CHAPTER 29

Tetracyclines and Chloramphenicol

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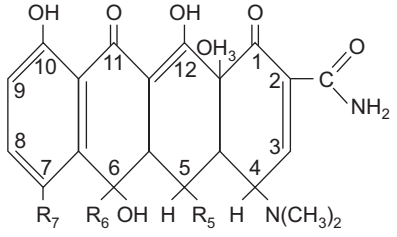
The antimicrobial agents that act by inhibiting bacterial protein synthesis are bacteriostatic in their action and include agents such as tetracyclines, chloramphenicol, macrolides, ketolides, clindamycin, quinupristin/dalfopristine, linezolid and spectinomycin. Though they can be broadly referred to as protein synthesis inhibitors, they have different target sites to elicit their action. Thus, they can act on 30S or 50S ribosomal subunits to inhibit bacterial protein synthesis and act as bacteriostatic agents.

TETRACYCLINES

Tetracyclines are a class of broad-spectrum antibiotics that are used in a wide variety of microbial diseases. In **1947**, in his study of thousands of microscopic fungi amongst the *Actinomycetes*, **Duggar** in collaboration with **Yellapragada Subba Rao** discovered a soil organism for which the name *Streptomyces aureofaciens* was proposed. When grown in culture broth, a golden yellow antibiotic was elaborated that was named *Aureomycin (chlortetracycline)*. In **1950**, **Finlay** and his associates isolated a new actinomycete, *Streptomyces rimosus* from which **tetracycline** was isolated. In **1952,** the unique chemical structure of these two antibiotics was determined and **oxytetracycline** was developed from tetracycline. Later, a few other tetracylines were developed and named such as **demethylchlortetracycline, demeclocycline, methacycline, doxycycline, minocycline and** tigecycline based on the structures of the originally discovered tetracyclines (Fig. 29.1).



	R_7	R_6	R_5
Chlortetracyline	— Cl	— CH_3	— H
Oxytetracycline	— H	— CH_3	— OH
Tetracycline	—H	— CH_3	— H
Demethylchlortetracycline (Demeclocycline)	— Cl	— H	— H
Methacycline	— H	— CH_2	— OH
Doxycycline	— H	— CH_3	— OH
Minocycline	— $N(CH_3)_2$	— H	— H

Fig. 29.1 Structural formulae of tetracyclines

Antimicrobial Spectrum

Tetracyclines are broad-spectrum antibiotics and are effective against Gram-positive, Gram-negative bacteria, protozoa and many other organisms.

Examples of Gram-positive organisms are *Enterococcus faecalis*, *Enterococcus faecium, Streptococcus viridans* group, *Streptococcus pneumoniae, Streptococcus pyogenes* and staphylococci. **However, the susceptibility of these organisms is variable and many of them have shown resistance to tetracyclines**. Hence, tetracyclines are not commonly used to treat clinical conditions caused by these organisms. *Bacillus anthracis* and *Listeria*

monocytogenes are also susceptible to tetracyclines. **Atypical organisms like *Mycoplasma pneumoniae* are highly susceptible to tetracyclines**.

Examples of Gram-negative organisms that are susceptible to tetracyclines include *Brucella* species, *Campylobacter jejuni*, *Calymmatobacterium granulomatis*, *Francisella tularensis*, *Hemophilus ducreyi*, *Hemophilus influenzae, Neisseria gonorrhoeae*, *Vibrio cholerae*, *Yersinia pestis and Acinetobacter, Klebsiella*, *E. coli, Shigella*, *Enterobacter* and *Helicobacter pylori*.

Tetracyclines are also effective against other organisms such as *Chlamydia psittaci, C. trachomatis*, *Rickettsiae* (*Rocky mountain* spotted fever, Q fever, murine typhus, epidemic typhus, rickettsial pox), *Treponema pallidum, Borrelia recurrentis, Balantidium coli*; *anaerobes* such as *Bacteroides* species, *Propionibacterium* and *Peptococcus*; and protozoa such as *Entameba histolytica* and *Plasmodium falciparum*.

The antimicrobial activities of most tetracyclines are similar except that tetracycline resistant strains may be susceptible to doxycycline, minocycline and tigecycline all of which are resistant to efflux pump mechanisms responsible for bacterial resistance.

Mechanism of Action (Fig. 29.2)

Tetracyclines bind reversibly to the 16S rRNA (ribose RNA) of the 30S subunit and prevent binding of aminoacyl tRNA to the A site on the mRNA ribosome complex. This action prevents the addition of further amino acids to the nascent peptide thus causing inhibition of peptide chain growth and subsequent bacterial protein synthesis.

