

University of Technology
Applied Science Department
Biotechnology Division



Antibiotics

4th Class

Prepared By
Lecturer Arieg Abdul Wahab Mohammed

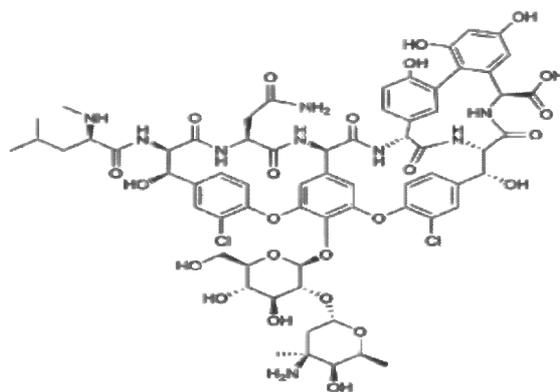
2013-2014

Part3

Vancomycin

Vancomycin is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. Vancomycin was first isolated in 1953 at Eli Lilly, from a soil sample collected from the interior jungles of Borneo by a missionary. It is a naturally occurring antibiotic made by the soil bacterium Actinobacteria species *Amycolatopsis orientalis* (formerly designated *Nocardia orientalis*). It is complex chemical compound and an example of a comparatively rare haloorganic natural compound, containing two organically bonded chlorine atoms.

The compound was industrially produced by fermentation and given the generic name vancomycin, derived from the term "vanquish." The original indication for vancomycin was for the treatment of penicillin-resistant *Staphylococcus aureus*, a use kept alive for many years by the fact that compound had to be given intravenously and was thus not abused outside hospitals, and the fact that organisms were relatively slow to evolve to adapt to it, even in experiments.



For many years since its initial use, vancomycin has traditionally been reserved as a drug of "last resort", used only after treatment with other antibiotics had failed. Today, vancomycin resistant organisms are finally becoming common (see MRSA). Thus, vancomycin is increasingly being displaced from this role by newer antibiotics (linezolid), daptomycin (Cubicin), quinupristin/dalfopristin (Synercid), etc.).

History

Vancomycin was first isolated in 1953 by Edmund Kornfeld (working at Eli Lilly) from a soil sample collected from the interior jungles of Borneo by a missionary. The organism that produced it was eventually named *Amycolatopsis orientalis*. The original indication for vancomycin was for the treatment of penicillin-resistant *Staphylococcus aureus*.

The compound was initially called compound 05865, but was eventually given the generic name vancomycin, derived from the term "vanquish". One advantage that was quickly apparent is that staphylococci did not develop significant resistance despite serial passage in culture media containing vancomycin. The rapid development of penicillin resistance by staphylococci led to the compound's being fast-tracked for approval by the Food and Drug Administration (FDA) in 1958. Eli Lilly first marketed vancomycin hydrochloride under the trade name Vancocin and as COVANC from Nucleus, India.

Vancomycin never became the first-line treatment for *Staphylococcus aureus* for several reasons:

1. It possesses poor oral bioavailability; it must be given intravenously for most infections.
2. β -Lactamase-resistant semi-synthetic penicillins such as methicillin (and its successors, nafcillin and cloxacillin) were subsequently developed, which have better activity against non-MRSA staphylococci.
3. Early trials used early impure forms of vancomycin ("Mississippi mud"), which were found to be toxic to the ears and to the kidneys; these findings led to vancomycin's being relegated to the position of a drug of last resort.

In 2004, Eli Lilly licensed *Vancocin* to ViroPharma in the U.S., Flynn Pharma in the UK, and Aspen Pharmacare in Australia. The patent expired in the early 1980s; the FDA authorized the sale of several generic versions in the USA, including from manufacturers Bioniche Pharma, Baxter Healthcare, Sandoz, Akorn Strides and Hospira.

An oral form of vancomycin was originally approved by the FDA in 1986 for the treatment of *Clostridium difficile* induced pseudomembranous colitis. It is not orally absorbed into the blood and remains in the gastrointestinal tract to eradicate *C. difficile*. This product is currently marketed by ViroPharma in the USA.

Mechanism of Action

Vancomycin acts by inhibiting proper cell wall synthesis in Gram-positive bacteria. Due to the different mechanism by which Gram-negative bacteria produce their cell walls and the various factors related to entering the outer membrane of Gram-negative organisms, vancomycin

is not active against Gram-negative bacteria (except some non-gonococcal species of *Neisseria*). The large hydrophilic molecule is able to form hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of the NAM/NAG-peptides. Under normal circumstances, this is a five-point interaction. This binding of vancomycin to the D-Ala-D-Ala prevents cell wall synthesis in two ways. It prevents the synthesis of the long polymers of N-acetylmuramic acid (NAM) and N-acetylglucosamine (NAG) that form the backbone strands of the bacterial cell wall, and it prevents the backbone polymers that do manage to form from cross-linking with each other.

