalian bone marrow cells but does not greatly affect other intact cells.



Antimicrobial Activity:

- Chloramphenicol is bacteriostatic for many bacteria and for Rickettsia, but is clinically ineffective against Chlamydia. Its action is reversible upon removal of the drug.
- Most gram-positive bacteria are inhibited by chloramphenicol in concentrations of 1-10 mcg/ml, and many gram-negative bacteria are inhibited by concentrations of 0.2-5 mcg/ml.
- Haemophilus influenzae, Neisseriae meningitidis, and some strains of Bacteroides are highly susceptible, and for them chloramphenicol may be bactericidal.
- Some Salmonellae are susceptible, but plasmid-mediated resistance to chloramphenicol has appeared with increasing frequency.

Chloramphenicol:

Resistance:

- In most bacteria species, large populations of chloramphenicol-susceptible cells contain occasional resistant mutants that are less permeable to the drug.
- These mutants are usually only two to four times more resistant than the parent populations; consequently, they emerge slowly in treated individuals.
- There is no cross-resistance between chloramphenicol and other drugs, but plasmids may transmit multiple drug resistance (chloramphenicol, tetracycline, streptomycin, etc.) from one bacterium to another by conjugation.

Resistance:

- Such plasmid-mediated resistance to chloramphenicol results from the production of chloramphenicol acetyltransferase, a bacterial enzyme that inactivates the drug.
- Consequently, the resistance of such plasmid-containing microorganisms is of high order.

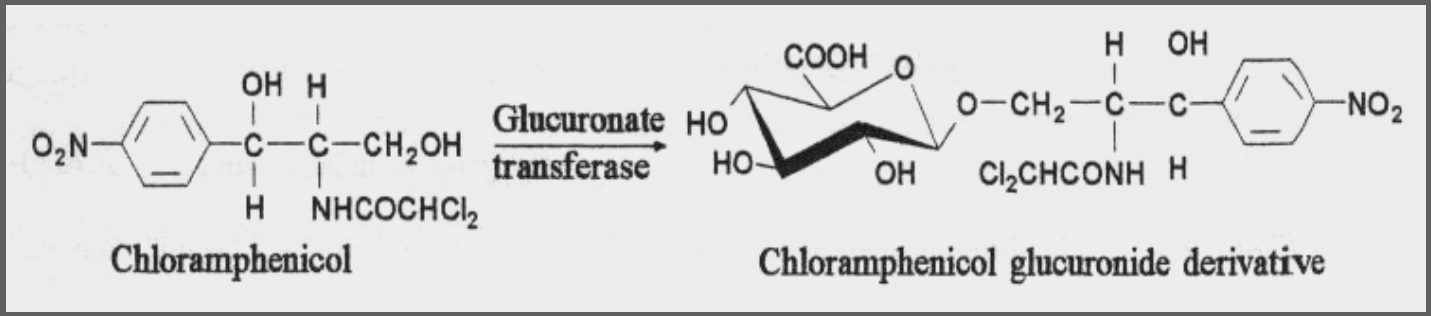
Chloramphenicol:

Pharmacokinetics:

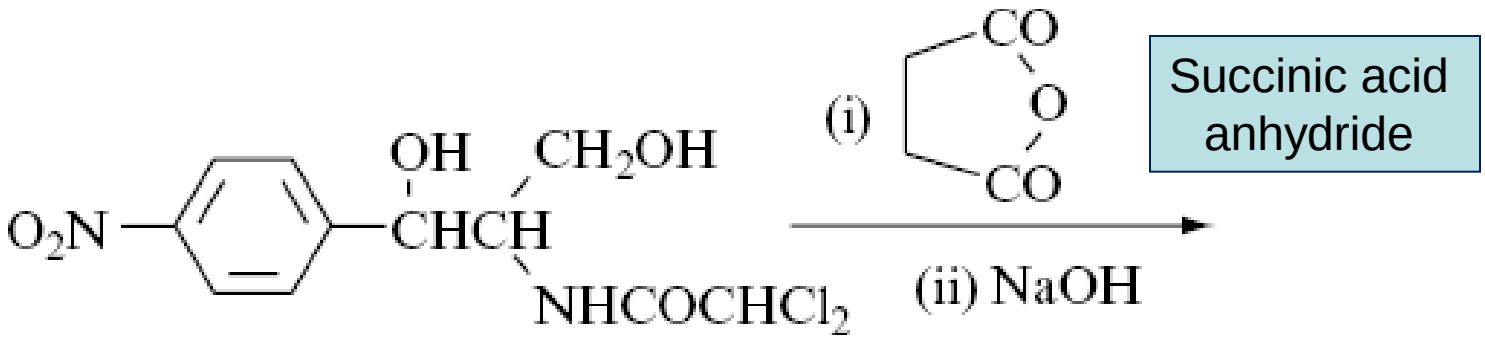
- After oral administration, crystalline chloramphenicol is rapidly and completely absorbed. With daily doses of 2 g orally, blood levels usually reach 8 mcg/ml.
- Chloramphenicol palmitate, administered to children in doses up to 50 mg/kg/day orally, is hydrolyzed in the intestine to yield free chloramphenicol, but the usual blood levels rarely exceed 10 mcg/ml.
- For parenteral injection, chloramphenicol succinate, 25-50 mg/kg/day intravenously or intramuscularly, yields free chloramphenicol by hydrolysis, giving blood levels somewhat lower than those achieved with the orally administered drug.

Pharmacokinetics:

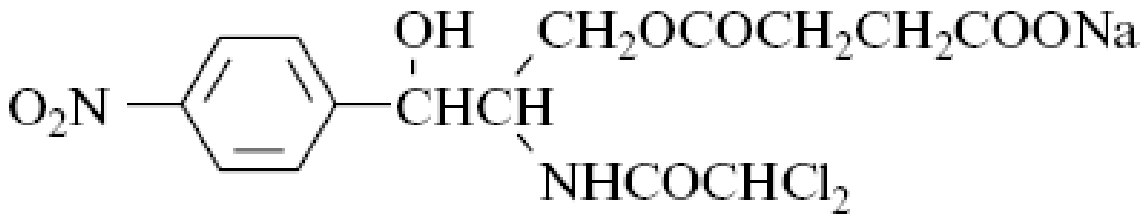
- After absorption, chloramphenicol is widely distributed to virtually all tissues and body fluids, including the central nervous system and cerebrospinal fluid.
- In fact, the concentration of chloramphenicol in brain tissue may be equal to that in serum- a unique property for the treatment of central nervous system infections.
- Circulating chloramphenicol is about 30% protein-bound. The drug penetrates cell membrane readily. Most of the drug is inactivated in the body either by conjugation with glucuronic acid (principally in the liver) or by reduction to inactive aryl amines.



The Formation of Chloramphenicol Succinate



Chloramphenicol (antibacterial)



Chloramphenicol sodium succinate (antibacterial)

Pharmacokinetics:

- Excretion of active chloramphenicol (about 10% of the total dose administered) and of inactive degradation products (about 90% of the total dose) occurs by way of the urine.
- Only small amounts of active drug are excreted into bile or feces.
- The systemic dosage of chloramphenicol need not be altered in renal insufficiency, but it must be reduced markedly in hepatic failure.

Chloramphenicol:

Clinical uses:

- **Because of potential toxicity and the availability of other effective drugs (e.g.. Cephalosporins), chloramphenicol is a possible choice only in the following infections:**

1) **Symptomatic Salmonella infection, e.g. typhoid fever. Many strains of Salmonella are now resistant, and trimethoprim-sulfamethoxazole is used often.**
2) **Serious infections with Haemophilus influenzae, e.g. meningitis, epiglottitis, or pneumonia.**
3) **Meningococcal or pneumococcal infections of the CNS in patients hypersensitive to beta-lactam drugs.**
4) **Anaerobic or mixed infections in the CNS, e.g. brain abscess.**
5) **Rarely as an alternative to tetracycline in severe rickettsial infections.**

Clinical uses:

- Chloramphenicol is occasionally used topically in the treatment of eye infections because of its wide antibacterial spectrum and its penetration of ocular tissues and the aqueous humor. However, it is not effective in Chlamydial infections.

A. Salmonellosis:

- For Salmonella infections (e.g. typhoid or paratyphoid fever), adults should receive chloramphenicol, 2-3 g/daily orally for 14-21 days, and children 30-50 mg/kg/day orally for 14-21 days.
- Prolonged treatment tends to reduce the frequency of relapses. A similar program may be followed in severe rickettsial infections (e.g. scrub typhus or Rocky Mountain spotted fever).