Tetracyclines enter the cytoplasm of the sensitive Gram-positive organisms by an energy-dependent process, but in Gram-negative organisms, they pass through the outer membrane by diffusion through pores. Because minocycline and doxycycline are more lipophilic they can enter Gram-negative cells through the outer lipid membrane and through the porins. Once in the periplasmic area, the tetracyclines are transported across the inner cytoplasmic membrane to the target site (30S ribosomal unit) by passive diffusion or through an active protein carrier system.

Bacterial Resistance

There are several mechanisms of developing resistance to tetracyclines; the important mechanisms are:

- **Plasmid-mediated decreased influx** and decreased accumulation of the antibiotic inside the cell,
- **Plasmid-encoded enhanced efflux of the drug** from inside the bacterial cell,
- **Plasmid-mediated production of protein** that protects the ribosomal binding site and prevents the binding of tetracyclines to the ribosome,
- **Enzymatic inactivation** of tetracyclines.

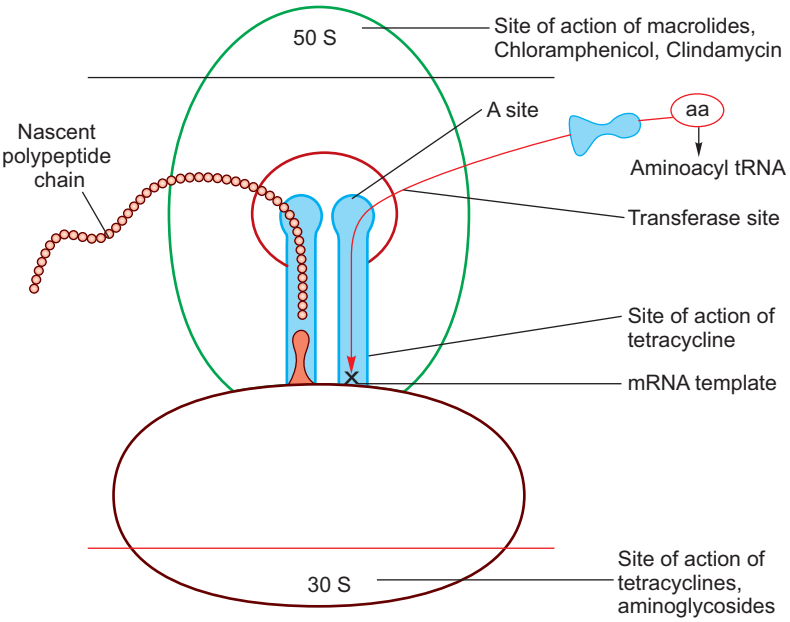


Fig. 29.2 Mechanism of action of tetracyclines

Pharmacokinetics

Tetracyclines are adequately but incompletely absorbed from the gastrointestinal (GI) tract and attain adequate plasma and tissue concentrations. **Minocycline and doxycycline are the most completely absorbed (95%–100%) and chlortetracycline the least (30%)**. Absorption of tetracyclines is fast on an empty stomach and they are likely to form complexes with divalent metals, including calcium, magnesium, aluminum and iron. Absorption of some tetracyclines is decreased when they are ingested with milk products, antacids or iron preparations. However, food does not interfere with absorption of minocycline or doxycycline which is rapidly absorbed and detectable in the blood 15–30 min after administration. Both doxycycline and minocycline have a half-life of 15–25 h. Tigecycline has a half-life of 36 h.

The plasma protein binding of tetracycline is 40%–80%. Peak plasma levels of 4–6 μg/ml are achieved with an oral dose of 500 mg of tetracycline or oxytetracycline given 6 hourly. A 200-mg dose of doxycycline or minocycline produces peak plasma levels of 2–4 μg/ml. Peak serum concentrations of tigecycline at steady state are 0.6 μg/ml at the usual dose.

The tetracyclines are widely distributed in the body compartments and higher concentrations are found in the liver, kidneys, bile, bronchial epithelium and breast milk. Tetracyclines do not enter the cerebrospinal fluid (CSF). **Minocycline reaches very high concentrations in tears and saliva which makes it useful for eradication of the meningococcal carrier state**. Tetracyclines do not bind to formed bone but are incorporated into calcifying tissue (forming bone) and into the dentin and enamel of unerupted teeth which explains their adverse effects if they are taken during childhood when formation of new bone and new dentition occurs.