Indications

Vancomycin is indicated for the treatment of serious, life-threatening infections by Gram-positive bacteria that are unresponsive to other less-toxic antibiotics. In particular, vancomycin should not be used to treat methicillin-sensitive *Staphylococcus aureus* because it is inferior to penicillins such as nafcillin.

The increasing emergence of vancomycin-resistant enterococci has resulted in the development of guidelines for use by the Centers for Disease Control (CDC) Hospital Infection Control Practices Advisory Committee. These guidelines restrict use of vancomycin to the following indications:

- Treatment of serious infections caused by susceptible organisms resistant to penicillins (methicillin-resistant *Staphylococcus aureus* and multi-resistant *Staphylococcus epidermidis* (MRSE)) or in individuals with serious allergy to penicillins
- Treatment of Pseudomembranous colitis caused by the bacterium *Clostridium difficile*; in particular, in cases of relapse or where the

infection is unresponsive to metronidazole treatment (for this indication, vancomycin is given orally, rather than via its typical, I.V. route)

- For treatment of infections caused by gram-positive microorganisms in patients with serious allergies to beta-lactam antimicrobials.
- Antibacterial prophylaxis for endocarditis following certain procedures in penicillin-hypersensitive individuals at high risk
- Surgical prophylaxis for major procedures involving implantation of prostheses in institutions with a high rate of MRSA or MRSE
- Early in treatment as an empiric antibiotic to cover for possible MRSA infection while waiting for culture identification of the infecting organism.

Adverse Effects

Although vancomycin levels are usually monitored, in an effort to reduce adverse events, the value of this is not beyond debate. Peak and trough levels are usually monitored, and, for research purposes, the area under the curve is also sometimes used. Toxicity is best monitored by looking at trough values.

Common adverse drug reactions ($\geq 1\%$ of patients) associated with IV vancomycin include: local pain, which may be severe and/or thrombophlebitis. Damage to the kidneys and to the hearing were a side-effect of the early impure versions of vancomycin, and these were prominent in the clinical trials conducted in the mid-1950s. Later trials using purer forms of vancomycin found that nephrotoxicity is an infrequent adverse effect (0.1–1% of patients), but that this is accentuated in the presence of aminoglycosides.

Rare adverse effects (<0.1% of patients) include: anaphylaxis, toxic epidermal necrolysis, erythema multiforme, red man syndrome, superinfection, thrombocytopenia, neutropenia, leucopenia, tinnitus, dizziness and/or ototoxicity. It has recently been emphasized that vancomycin can induce platelet-reactive antibodies in the patient, leading to severe thrombocytopenia and bleeding with florid petechial hemorrhages, ecchymoses, and wet purpura.

Toxicity

Vancomycin has traditionally been considered a nephrotoxic and ototoxic drug, based on observations by early investigators of elevated serum levels in renally impaired patients that had experienced ototoxicity, and subsequently through case reports in the medical literature. However, as the use of vancomycin increased with the spread of MRSA beginning in the 1970s, it was recognized that the previously reported rates of toxicity were not being observed. This was attributed to the removal of the impurities present in the earlier formulation of the drug, although those impurities were not specifically tested for toxicity.

Nephrotoxicity

Subsequent reviews of accumulated case reports of vancomycin-related nephrotoxicity found that many of the patients had also received other known nephrotoxins, in particular, aminoglycosides. Most of the rest had other confounding factors, or insufficient data regarding the possibility of such, that prohibited the clear association of vancomycin with the observed renal dysfunction. In 1994, Cantu and colleagues found that the use of vancomycin monotherapy was clearly documented in only three of 82 available cases in the literature.^[28] Prospective and retrospective studies attempting to evaluate the incidence of vancomycin-related

nephrotoxicity have largely been methodologically flawed and have produced variable results. The most methodologically sound investigations indicate that the actual incidence of vancomycin-induced nephrotoxicity is around 5–7%. To put this into context, similar rates of renal dysfunction have been reported for cefamandole and benzylpenicillin, two reputedly non-nephrotoxic antibiotics.

