does not undergo significant liver metabolism, but it is primarily eliminated via biliary/fecal excretion. No dose adjustment is necessary for patients who are renally impaired, but is needed in severe hepatic dysfunction.

Adverse effects

Tigecycline is associated with significant nausea and vomiting. Other adverse effect are similar to those of the tetracycline class; and include photosensitivity, intracranial hypertension, discoloration of permanent teeth when used during tooth development, and fetal harm when administered to a pregnant woman.

Drug interactions

It is not affected by medications that induce or inhibit cytochrome P450 liver enzymes. It inhibits the clearance of *warfarin*. Therefore, it is recommended that anticoagulation be monitored closely when *tigecycline* is coadministered with *warfarin*.

No dose adjustment of *digoxin* is necessary with concomitant use of *tigecycline*.

However, another (additional) method of contraception is suggested when *tigecycline* and oral contraceptives are coadministered.

x P450

✓ inhibit clearance of warfarin

x digoxin

✓ another method of contraception

8. Contraindications: Renally impaired patients should not be treated with any of the tetracyclines except *doxycycline*. Accumulation of tetracyclines may aggravate preexisting azotemia by interfering with protein synthesis. The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age.

GLYCYLCYCLINES

Tigecycline is a member of a new class of antimicrobial agents called glycylcyclines. *Tigecycline*, a derivative of *minocycline*, is structurally similar to the tetracyclines and has a broad-spectrum activity

Tigecycline is indicated for treatment of complicated skin and soft tissue infections, as well as, complicated intra-abdominal infections.

Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation.

Antibacterial spectrum

Tigecycline exhibits expanded broad-spectrum activity that includes:

1. methicillin-resistant staphylococci,
2. multidrug-resistant Streptococcus pneumoniae, and other susceptible strains of streptococcal species,
3. *vancomycin*-resistant enterococci,
4. extended-spectrum β-lactamase producing gram-negative bacteria,
5. Acinetobacter baumannii,
6. And many anaerobic organisms.

However, *tigecycline* is not active against Proteus, Providencia, or Pseudomonas species.

Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline-resistant organisms that utilize efflux and ribosomal protection to confer resistance (Thus currently there may be no resistance to it).

Pharmacokinetics

Tigecycline rapidly distributes into the body tissues, and thus should never be used to treat bacteremia.

2 providencia
1 proteus
3 pseudo mona

Elimination: All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and metabolites are secreted into the bile.
Most tetracyclines are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration. Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives.
Unlike other tetracyclines, *doxycycline* can be employed for treating infections in renally compromised patients because it is preferentially excreted via the bile.

Adverse effects

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance in patients.

2. **Effects on calcified tissues:** Deposition in the bone and primary dentition (teeth) occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.

3. **Fatal hepatotoxicity:** May occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.

4. **Phototoxicity:** Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays.
This is encountered most frequently with *tetracycline*, *doxycycline*, and *demeclocycline*.

5. **Vestibular problems:** These side effects (for example, dizziness, nausea, and vomiting) occur particularly with *minocycline*. *Doxycycline* may also cause vestibular effects.

6. Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults.

7. **Superinfections:** Overgrowths of Candida or of resistant staphylococci (in the intestine) may occur.
Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

Contraindication:-

1- Gastric discomfort 7 super
2- Fatal

Tetracyclines are the drugs of choice for many infections such as:

1. Gr+ve bacilli (Bacillus Anthracis)
2. Gr-ve rods (Brucella species, Vibrio Cholera, Yersinia Pestis)
3. Anaerobic organisms (Closteridium Perefringenes, Closteridium Tetani)
4. Spirochetes (Borrelia and Liptospira)
5. Mycoplasma (Mycoplasma Pneumoniae)
6. Chlamydia
7. Others (Rickettsia rickettsii)

Resistance

The resistance ("R") factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by active efflux of the drug.
Other mechanisms include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome (Ribosomal protection).
Any organism resistant to one tetracycline is resistant to all.

Pharmacokinetics

1. Absorption: All tetracyclines are adequately, yet incompletely, absorbed after oral ingestion. However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions.
Non absorbable chelates are also formed with other divalent and trivalent cations, for example, those found in magnesium and aluminum antacids and in iron preparations.
Doxycycline and *minocycline* are almost totally absorbed on oral administration.

2. Distribution: The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma).
All tetracyclines enter the cerebrospinal fluid (CSF), but levels are insufficient for therapeutic efficacy, except for *minocycline*. *Minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva.

Protein Synthesis Inhibitors

A number of antibiotics exert their antimicrobial effects by targeting the **bacterial ribosome**. The bacterial ribosome is smaller (70S) than the **mammalian ribosome** (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits). The **mammalian mitochondrial ribosome**, however, more closely resembles the bacterial ribosome. high levels of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the host mitochondrial ribosomes.

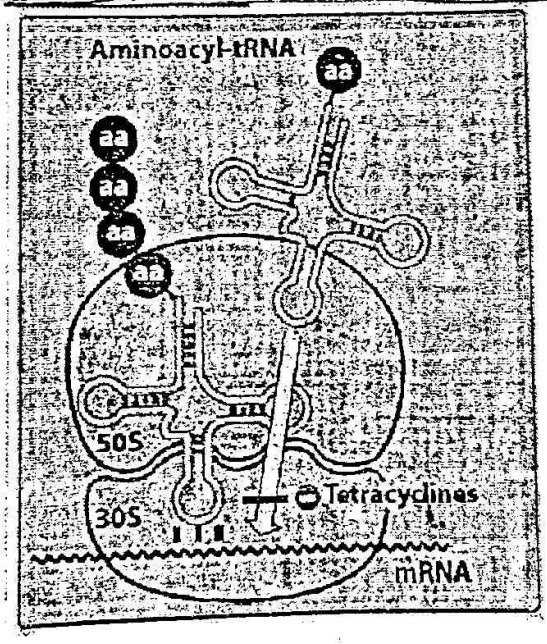
TETRACYCLINES

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds.

Mechanism of action

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism.

The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the aminoacyl-tRNA to the mRNA-ribosome complex at the acceptor site. By this mechanism, bacterial protein synthesis is inhibited.



Tetracycline

glycylcycline

Antibacterial spectrum

The tetracyclines are broad-spectrum bacteriostatic antibiotics