NAME: EGAGHARA ESE ESTHER

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1.

**BACTERIAL PROTEIN SYNTHESIS INHIBITORS**

A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome which has components that differ structurally from those of the mammalian cytoplasmic 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 bacterial ribosome. Thus, although drugs that interact with the bacterial site usually spare the host cells, high levels of drugs like chloramphenicol or the tetracyclines may cause toxic effects as a result of interaction with the mitochondrial ribosomes. An example of a bacterial protein synthesis inhibitors is the TETRACYCLINE.

**TETRACYCLINES**

Tetracyclines (tet ra SYE KLEEN) are a large group of closely related compounds that, as the name implies, consists of 4 fused rings with a system of conjugated double bonds. Their small differences in clinical efficacy reflect a variation in their individual pharmacokinetics due to substitutions on these rings.

Tetracyclines are classified as:

* Short acting (chlortetracycline, tetracycline, oxytetracycline)
* Intermediate acting (demeclocycline and metacycline)
* Long acting (doxycycline and minocycline) based on serum half lives

**MECHANISM OF ACTION**

They inhibit protein synthesis by binding to 30S ribosomal subunit at a site that blocks binding of charged tRNA to the 30S site of the ribosome. They are bacteriostatic.

Tetracyclines can inhibit mammalian protein synthesis but because they are ‘’pumped’’ out of mammalian cells do not usually reach concentrations needed to significantly reduce mammalian protein synthesis.

**ANTIMICROBIAL ACTIVITY**

 Tetracyclines are broad spectrum antibiotics. They are active against many gram-positive and gram-negative bacteria, including anaerobes, rickettsia, chlamydiae, mycoplasms and are active against some protozoa. The main mechanisms of resistance to tetracyclines, is decreased intracellular accumulation due to either impaired influx or increased efflux by an active transport protein pump

**RESISTANCE**

Widespread resistance to tetracyclines limits their clinical use. The most commonly encountered naturally occurring R factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by a Mg++ dependent active efflux of the drug mediated by the resistance protein TetA. Other mechanisms such as possible modification of the tetracyclines binding site have also been reported. Any organism resistant to one tetracycline is resistant to all. The majority of penicillinase- producing staphylococcus are now also insensitive to tetracyclines.

**PHARMACOKINETICS**

* Absorption: All tetracyclines are adequately but incompletely absorbed after oral ingestion. However, taking these drugs concomitantly with diary foods in the diet decreases absorption because of the formation of nonabsorbable chelates to the tetracyclines with calcium ions. This is less of a problem with doxycycline with calcium ions. This is less of a problem with doxycycline [dox I SYE kleen]. Nonabsorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids, and in iron preparations). N/B this presents a problem if the patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids
* Distribution: he tetracyclines concentrate in the liver, kidney, spleen and skin and bind to tissues undergoing calcification (for example, teeth and bones), or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fluids is adequate. Although all tetracyclines enter the cerebrospinal fluid, 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. Though useful in eradicating the meningococcal carrier state, minocycline is not effective for central nervous system (CNS) infections. All tetracyclines cross the placenta barrier and concentrate on the fetal bones and dentition.
* Fate: All the tetracyclines concentrate in the liver, where there are in parts, metabolized and conjugated to form soluble glucuronides. The parent drug and/or is metabolite are secreted into the bile: most tetracyclines are reabsorbed in the intestine and enter the urine by glomerular filtration. Doxycycline is an exception, since its metabolite is preferentially excreted via the bile into the feces. Thus, unlike other tetracycline, doxycycline can be employed in treating infections in renally compromised patient.

**CLINICAL USES**

Tetracyclines is the drug of choice for:

* Chlamydial infections

Lymphogranuloma venereum: an infectious venereal disease marked progressively by lymph nodes hypertrophy, lymphatic obstruction and elephantiasis of external genitalia.

Psittacosis: Usually takes the form of pneumonia: other clinical; forms include hepatitis, myocarditis and coma.

* Rocky mountain spotted fever

A rickettsial disease characterized by fever, chills, aches in bone and joints.

 Response to tetracyclines is prompt if drug is started early in disease process.

* Mycoplasma pneumonia

common cause of pneumonia in young adults and in people who live in close confines, as in military camps.

Treatment leads to shorter duration of fever cough and malaise

 Treatment with erythromycin also effective

* Cholera

Cholera is caused by *Vibrio cholerae* ingested as part of fecally contaminated food or water

The organism multiplies in the gastrointestinal tract where it secretes and enterotoxin producing diarrhea.

Treatment include doxycycline, which reduces the number of intestinal vibros, fluid replacement.

* Lyme disease

A spirochetal infection cause by *Borrelia burgdorferi*

Infection results in skin lesions, headache, fever, followed by meningoencephalitis and eventually arthritis.

Disease transmitted by bites of infected ticks

**ADVERSE EFFECTS**

1. Gastric discomfort: Epigastric distress commonly results from an irritation of the gastric mucosa and is often responsible for noncompliance in patient treated with this drug. The discomfort can be controlled if the drug is taken with foods other than diary product.
2. Effects on calcified tissue: Deposition in the bone and primary dentition occur during calcification in growing children: this causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.
3. Fatal hypertoxicity: This side effect has been known to occur in pregnant women who receives high doses of tetracycline, especially if they are experiencing pyelonephritis.
4. Phototoxicity: phototoxicity, for example, severe sun burn, occur when the patient receives a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with tetracycline, doxycycline and demeclocycline.
5. Vestibular problems: This side effects (for example, dizziness, nausea, and vomiting) occur with minocycline, which concentrates in the endolymph of the ear and affect function of the ear
6. Pseudotumor cerebri: Benign intracranial hypertension characterized by headache and blur vision may occur in adults. Though discontinuation of the drug reverses the condition, it is not clear whether permanent sequalae may occur.
7. Superinfections: over growth of candida (for example in the vagina) or of resistant staphylococci (in the intestine) may occur.
8. Contraindications: Renally-impaired patient should not be treated with any of the tetracyclines except doxycycline. Accumulation of tetracyclines may aggravate pre-existing azotemia by interfering with protein synthesis, thus promoting amino acid degradation. The tetracycline should not be employed in pregnant or breast-feeding women, or in children under 8 years of age.

**PRECAUTIONS**

* Not used in pregnancy, lactation and in children
* Avoided in patient on diuretics because blood urea may rise
* Use cautiously in patients with renal or hepatic insufficiency
* Injectable tetracycline should not be mixed with penicillin because of inactivation
* Tetracyclines should not be injected intrathecally.