In addition, evidence to relate nephrotoxicity to vancomycin serum levels is inconsistent. Some studies have indicated an increased rate of nephrotoxicity when trough levels exceed 10 µg/mL, but others have not reproduced these results. Nephrotoxicity has also been observed with concentrations within the "therapeutic" range as well. In essence, the reputation of vancomycin as a nephrotoxin is over-stated, and it has not been demonstrated that maintaining vancomycin serum levels within certain ranges will prevent its nephrotoxic effects, when they do occur.

Ototoxicity

Attempts to establish rates of vancomycin-induced ototoxicity are even more difficult due to the scarcity of quality evidence. The current consensus is that clearly related cases of vancomycin ototoxicity are rare. The association between vancomycin serum levels and ototoxicity is also uncertain. While cases of ototoxicity have been reported in patients whose vancomycin serum level exceeded 80 µg/mL, cases have been reported in patients with therapeutic levels as well. Thus, it also remains unproven that therapeutic drug monitoring of vancomycin for the purpose of maintaining "therapeutic" levels will prevent ototoxicity.

Interactions with Other Nephrotoxins

Another area of controversy and uncertainty concerns the question of whether, and, if so, to what extent, vancomycin increases the toxicity of other nephrotoxins. Clinical studies have yielded variable results, but

animal models indicate that there probably is some increased nephrotoxic effect when vancomycin is added to nephrotoxins such as aminoglycosides. However, a dose- or serum level-effect relationship has not been established.

Antibiotic Resistance

Intrinsic Resistance

There are a few gram-positive bacteria that are intrinsically resistant to vancomycin: *Leuconostoc* and *Pediococcus* species, but these organisms are rare causes of disease in humans. Most *Lactobacillus* species are also intrinsically resistant to vancomycin (the exception is the finding of a few strains (but not all) of *L. acidophilus*).

Most gram-negative bacteria are intrinsically resistant to vancomycin because their outer membrane is impermeable to large glycopeptide molecules (with the exception of some non-gonococcal *Neisseria* species).

Acquired Resistance

Evolution of microbial resistance to vancomycin is a growing problem, in particular, within healthcare facilities such as hospitals. While newer alternatives to vancomycin exist, such as Linezolid (2000) and daptomycin (2003), the widespread use of vancomycin makes resistance to the drug a significant worry, especially for individual patients if resistant infections are not quickly identified and the patient continues the ineffective treatment. Vancomycin-resistant *Enterococcus* (VRE) emerged in 1987. Vancomycin resistance evolved in more common pathogenic organisms during the 1990s and 2000s, including vancomycin-intermediate *Staphylococcus aureus* (VISA) and

vancomycin-resistant *Staphylococcus aureus* (VRSA). There is some suspicion that agricultural use of avoparcin, another similar glycopeptide antibiotic, has contributed to the evolution of vancomycin-resistant organisms.

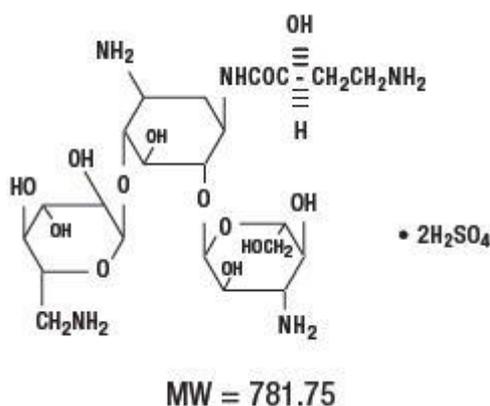
One mechanism of resistance to vancomycin involves the alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits, under normal conditions, D-alanyl-D-alanine, to which vancomycin binds. The D-alanyl-D-lactate variation results in the loss of one hydrogen-bonding interaction (4, as opposed to 5 for D-alanyl-D-alanine) possible between vancomycin and the peptide. This loss of just one point of interaction results in a 1000-fold decrease in affinity. The D-alanyl-D-serine variation causes a six-fold loss of affinity between vancomycin and the peptide, likely due to steric hindrance. In enterococci, this modification appears to be due to the expression of an enzyme that alters the terminal residue. Three main resistance variants have been characterised to date among resistant *Enterococcus faecium* and *E. faecalis* populations.

- VanA - resistance to vancomycin and teicoplanin; inducible on exposure to these agents
- VanB - lower-level resistance; inducible by vancomycin, but strains may remain susceptible to teicoplanin
- VanC - least clinically important; resistance only to vancomycin; constitutive resistance

Antibacterial which inhibit protein synthesis

Aminoglycoside

An aminoglycoside is a molecule or a portion of a molecule composed of amino-modified sugars.



Several aminoglycosides function as antibiotics that are effective against certain types of bacteria. They include amikacin, arbekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, tobramycin, and apramycin.