Rocky Mountain spotted fever : An infectious disease that is caused by a microorganism and spread by ticks. High fever, muscle pain, and spots on the skin are among the symptoms .

Clinical uses:

B. Haemophilus:

- For *Haemophilus influenzae meningitis* or *laryngotracheitis* (in small children) or *pneumonia* (in the elderly), chloramphenicol, 50-100 mg/kg/day orally or intravenously, has been given for 8-14 days, depending upon clinical response and cerebrospinal fluid changes.
- Since chloramphenicol-resistant *Haemophilus* strains have appeared, Ceftriaxone or Cefotaxime may now be the drugs of choice.

Clinical uses:

C. Other Uses:

- In the life-threatening sepsis probably originating in the lower bowel, chloramphenicol, 2 g/day, is sometimes combined with an aminoglycoside (e.g. Amikacin, 15 mg/kg/day).
- Because of the excellent penetration by chloramphenicol of all parts of the central nervous system, it is sometimes used in cerebritis, brain abscess, or meningitis of ill-defined origin.
- In adult meningitis, the dose of chloramphenicol is 50 mg/kg/day in four divided doses. Sepsis caused by some species of Bacteroides and severe melioidosis may respond to chloramphenicol.

Chloramphenicol:

Adverse Reactions:

A. Gastrointestinal Disturbances:

- Adults taking chloramphenicol, 1.5-2.5 g/day, occasionally develop nausea, vomiting, and diarrhea in 2-5 days.
- This is rare in children. After 5-10 days, the results of microbial flora alteration may become apparent, with prominent candidiasis of mucous membranes (especially of the mouth and vagina).

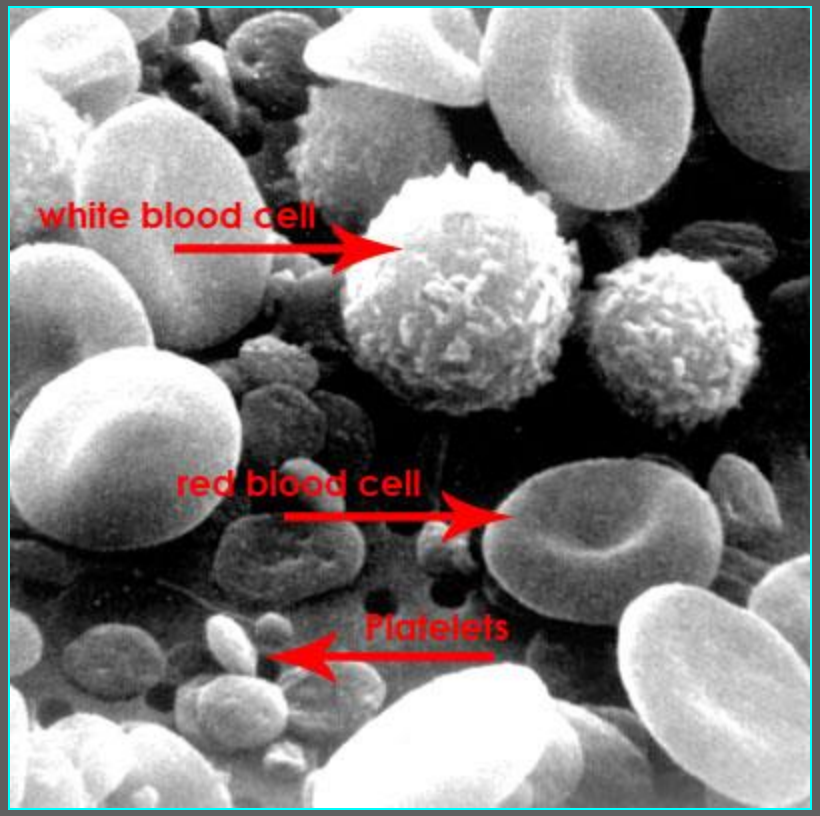
Chloramphenicol:

Adverse Reactions:

B. Bone Marrow Disturbances:

- Adults taking chloramphenicol in excess of 50 mg/kg/day regularly, exhibit disturbances in red cell maturation after 1-2 weeks of blood levels above 25-30 mcg/ml.
- These are characterized by the appearance of markedly vacuolated nucleated red cells in the marrow, anemia, and reticulocytopenia. These anomalies usually disappear when chloramphenicol is discontinued.
- The disturbance appears to be a maturation arrest associated with a rise in serum iron concentration and a depression of serum phenylalanine levels and is not related to the rare occurrence of aplastic anemia.