The disposal of tetracyclines is by renal and biliary elimination and by metabolism. Excretion into the bile results in the enterohepatic circulation of tetracyclines which facilitates the maintenance of adequate serum levels. This occurs even for drugs administered parenterally. Renal elimination of tetracyclines is by glomerular filtration and the chelated portion of the drug is excreted through feces. **All tetracyclines, except doxycycline, accumulate in patients with decreased renal function. Thus, only doxycycline should be given to patients with renal impairment**. Some important pharmacokinetic parameters and doses are listed in Table 29.1

Classification of Tetracyclines

Tetracyclines are classified according to their duration of action. Thus they may be classified as follows:

1. **Short acting (6–8 h)** such as chlortetracycline, tetracycline and oxytetracycline
2. **Intermediate acting (12 h)** such as demeclocycline and methacycline
3. **Long acting (16–18 h)** such as doxycycline and minocycline.

Tigecycline has a half-life of 36 h.

Clinical Uses of Tetracyclines

Tetracyclines are useful in a variety of clinical conditions because of their broad spectrum of antimicrobial

Table 29.1 Pharmacokinetic parameters and usual therapeutic doses of tetracyclines

Drug	Absorption	Route of administration	Half-life (hours)	Plasma protein binding (%)	Dose
Chlortetracycline	30%	Oral	6	50	250–500 mg 6 hourly
Tetracycline	75%	Oral, IM, IV	8	55	250–500 mg (oral) 6 hourly 100 mg IM/IV 6 hourly
Oxytetracycline	30%–40%	Oral, IM, IV	9	85	250–500 mg (oral) 6 hourly 100 mg IM/IV 6 hourly
Demethyl chlortetracycline	80%	Oral	12	85	150–300 mg 8 hourly
Doxycycline	93%	Oral, IV	16	85	200 mg on the first day and 100 mg on subsequent days.
Minocycline	95%	Oral	16	75	200 mg on the first day and 100 mg on subsequent days
Tigecycline	-------	IV	36	71%–89%	100 mg infusion initially on day one followed by 50 mg infusion twice daily for 5–14 days

meningococci from the nasopharynx. It is given in doses of 100 mg every 12 h for 5 days to eradicate the carrier state. It is not useful in treating the acute meningitis. Because of the existence of resistant strains and adverse effects; **rifampicin** is advocated for such indication.

Acne

Tetracyclines along with topically applied antibiotics like clindamycin, erythromycin base and metronidazole and sodium sulfacetamide are found to be effective in the treatment of acne. All the antibiotics including tetracyclines are useful against the acne caused by propionibacteria (*Propianibacterium acnes*, *Acne rosacea*). Either minocycline or doxycycline 100 mg/day is highly effective in reducing the inflammatory lesions more rapidly than the other tetracyclines given for the condition.

Mycobacterium marinum infections

Minocycline has been successfully used in the treatment of infections caused by *Mycobacterium marinum*.

H. Pylori Infection

Tetracyclines are effective to treat *H. pylori* infection as a part of rescue therapy or **third-line therapy in combination with lansoprazole –30 mg BID (proton pump inhibitor), bismuth potassium citrate –220 mg BID and metronidazole –400 mg QID.**

Tigecycline

It is a glycylcycline compound and a derivative of minocycline and has wider antimicrobial effects and clinical uses in comparison to older tetracyclines. The organisms sensitive to it include coagulase-negative staphylococci, and *S. aureus* including methicillin resistant and vancomycin resistant strains; streptococci both penicillin sensitive and resistant strains; gram-positive rods; Enterobacteriaceae; multidrug resistant strains of *Acinetobacter* spp.; anaerobes; mycoplasma; rickettsiae; *Klebsiella pneumoniae*; *E. coli; Chlamydia; Legionella;* rapidly growing *Mycobacteria* and *Bacteroides* spp. **However it is not effective against *Pseudomonas, Proteus and Gonococci***.

Clinical uses

Tigecycline is used for the treatment of skin and skin structure infections and intra-abdominal infections (appendictis with perforation, diverticulitis and cholycystitis with perforation, empyema, gastric/duodenal perforation and purulent peritonitis). It is used in combination with colistin to treat serious infections wit multidrug resistant Gram-negative organisms. It is one of the most effective drug to treat **community-acquired pneumonia**. It is also found to be effective in Donovanosis though azithromycin is the first line drug to treat the condition.