Mechanisms of Action

Aminoglycosides have several potential antibiotic mechanisms, some as protein synthesis inhibitors, although their exact mechanism of action is not fully known:

- They interfere with the proofreading process, causing increased rate of error in synthesis with premature termination.
- Also, there is evidence of inhibition of ribosomal translocation where the peptidyl-tRNA moves from the A-site to the P-site.
- They can also disrupt the integrity of bacterial cell membrane.

They bind to the bacterial 30S ribosomal subunit. There is a significant variability in the relationship between the dose administered and the

resultant plasma level in blood. Therapeutic drug monitoring (TDM) is necessary to obtain the correct dose. These agents exhibit a post-antibiotic effect in which there is no or very little drug level detectable in blood, but there still seems to be inhibition of bacterial re-growth. This is due to strong, irreversible binding to the ribosome, and remains intracellular long after plasma levels drop. This allows a prolonged dosage interval. Depending on their concentration, they act as bacteriostatic or bactericidal agents.

The protein synthesis inhibition of aminoglycosides does not usually produce a bactericidal effect, let alone a rapid one as is frequently observed on susceptible Gram-negative bacilli. Aminoglycosides competitively displace cell biofilm-associated Mg^{2+} and Ca^{2+} that link the polysaccharides of adjacent lipopolysaccharide molecules. "The result is shedding of cell membrane blebs, with formation of transient holes in the cell wall and disruption of the normal permeability of the cell wall. This action alone may be sufficient to kill most susceptible Gram-negative bacteria before the aminoglycoside has a chance to reach the 30S ribosome."

The antibacterial properties of aminoglycosides were believed to result from inhibition of bacterial protein synthesis through irreversible binding to the 30S bacterial ribosome. This explanation, however, does not account for the potent bactericidal properties of these agents, since other antibiotics that inhibit the synthesis of proteins (such as tetracycline) are not bactericidal. Recent experimental studies show that the initial site of action is the outer bacterial membrane. The cationic antibiotic molecules create fissures in the outer cell membrane, resulting in leakage of intracellular contents and enhanced antibiotic uptake. This rapid action at the outer membrane, it is presumed, accounts for most of the bactericidal activity. Energy is needed for aminoglycoside uptake into the bacterial

cell. Anaerobes have less energy available for this uptake, so aminoglycosides are less active against anaerobes. Aminoglycosides are useful primarily in infections involving aerobic, gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter*, and *Enterobacter*. In addition, some *Mycobacteria*, including the bacteria that cause tuberculosis, are susceptible to aminoglycosides. The most frequent use of aminoglycosides is empiric therapy for serious infections such as septicemia, complicated intraabdominal infections, complicated urinary tract infections, and nosocomial respiratory tract infections. Usually, once cultures of the causal organism are grown and their susceptibilities tested, aminoglycosides are discontinued in favor of less toxic antibiotics. Streptomycin was the first effective drug in the treatment of tuberculosis, though the role of aminoglycosides such as streptomycin and amikacin has been eclipsed (because of their toxicity and inconvenient route of administration) except for multiple-drug-resistant strains.

Infections caused by gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past, the aminoglycosides have been used in conjunction with beta-lactam antibiotics in streptococcal infections for their synergistic effects, in particular in endocarditis. One of the most frequent combinations is ampicillin (a beta-lactam, or penicillin-related antibiotic) and gentamicin. Often, hospital staff refer to this combination as "amp and gent" or more recently called "pen and gent" for penicillin and gentamicin. Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi, and viruses.