Blood contents



Chloramphenicol: Adverse Reactions:

B. Bone Marrow Disturbances:

- Aplastic anemia is a rare consequence of chloramphenicol administration by any route.
- Aplastic anemia probably develops in one of every 24.000-40.000 patients who have taken chloramphenicol. Leukemia may follow the development of hypoplastic anemia.
- The disturbance appears to be a maturation arrest associated with a rise in serum iron concentration and a depression of serum phenylalanine levels and is not related to the rare occurrence of aplastic anemia.

Chloramphenicol: Adverse Reactions:

C. Toxicity for newborn infants:

- Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol.
- Consequently, when infants are given doses of 75 mg/kg/day or more, the drug may accumulate, resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse.
- To avoid this toxic effect, chloramphenicol should be used with caution in infants and the dosage limited to 50 mg/kg/day or less in full-term infants and 30 mg/kg/day or less in prematures.

Chloramphenicol: Adverse Reactions:

D. Interaction With Other Drugs:

- chloramphenicol may prolong the half-life and raise the blood concentration of phenytoin, tolbutamide, chlorpropamide, and warfarin.
- This is attributable to inhibition of liver microsomal enzymes by chloramphenicol. It may precipitate a variety of other drugs from solutions.
- Like other bacteriostatic inhibitors of microbial protein synthesis, chloramphenicol can antagonize the bactericidal action of penicillins or aminoglycosides.

Chloramphenicol: Adverse Reactions:

E. Medical & Social Implications of Overuse:

- Because of its “broad spectrum” and its apparent lack of toxicity, chloramphenicol was used indiscriminately between 1948 and 1951 without specific indications.
- It has been estimated that more than 8 million people received the drug for minor complaints, respiratory (usually viral) illnesses, etc.
- This inappropriate use was followed by a wave of cases of aplastic anemia, which, in turn, almost resulted in the complete abandonment of an effective drug.

Chloramphenicol & Tetracyclines

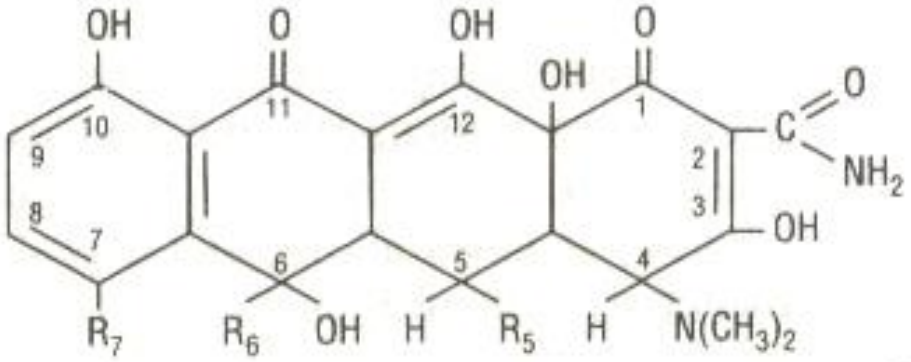
II- Tetracyclines:

- The tetracyclines are a large group of drugs with a common basic structure and activity.
- Chlortetracycline, isolated from *Streptomyces Aureofaciens*, was introduced in 1948. Oxytetracycline, derived from *Streptomyces Rimosus, was introduced in 1950*. Tetracycline, obtained by catalytic dehalogenation of chlortetracycline, has been available since 1953.
- Demeclocycline was obtained by demethylation of chlortetracycline. More recently developed tetracyclines have emphasized good absorption combined with prolonged blood levels.

Tetracyclines:

Chemistry:

- All of the tetracyclines have the basic structure shown below:



	R_7	R_6	R_5	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH_3	—H	35
Oxytetracycline	—H	—CH_3	—OH	90
Tetracycline	—H	—CH_3	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH_2*	—OH	31
Doxycycline	—H	—CH_3*	—OH	16
Minocycline	—$N(CH_3)_2$	—H	—H	10

*There is no —OH at position 6 on methacycline and doxycycline.