Dose and route of administration Tigecycline is administered intravenously only. The usual dose is 100 mg as a loading dose followed by 50 mg over a period of 30–60 min every 12 h for a duration of 14 days.

Adverse Effects of Tetracyclines

Tetracyclines produce moderate to severe adverse effects which are reversible. Therefore, therapy need not be discontinued if the prescribed doses are used for appropriate duration.

Gastrointestinal

The common GI adverse effects of tetracyclines include GI irritation, abdominal discomfort, nausea, vomiting and diarrhea. Tetracyclines modify the normal intestinal flora and cause overgrowth of *Pseudomonas*, *Proteus*, staphylococci, resistant coliforms, *Candida* and *Clostridia*. Pseudomembranous colitis is the result of a toxin produced by *Clostridium difficile*. Because of overgrowth of Candida, there may be oral or vaginal candidiasis.

Effects on bones and teeth

The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood up to 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). The discoloration usually occurs on long-term use but has been observed following repeated short-term courses also and is often associated with use of higher doses than prescribed. Enamel hypoplasia has also been reported. **The deposition of the drug in the teeth and bones is due to its chelating property and formation of a tetracycline–calcium orthophosphate complex**. Hence, tetracyclines are contraindicated during this period.

Retardation of bone growth

As a stable tetracycline–calcium orthophosphate complex is formed in the developing bones, bone growth is retarded if tetracyclines are given in early childhood up to 8 years.

Photosensitivity

Demethylchlortetracycline (demeclocycline), doxycycline and minocycline may produce photosensitivity manifested

as an exaggerated sunburn reaction. Onycholysis and pigmentation of the nails may also appear with or without photosensitivity reaction.

Hepatotoxicity

It has been reported with the use of minocycline and therefore, tetracycline should be used with caution in patients with hepatic dysfunction. Hepatotoxicity is more likely to occur during pregnancy and when large doses of tetracyclines are administered.

Renal toxicity

Tetracyclines can cause renal tubular necrosis and interstitial nephritis resulting in nitrogen retention in patients with renal disease. Nephrogenic diabetes insipidus has been observed in some patients receiving demeclocycline. However, the renal changes do not necessarily occur with regular tetracycline use in other clinical conditions. **Fanconi syndrome, characterized by nausea, vomiting, polyuria, polydipsia, acidosis, glycosuria and aminoaciduria has been observed in patients ingesting outdated and degraded tetracycline preparations.**

Pseudotumur Cerebri

(Benign intracranial hypertension) has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanelles have been associated with the use of tetracyclines in infants.

Drug Interactions of Tetracyclines

Tetracyclines can produce the following drug interactions which are both pharmacokinetic and pharmacodynamic in nature.

Drug interactions	Pharmacokinetic or pharmacodynamic effect
Antacids and iron preparations	Tetracycylines chelate aluminum, calcium, magnesium and iron salts, produce insoluble salts and reduce their absorption
Anticonvulsants (carbamazepine, phenytoin) Barbiturates Alcohol	Reduced half-life of tetracyclines
Oral contraceptives	Reduced conjugate estrogen levels
Penicillins	Interference with bactericidal action of penicillin

CHLORAMPHENICOL

Chloramphenicol is a bacteriostatic antibiotic obtained from *Streptomyces venezuelae* and introduced into clinical practice in **1948**. It was the drug of first choice to treat typhoid fever for many years but has been replaced by cotrimoxazole, aminopenicillins and later cephalosporins because of the fatal blood dyscrasias produced by it. Now, the use of chloramphenicol is confined to life-threatening infections (such as meningitis and rickettsial infections) and for topical use in treating ocular and middle ear infections.

Antimicrobial Spectrum

The organisms sensitive to chloramphenicol are *H. influenzae, N. meningitidis*, *N. gonorrhoeae*, *Brucella* spp. and *Bordetella pertussis*. Similarly, most anaerobic bacteria, including Gram-negative cocci and *Clostridium* spp. and Gram-negative rods including *Bacteroides fragilis* are also sensitive. Chloramphenicol is also active against aerobic Gram-positive cocci such as *S. pyogenes*, *Streptococcus agalactiae* (Group B streptococci) and *S. pneumoniae*. Most strains of *E. coli*, *K. pneumoniae*, *Proteus mirabilis* and indole-positive *Proteus* spp. are also sensitive. The other organisms sensitive to chloramphenicol include *Salmonella*, *Shigella*, *V. cholerae* and *Rickettsia*. However, *P. aeruginosa* is not sensitive to chloramphenicol.