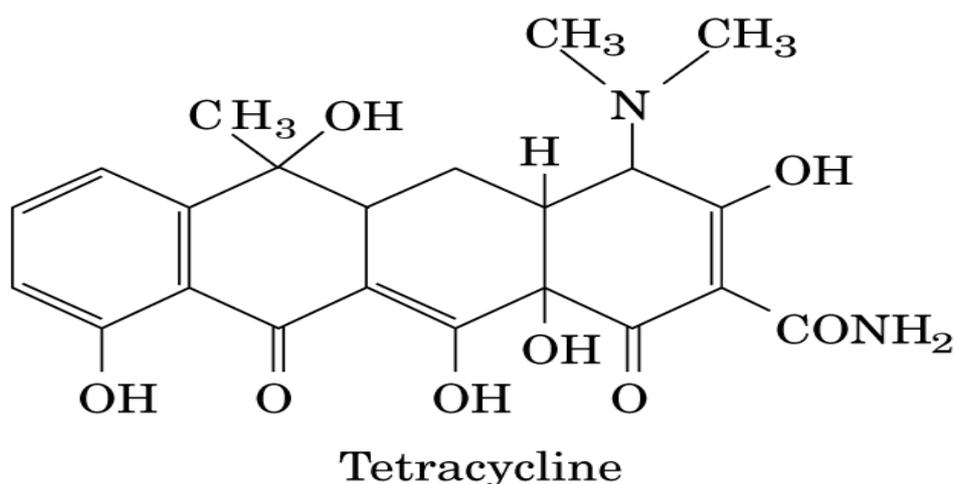
Clinical Use

The recent emergence of infections due to Gram-negative bacterial strains with advanced patterns of antimicrobial resistance has prompted physicians to reevaluate the use of these antibacterial agents. This revived interest in the use of aminoglycosides has brought back to light the debate on the two major issues related to these compounds, namely the spectrum of antimicrobial susceptibility and toxicity. Current evidence shows that aminoglycosides do retain activity against the majority of Gram-negative clinical bacterial isolates in many parts of the world. Still, the relatively frequent occurrence of nephrotoxicity and ototoxicity during aminoglycoside treatment makes physicians reluctant to use these compounds in everyday practice. Recent advances in the understanding of the effect of various dosage schedules of aminoglycosides on toxicity have provided a partial solution to this problem, although more research still needs to be done in order to overcome this problem entirely.

Aminoglycosides are in pregnancy category D, that is, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Tetracycline

Tetracycline is a broad-spectrum polyketide antibiotic produced by the *Streptomyces* genus of Actinobacteria, indicated for use against many bacterial infections. It is a protein synthesis inhibitor. It is commonly used to treat acne today, and, more recently, rosacea, and is historically important in reducing the number of deaths from cholera. Tetracycline is marketed under the brand names Sumycin, Tetracyn, and Panmycin, among others. Actisite is a thread-like fiber formulation used in dental applications. It is also used to produce several semisynthetic derivatives, which together are known as the tetracycline antibiotics. The term "tetracycline" is also used to denote the 4-ring system of this compound; "tetracyclines" are related substances that contain the same 4-ring system.



History

The tetracyclines are a large family of antibiotics that were discovered as natural products by Benjamin Minge Duggar in 1945 and first described in 1948.^[2] Under Yellapragada Subbarao, Benjamin Duggar made his discovery of the first tetracycline antibiotic, chlortetracycline (Aureomycin), at Lederle Laboratories in 1945.

In 1950, Harvard Professor Robert Woodward determined the chemical structure of the related substance, oxytetracycline (Terramycin); the patent protection for its fermentation and production was also first issued in 1950. A research team of seven scientists (K.J. Brunings, Francis A. Hochstein, C.R. Stephens, L.H. Conover, Abraham Bavley, Richard Pasternack, and Peter P. Regna) at Pfizer, in collaboration with Woodward, participated in the two-year research leading to the discovery. Pfizer was of the view that it deserved the right to a patent on tetracycline and filed its Conover application in October 1952. Cyanamid filed its Boothe Morton application for similar rights in March 1953, while Heyden Chemicals filed its Minieri application in September 1953, named after scientist P. Paul Minieri, to obtain a patent on tetracycline and its fermentation process. This resulted in tetracycline litigation in which the winner would have to prove beyond reasonable doubt of priority invention and tetracycline's natural state.

Nubian mummies studied in the 1990s were found to contain significant levels of tetracycline; there is evidence that the beer brewed at the time could have been the source.^[8] Tetracycline sparked the development of many chemically altered antibiotics, so has proved to be one of the most important discoveries made in the field of antibiotics. It is used to treat many Gram-positive and Gram-negative bacteria. Like some other antibiotics, it is also used in the treatment of acne.

Mechanism of Action

Tetracyclines bind to the 30S subunit of microbial ribosomes. They inhibit protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome. Thus, they prevent introduction of new amino acids to the nascent peptide chain. The action is usually inhibitory and reversible upon withdrawal of the drug. Resistance to the tetracyclines results from changes in permeability of the microbial cell envelope. In susceptible cells, the drug is concentrated from the environment and does not readily leave the cells. In resistant cells, the drug is not actively transported into the cells or leaves it so rapidly that inhibitory concentrations are not maintained. This is often plasmid-controlled. Mammalian cells are not vulnerable to the effect of tetracyclines, as these contain no 30S ribosomal subunits and therefore do not accumulate the drug.