Tetracyclines:

Chemistry:

- Free tetracyclines are crystalline amphoteric substances of low solubility.
- They are available as hydrochlorides, which are more soluble.
- Such solutions are acid and, with the exception of chlortetracycline, fairly stable.

Tetracyclines- chemistry:

- Tetracyclines combine firmly with divalent metal ions, and this chelation can interfere with absorption and activity of the molecule.

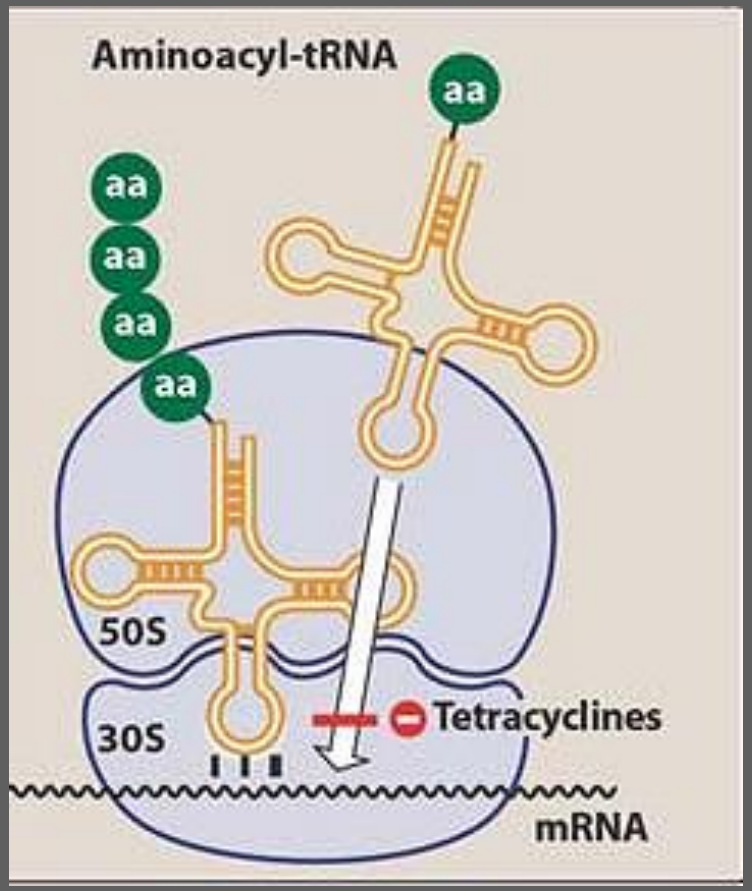
- Tetracyclines fluoresce bright yellow in ultraviolet light of 360 nm wavelength.

1- Antimicrobial Activity: tetracyclines are the prototype broad-spectrum antimicrobial drugs. They are bacteriostatic for many gram-positive and gram-negative bacteria, including some anaerobes; for Rickettsiae, Chlamydiae, Mycoplasmas, and for some protozoa, e.g. Amebas.

Tetracyclines- Antimicrobial Activity:

- Minocycline may have greater lipophilic properties than other congeners. Differences in clinical efficacy are attributable largely to features of absorption, distribution, and excretion of individual drugs.
- However, great differences exist in the susceptibility of different strains of a given species of microorganism.
- Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport.
- As a result, susceptible cells concentrate the drug so that the intracellular drug concentration is much higher than the extracellular one.

Mechanism of action



- **Tetracyclines binds to the 30S ribosomal subunit, thus preventing the binding of aminoacyl- tRNA to the ribosome. aa = amino acid.**

Tetracyclines- Antimicrobial Activity:

- Once inside the cell, tetracyclines bind reversibly to receptors on the 30S subunit of the bacterial ribosome in a position that blocks the binding of the aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex.
- This effectively prevents the addition of new amino acids to the growing peptide chain, inhibiting protein synthesis.