Mechanism of Action

Chloramphenicol inhibits protein synthesis in bacteria by binding to the **50S ribosomal subunit** which is in close proximity to the binding sites of macrolides and clindamycin. The common binding of the three drugs may result in the inhibition of activity of any two by the other drug binding at the same site.

Bacterial Resistance

Most resistance to chloramphenicol is caused by **chlorampenicol acetyl transferase**. This enzyme catalyzes the acetylation of the hydroxyl group of chlorampenicol, which makes it unable to bind to the 50S subunit.

The less common mechanism of resistance is due to inadequate cell permeability or alteration of ribosomal proteins.

more than 25 µg/ml. The idiosyncratic response occurs on prolonged therapy or on repeated administration of the drug.

GI Effects

Chloramphenicol may produce gastric irritation and cause nausea and vomiting.

Toxicity in Newborn Infants

A complication known as the **gray baby syndrome** is encountered in infants given chloramphenicol. ***This syndrome of pallor, cyanosis, abdominal distension, vomiting and circulatory collapse with 50% mortality, develops in neonates with exceedingly high plasma concentrations of the drug which result from inadequate glucuronidation and failure to excrete the drug by the kidneys.*** Neonates lack an effective glucuronic acid metabolism for the metabolic degradation and detoxification of chloramphenicol. In neonates, the dose of chloramphenicol should not exceed 25 mg/kg body weight which may be increased to 50 mg/kg for full-term infants.

Drug Interactions

Chloramphenicol inhibits hepatic CYP450 enzymes and thereby prolongs the half-lives of many drugs that are metabolized by this system which include warfarin, dicoumarol, phenytoin, chlorpropamide, antiretroviral protease inhibitors, rifabutin and tolbutamide. Barbiturates, on the other hand, decrease the half-life of chloramphenicol.

Clinical Case Study

A male patient aged 36 years reports to the venereology department with the features of tender inguinal lymphadenopathy. The patient had a history of having sexual exposure 20 days earlier after which he had initially noticed a genital ulcer.

1. What could be the clinical condition called?
2. What could be course of the disease usually before an effective treatment is initiated?
3. What could be the symptoms seen in women with a possibility of similar disease?
4. How do you treat the condition?

RECAP

- Tetracyclines are a group of broad spectrum antibiotics having wide range of clinical uses.
- The commonly used tetracyclines include tetracycline, chlortetracycline, oxytetracycline, demethylchlortetracycline, methacycline, doxycycline, minocycline and tigecycline.
- Tetracyclines are classified according to their duration of action. Thus, they may be short acting (chlortetracycline, tetracycline, oxytetracycline) of 6-8 hours duration of action; intermediate acting (demethylchlortetracycline, methacycline) of 12 hours duration of action and long acting (minocycline, doxycycline and tigecycline) of 16–36 hours of duration action.
- Tetracyclines are effective against most species of Gram-positive and Gram-negative organisms such as Sreptococci, Staphylococci and enterococci. However bacterial resistance has developed to most of these strains and they are generally not effective in treating infections caused by these organisms. The other organisms that are sensitive to tetracyclines include Bacillus anthracis, Listeria monocytogenes, Mycoplasma pneumoniae, Brucella spp, Campylobacter jejuni, Calymmatobacterium granulomatis, Hemophilus ducreyi, Hemophilus influenza, Vibrio cholera, Yersinia pestis, Klebsiella pneumoniae, Chlamydiae, E. coli, Shigella, Treponema pallidum, Rickettsiae, Enterobacter spp, H. pylori, Protozoa (malarial parasites and amoebae), B. coli, and Bacteroides spp.
- Tetracyclines are bacteriostatic and bind reversibly to 16S rRNA of 30S ribosomal subunit of the microbial organisms and inhibit protein synthesis. They enter the bacteria either through an energy dependent process in Gram-positive organisms or through transmembrane porins by diffusion in Gram-negative organisms.
- Bacterial resistance to tetracyclines develops through decreased plasmid mediated influx or a plasmid encoded efflux from inside the bacteria or the production of a protein that prevents the binding of the tetracycline to the ribosome. Inactivation may also result from the production of an inactivating enzyme.
- Tetracyclines are widely distributed in the body, but higher levels are found in the liver, kidneys, bile, bronchial epithelium and breast milk. However they do not enter CSF.