Spectrum of Bacterial Susceptibility and Resistance

Tetracyclines have a broad spectrum of antibiotic action. Originally, they possessed some level of bacteriostatic activity against almost all medically relevant aerobic and anaerobic bacterial genera both Gram positive and Gram negative, with a few exceptions such as *Pseudomonas aeruginosa* and *Proteus spp.* which display intrinsic resistance. However, acquired (as opposed to inherent) resistance has proliferated in many pathogenic organisms and greatly eroded the formerly vast versatility of this group of antibiotics. Resistance amongst *Staphylococcus spp.*, *Streptococcus spp.*, *Neisseria gonorrhoeae*, anaerobes, members of the *Enterobacteriaceae* and several other previously sensitive organisms is now quite common. Tetracyclines remain especially useful in the management of infections by certain obligately intracellular bacterial

pathogens such as *Chlamydia*, *Mycoplasma* and *Rickettsia*. They are also of value in spirochaetal infections such as syphilis, leptospirosis and Lyme disease. Certain rare or exotic infections, including anthrax, plague and brucellosis, are also generally susceptible to tetracyclines. These agents also have activity against certain eukaryotic parasites including those responsible for diseases such as malaria and balantidiasis.

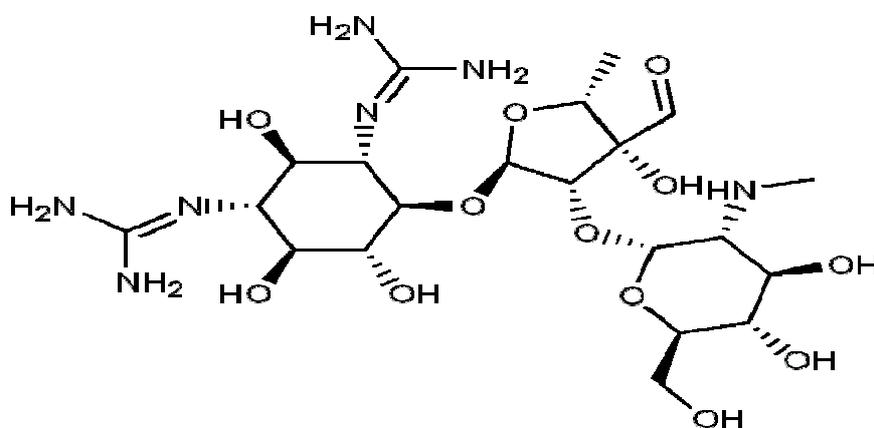
Indications

It is first-line therapy for Rocky Mountain spotted fever (*Rickettsia*), Lyme disease (*B. burgdorferi*), fever, psittacosis and lymphogranuloma venereum (*Chlamydia*), and to eradicate nasal carriage of meningococci. Tetracycline tablets were used in the plague outbreak in India in 1992. Doxycycline is also one (of many) recommended drugs for chemoprophylactic treatment of malaria in travels to areas of the world where malaria is endemic. Since tetracycline is absorbed into bone, it is used as a marker of bone growth for biopsies in humans. Tetracycline labeling is used to determine the amount of bone growth within a certain period of time, usually a period of approximately 21 days. Tetracycline is incorporated into mineralizing bone and can be detected by its fluorescence. In "double tetracycline labeling", a second dose is given 11–14 days after the first dose, and the amount of bone formed during that interval can be calculated by measuring the distance between the two fluorescent labels. Tetracycline is also used as a biomarker in wildlife to detect consumption of medicine- or vaccine-containing baits.

In genetic engineering, tetracycline is used in transcriptional activation. Tetracycline is also one of the antibiotics used to treat ulcers caused by bacterial infections. In cancer research at Harvard Medical School, tetracycline has been used to switch off leukemia in genetically altered mice, and to do so reliably, when added to their drinking water.

Streptomycin

It is an antibiotic drug, the first of a class of drugs called aminoglycosides to be discovered, and was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium *Streptomyces griseus*. Streptomycin is a bactericidal antibiotic. Streptomycin cannot be given orally, but must be administered by regular intramuscular injections. An adverse effect of this medicine is ototoxicity, nephrotoxicity, fetal auditory toxicity and neuromuscular paralysis.



History

Streptomycin was first isolated on October 19, 1943, by Albert Schatz, a graduate student, in the laboratory of Selman Abraham Waksman at Rutgers University. Dr. Waksman and his laboratory discovered several antibiotics, including actinomycin, clavacin, streptothricin, streptomycin, grisein, neomycin, fradycin, candicidin and candidin. Of these, streptomycin and neomycin found extensive application in the treatment of numerous infectious diseases. Streptomycin was the first antibiotic that could be used to cure the disease tuberculosis; early production of the drug was dominated by Merck & Co. under George W. Merck. The first randomized trial of streptomycin against pulmonary tuberculosis was carried out in 1946-1947 by the MRC Tuberculosis Research Unit under

the chairmanship of Sir Geoffrey Marshall (1887–1982). The trial was both double-blind and placebo-controlled. It is widely accepted to have been the first randomised curative trial. Results showed efficacy against TB, albeit with minor toxicity and acquired bacterial resistance to the drug.