Tetracyclines:

Resistance:

- Microbial populations containing mostly susceptible organisms also contain small numbers of organisms resistant to tetracyclines.
- These lack an active transport mechanism across cell membranes and thus do not concentrate tetracycline in their cells. Alternatively, resistant bacteria may lack passive permeability to tetracyclines.
- The degree of resistance is variable. Among gram-negative bacteria species (especially *Pseudomonas*, *Proteus*, and *Coliforms*), the selection of highly resistant types has already occurred, and tetracyclines have therefore lost much of their usefulness.

Tetracyclines- Resistance:

- Tetracycline resistance is usually transmitted by plasmids. With widespread use, resistance is increasing even among what were at first highly susceptible bacterial species (e.g. *Pneumococci*, *Bacteroides*).

- Plasmids controlling resistance may be transmitted by transduction or by conjugation. The genes for tetracycline resistance are closely associated with those for other drugs, e.g. *aminoglycosides*, *sulfonamides*, and *chloramphenicol*.

- Plasmids therefore usually transmit resistance to multiple drugs rather than to tetracyclines alone.

Tetracyclines:

Pharmacokinetics:

- Tetracyclines are absorbed somewhat irregularly from the gastrointestinal tract. A portion of an orally administered dose of tetracycline remains in the gut lumen, modifies intestinal flora, and is excreted in the feces.
- While only 30% of chlortetracycline and 60-80% of tetracycline, oxytetracycline, and demeclocycline are absorbed in the gut, absorption is 90-100% for doxycycline and minocycline.
- Absorption occurs mainly in the upper small intestine and is best in the absence of food. It is impaired by chelation with divalent cations ($Ca^{2+,}$ $Mg^{2+,}$, Fe^{2+}, or with Al^{3+}) especially in milk and antacids, Laxatives and by alkaline PH.

Tetracyclines- Pharmacokinetics:

- Specially buffered tetracycline solutions are formulated for parenteral (usually intravenous) administration in persons unable to take oral medication. The parenteral dosage is generally similar to the oral dosage.
- In blood, 40-80% of various tetracyclines is protein-bound. With oral doses of 500 mg every 6 hours, tetracycline hydrochloride and oxytetracycline reach peak levels of 4- 6 mcg/ml.
- With doxycycline and minocycline, the peak levels are somewhat lower (2- 4 mcg/ml).

Tetracyclines- Pharmacokinetics:

- **Intravenously injected tetracyclines give somewhat higher levels only temporarily. The drugs are distributed widely to tissues and body fluids, except for the cerebrospinal fluid, where concentrations are low.**
- **Minocycline is unique in reaching very high concentrations in tears and saliva- a feature that permits it to eradicate the meningococcal carrier state.**
- **Tetracyclines cross the placenta top reach the fetus and are also excreted in milk. As a result of chelation with calcium, tetracyclines are bound to growing bones and teeth.**

Tetracyclines- Pharmacokinetics:

- Absorbed tetracyclines are excreted mainly in bile and urine. Concentrations in bile are ten times higher than in serum; some of the drug excreted in bile is reabsorbed from the intestine (enterohepatic circulation) and contributes to maintenance of serum levels.
- Ten to 50 percent of various tetracyclines is excreted into the urine, mainly by glomerular filtration. The renal clearance of tetracyclines ranges from 10 to 90 ml/min.
- Ten to 40 percent of the drug in the body is excreted in feces.

Tetracyclines- Pharmacokinetics:

- **Doxycycline and Minocycline are almost completely absorbed from the gut and are excreted more slowly, leading to persistent serum levels.**
- **Doxycycline does not require renal excretion and does not accumulate significantly in renal failure.**

Tetracyclines

Clinical uses:

- **Tetracyclines were the first broad-spectrum antibiotics. They are effective against a variety of microorganisms and are thus often used indiscriminately.**
- **Tetracyclines are the drugs of choice in infections with *Mycoplasma pneumoniae*. They are useful in mixed bacteria infections related to the respiratory tract, e.g. sinusitis and bronchitis.**
- **They may be employed in various gram-positive and gram-negative bacterial infections, including *vibrio* infections, provided the organism has not become resistant.**

Tetracyclines- Clinical uses:

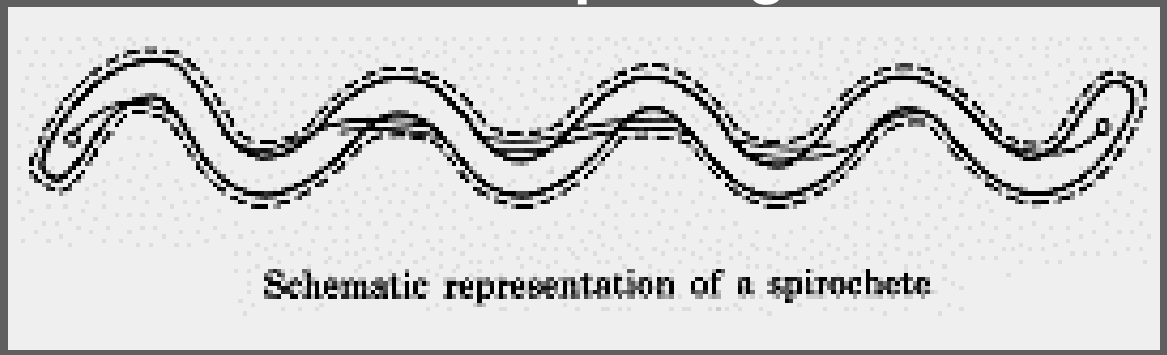
- **In cholera, tetracyclines rapidly stop the shedding of *vibrios*, but tetracycline resistance has appeared during epidermics.**
- **Tetracyclines are effective in most chlamydial infections, including sexually transmitted diseases in which chlamydiae participate.**
- **Other uses include treatment of acne, urinary tract infections, exacerbations of bronchitis, Lyme disease, relapsing fever, and leptospirosis.**
- **Doxycycline is effective for the prophylaxis of leptospirosis.**

- **Leptospirosis :** Spirochetes داء الليبتوسبيرا تسببه البيريميات

The order Spirochaetales has two families:

1-the Spirochaetaceae, which include two important genera of human pathogens (Treponema and Borrelia) .

2- the Leptospiraceae, whose single genus, Leptospira, also includes human pathogens.



Schematic representation of a spirochete

Tetracyclines- Clinical uses:

- In brucellosis, tularemia, and plague, tetracyclines may be given in combination with an aminoglycoside. Tetracyclines are sometimes employed in the treatment of protozoal infections, e.g. those due to *Entamoeba histolytica* or *Plasmodium falciparum*.
- While minocycline, 200 mg orally daily for 5 days, can eradicate the meningococcal carrier state, rifampin is generally preferred.
- Demeclocycline inhibits the action of ADH in the renal tubule and has been used in the treatment of inappropriate secretion of ADH or similar peptides by certain tumors.

- ADH: Anti- Diuretic Hormone الهرمون المضاد للإدرار

Tetracyclines- Clinical uses:

A. Oral Dosage:

- The minimal effective oral dose for rapidly excreted tetracyclines, equivalent to tetracycline hydrochloride, is 0.25 g 4 times daily for adults and 20 mg/kg/day for children.
- For severe systemic infections, a dose two to three times larger for at least 3-5 days is indicated.
- For chlamydial genital infections, treatment for 10-14 days is advisable.
- The minimal effective daily dose is 600 mg for Demeclocycline or Methacycline, 100 mg for Doxycycline, and 200 mg for Minocycline.

Tetracyclines- Clinical uses:

A. Oral Dosage:

- Tetracyclines chelate with metals, as noted above, and thus should not be administered with milk, antacids, or ferrous sulfate.
- To avoid deposition in growing bones or teeth, tetracyclines are not usually indicated for pregnant women or for children under 8 years of age.
- Tetracycline hydrochloride, 250-500 mg daily, is commonly taken for many months to suppress acne, especially in adolescents and young adults. This low dose presumably suppresses lipase activity of propionibacteria.

Tetracyclines- Clinical uses:

B. Parenteral Dosage:

- Several tetracyclines are available for intravenous injection in doses of 0.1-0.5 g every 6-12 hours (10-15 mg/kg/d in children).
- Intramuscular injection is usually unsatisfactory because of pain and inflammatory reactions.
- There are very few instances (e.g. an unconscious patient with rickettsial disease) that warrant parenteral tetracycline administration.

Tetracyclines:

Adverse Reactions:

- Hypersensitivity reactions (drug fever, skin rashes) to tetracyclines appear to be uncommon. Most adverse effects are due to direct toxicity of the drug or to alteration of microbial flora.