Mechanism of Action

Streptomycin is a protein synthesis inhibitor. It binds to the small 16S rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit. This leads to codon misreading, eventual inhibition of protein synthesis and ultimately death of microbial cells through mechanisms that are still not understood. Speculation on this mechanism indicates that the binding of the molecule to the 30S subunit interferes with 50S subunit association with the mRNA strand. This results in an unstable ribosomal-mRNA complex, leading to a frameshift mutation and defective protein synthesis; leading to cell death. Humans have structurally different ribosomes from bacteria, thereby allowing the selectivity of this antibiotic for bacteria. However at low concentrations Streptomycin only inhibits growth of the bacteria by inducing prokaryotic ribosome to misread mRNA. Streptomycin is an antibiotic that inhibits both Gram-positive and Gram-negative bacteria, and is therefore a useful broad-spectrum antibiotic.

Uses

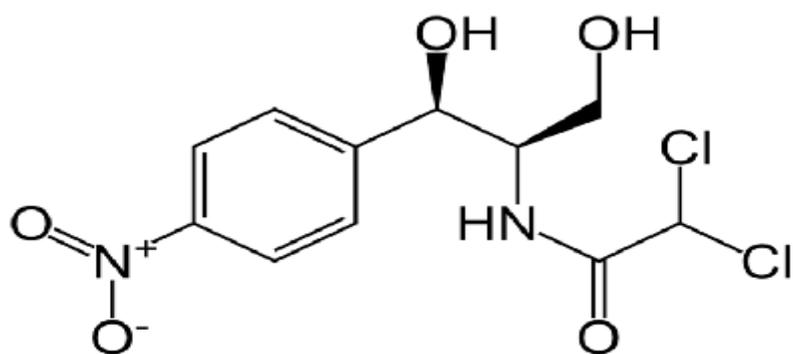
- Infective endocarditis caused by enterococcus when the organism is not sensitive to Gentamicin
- Tuberculosis in combination with other anti-TB drugs. It is not the first-line treatment, except in medically under-served populations where the cost of more expensive treatments is prohibitive.

- Plague (*Yersinia pestis*) has historically been treated with it as the first-line treatment. It is approved for this purpose by the U.S. Food and Drug Administration.
- In veterinary medicine, streptomycin is the first-line antibiotic for use against gram negative bacteria in large animals (horses, cattle, sheep etc.). It is commonly combined with procaine penicillin for intramuscular injection.

While streptomycin is traditionally given intramuscularly (indeed, in many countries it is only licensed to be used intramuscularly), the drug may also be administered intravenously.

Chloramphenicol

Chloramphenicol is a bacteriostatic antimicrobial that became available in 1949. It is considered a prototypical broad-spectrum antibiotic, alongside the tetracyclines, and as it is both cheap and easy to manufacture it is frequently an antibiotic of choice in the Third World. Chloramphenicol, also known as chlornitromycin, is effective against a wide variety of Gram-positive and Gram-negative bacteria, including most anaerobic organisms. Due to resistance and safety concerns, it is no longer a first-line agent for any infection in developed nations, although it is sometimes used topically for eye infections. Nevertheless, the global problem of advancing bacterial resistance to newer drugs has led to renewed interest in its use. In low-income countries, chloramphenicol is still widely used because it is inexpensive and readily available.



The most serious adverse effect associated with chloramphenicol treatment is bone marrow toxicity, which may occur in two distinct forms: bone marrow suppression, which is a direct toxic effect of the drug and is usually reversible and aplastic anemia, which is idiosyncratic (rare, unpredictable, and unrelated to dose) and in general fatal.

Mechanism of Action

Chloramphenicol is a bacteriostatic drug that stops bacterial growth by inhibiting protein synthesis. Chloramphenicol prevents protein chain elongation by inhibiting the peptidyl transferase activity of the bacterial ribosome. It specifically binds to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit, preventing peptide bond formation.^[21] While chloramphenicol and the macrolide class of antibiotics both interact with ribosomes, chloramphenicol is not a macrolide. It directly interferes with substrate binding, whereas macrolides sterically block the progression of the growing peptide.

Resistance

There are three mechanisms of resistance to chloramphenicol: reduced membrane permeability, mutation of the 50S ribosomal subunit and elaboration of chloramphenicol acetyltransferase. It is easy to select for reduced membrane permeability to chloramphenicol *in vitro* by serial

passage of bacteria, and this is the most common mechanism of low-level chloramphenicol resistance. High-level resistance is conferred by the *cat*-gene; this gene codes for an enzyme called chloramphenicol acetyltransferase, which inactivates chloramphenicol by covalently linking one or two acetyl groups, derived from acetyl-S-coenzyme A, to the hydroxyl groups on the chloramphenicol molecule. The acetylation prevents chloramphenicol from binding to the ribosome. Resistance-conferring mutations of the 50S ribosomal subunit are rare. Chloramphenicol resistance may be carried on a plasmid that also codes for resistance to other drugs. Currently, some *Enterococcus faecium* and *Pseudomonas aeruginosa* strains are resistant to chloramphenicol. Some *Veillonella* spp. and *Staphylococcus capitis* strains have also developed resistance to chloramphenicol to varying degrees.

Therapeutic Uses

The original indication of chloramphenicol was in the treatment of typhoid, but the now almost universal presence of multiple drug-resistant *Salmonella typhi* has meant it is seldom used for this indication except when the organism is known to be sensitive. Chloramphenicol may be used as a second-line agent in the treatment of tetracycline-resistant cholera.

Because of its excellent BBB penetration (far superior to any of the cephalosporins), chloramphenicol remains the first choice treatment for staphylococcal brain abscesses. It is also useful in the treatment of brain abscesses due to mixed organisms or when the causative organism is not known. Chloramphenicol is active against the three main bacterial causes of meningitis: *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*.

In the West, chloramphenicol remains the drug of choice in the treatment of meningitis in patients with severe penicillin or cephalosporin allergy and GPs are recommended to carry intravenous chloramphenicol in their bag. In low income countries, the WHO recommends that oily chloramphenicol be used first-line to treat meningitis.

Chloramphenicol has been used in the U.S. in the initial empirical treatment of children with fever and a petechial rash, when the differential diagnosis includes both *Neisseria meningitidis* septicaemia as well as Rocky Mountain spotted fever, pending the results of diagnostic investigations. Chloramphenicol is also effective against *Enterococcus faecium*, which has led to its being considered for treatment of vancomycin-resistant enterococcus.

Although unpublished, recent research suggests chloramphenicol could also be applied to frogs to prevent their widespread destruction from fungal infections.^[4] Chloramphenicol has recently been discovered to be a life-saving cure for chytridiomycosis in amphibians. Chytridiomycosis is a fungal disease, blamed for the extinction of one-third of the 120 frog species lost since 1980.

Adverse Effects

A plastic Anemia

The most serious side effect of chloramphenicol treatment is a plastic anemia. This effect is rare and is generally fatal: there is no treatment and no way of predicting who may or may not get this side effect. The effect usually occurs weeks or months after chloramphenicol treatment has been stopped, and there may be a genetic predisposition. It is not known whether monitoring the blood counts of patients can prevent the development of a plastic anemia, but patients are recommended to have a blood count check twice weekly while on treatment.

The highest risk is with oral chloramphenicol (affecting 1 in 24,000–40,000) and the lowest risk occurs with eye drops (affecting less than 1 in 224,716 prescriptions). Thiamphenicol, a related compound with a similar spectrum of activity, is available in Italy and China for human use, and has never been associated with aplastic anaemia. Thiamphenicol is available in the U.S. and Europe as a veterinary antibiotic, and is not approved for use in humans.

Bone Marrow Suppression

Chloramphenicol commonly causes bone marrow suppression during treatment; this is a direct toxic effect of the drug on human mitochondria. This effect manifests first as a fall in hemoglobin levels, which occurs quite predictably once a cumulative dose of 20 g has been given. The anemia is fully reversible once the drug is stopped and does not predict future development of a plastic anemia.

Leukemia

There is an increased risk of childhood leukemia, as demonstrated in a Chinese case-controlled study and the risk increases with length of treatment.

Gray Baby Syndrome

Intravenous chloramphenicol use has been associated with the so-called gray baby syndrome. This phenomenon occurs in newborn infants because they do not yet have fully functional liver enzymes (i.e. UDP-glucuronyl transferase), so chloramphenicol remains unmetabolized in the body. This causes several adverse effects, including hypotension and cyanosis. The condition can be prevented by using the drug at the recommended doses, and monitoring blood levels.