A- Gastrointestinal Adverse Effects:

- Nausea, vomiting, and diarrhea are the commonest reasons for discontinuing tetracycline medication. During the first few days of administration, they appear to be attributable to direct local irritation of the intestinal tract.
- After a few days of oral use, tetracyclines tend to modify the normal flora. Although some coliform organisms are suppressed, Pseudomonas, Proteus, Staphylococci, resistant coliform, clostridia, and Candida become prominent.

Tetracyclines- Adverse Reactions:

A- Gastrointestinal Adverse Effects:

- This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or even enterocolitis with shock and death.
- Nausea, anorexia, and diarrhea can usually be controlled by administering the drug with food or carboxymethylcellulose, reducing drug dosage, or discontinuing the drug.
- Pseudomembranous enterocolitis associated with Clostridium difficile or Staphylococci must be recognized promptly and treated with oral vancomycin.

Tetracyclines- Adverse Reactions:

B- Bony Structure and Teeth:

- Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. When the drug is given during pregnancy, it can be deposited in fetal teeth, leading to fluorescence, discoloration, and enamel dysplasia;
- It can also be deposited in bone, where it may cause deformity or growth inhibition. If the drug is given to children under 8 years of age for long periods, similar changes can result.

C- Liver Toxicity:

- Tetracyclines can probably impair hepatic function, especially during pregnancy, in patients with preexisting hepatic insufficiency, and when high doses are given intravenously. Hepatic necrosis has been reported with daily doses of 4 g intravenously or more.
-
- Enamel Dysplasia: النمو الشاذ لطبقة المينا في الأسنان

Tetracycline Staining

- Use of tetracycline during the period of tooth formation - including the last half of in utero development - leads to its incorporation into the tooth structure. The resulting appearance depends both on intensity of use and the type of tetracycline employed.
- Often, however, the outcome is a bluish-gray stain affecting only the part of the tooth that was being formed during the period of use.

Tetracyclines- Adverse Reactions:

D- Kidney Toxicity:

- Renal tubular acidosis and other renal injury resulting in nitrogen retention have been attributed to the administration of outdated tetracycline preparations.
- Tetracyclines given along with diuretics may produce nitrogen retention. Tetracyclines, except doxycycline, may accumulate to toxic levels in patients with impaired kidney function and may aggravate the condition.

E- Local Tissue Toxicity:

- Intravenous injection can lead to venous thrombosis. Intramuscular injection produces painful local irritation and should be avoided.

Tetracyclines- Adverse Reactions:

F- Photosensitization:

- Systemic tetracycline administration, especially of demeclocycline, can induce sensitivity to sunlight or ultraviolet light, particularly in fair-skinned persons.

G- Vascular Reactions:

- Dizziness, vertigo, nausea, and vomiting have been particularly noted with minocycline. After doses of 200-400 mg/d of minocycline, 35-70% of patients exhibited such reactions.

- Fair-Skinned: أبيض البشرة
- Dizziness : دوخة

Tetracyclines

Medical & Social Implications of Overuse:

- **The widespread use of tetracyclines for minor illnesses has led to the emergence of resistance even among highly susceptible species, e.g. *Pneumococci* and group A *Streptococci*.**
- **The large-scale use of these drugs in hospitals has resulted in the emergence of tetracycline-resistant organisms as superinfecting agents.**
- **In some measure, the misuse of tetracyclines (among other antibiotics) must be blamed for the rising incidence of mycotic infection in hospitalized severely ill patients.**

Medical & Social Implications of Overuse:

- Tetracyclines have been extensively used in animal feeds to increase the rate of growth. This practice has been widely blamed for the steadily increasing spread of tetracycline resistance among bacteria and plasmids that promote it.
- Such use has resulted in tetracycline-resistant infections among farmers, animal handlers, slaughterhouse workers, and perhaps the general public.
- For this reason, some countries forbid the use of tetracyclines in animal feeds. On the other hand, tetracyclines have been of great benefit not only for the control of existing infection but also for the early treatment of acute exacerbations in chronic bronchitis and bronchiectasis, keeping many persons well and at work.

Slaughterhouse: المسلخ

Bronchiectasis : توسع القصبات

The End