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**17/MHS06/030**

**PHA 302(INTRODUCTORY TO PHAMARCOLOGY AND TOXICOLOGY II)**

1. **Write a named bacterial protein synthesis inhibitor, stating its mechanism of action, indication of use, toxicity and adverse effects.**

**ANSWER**

**A protein synthesis inhibitor** is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins. Compounds which inhibit the synthesis of proteins. They are usually ANTI-BACTERIAL AGENTS or toxins. Mechanism of the action of inhibition includes the interruption of peptide-chain elongation, the blocking the A site of ribosomes, the misreading of the genetic code or the prevention of the attachment of oligosaccharide side chains to glycoproteins.

Antibiotics can inhibit protein synthesis by targeting either the 30S subunit, examples of which include **spectinomycin, tetracycline, and the aminoglycosides kanamycin and streptomycin**, or to the 50S subunit, examples of which include  e.g **erythromycin, clarithromycin and azithromycin**.

* **Chloramphenicol**

Chloramphenicol is a broad-spectrum antibiotic whose spectrum includes several gram-positive and gram-negative bacteria, spirochetes, and Rickettsiae.it is a broad spectrum antibiotic that is effective against a variety of susceptible and serious bacterial infections but is not frequently used because of its high risk of bone marrow toxicity. Chloramphenicol is bacteriostatic because of its capability to inhibit protein synthesis. Chloramphenicol hinders protein chain elongation by peptidyl transferase inhibition of bacterial ribosome.

**Mechanism of action**

* Inhibition of protein synthesis by binding to the 50S bacterial ribosome subunit. Chloramphenicol hinders the transfer of an elongated peptide chain protein synthesis
* Chloramphenicol blocksproper binding of 50S site which, stops protein synthesis.
* It does inhibit mitochondrial ribosomal protein synthesis because these ribosomes are 70S, the same as those in bacteria.
* It hinders the transfer of the elongating peptide chain to the newly attached amino acyl tRNA at the ribosome mRNA complex.
* It specifically attaches to the 50S ribosome and therefore hinder the access of aminoacyl-tRNA to the acceptor for amino acid incorporation
* It prevents formation of peptide bond
* This may be responsible for the dose related anemia caused by chloramphenicol

**Indication of use:**

Because of potential toxicity, bacterial resistance, and the availability of other effective drugs, chloramphenicol may be considered mainly for treatment of serious rickettsial infections, bacterial meningitis caused by a markedly penicillin-resistant strain of pneumococcus or meningococcus, and typhoid fever.

**Pharmacokinetics:**

Following oral administration, chloramphenicol is rapidly and completely absorbed.

It is widely distributed to virtually all tissues and body fluids. The drug penetrates cell membranes readily.

Excretion of active chloramphenicol and of inactive degradation products occurs by way of the urine. A small amount of active drug is excreted into bile or feces.

**Toxicity**

Chloramphenicol (CAP) is a potent and efficient antibiotic used since years against many pathogens. Despite being highly effective, it shows severe toxicity in the form of Aplastic anemia (AA) and bone marrow suppression. Its D – form is the toxic one and inhibits protein synthesis. In living system, CAP is hydrolyzed and absorbed completely. Its excretion is also at a high rate but is highly impaired in disorders associate liver and kidneys. It is metabolized in liver to Chloramphenicol glucuronide. Being highly toxic, it is still prescribed at a noticeable rate. It is recommended to be prescribed to be only when there is no other alternative is present with a monitoring of its concentration in patients body. Chloramphenicol induced hematotoxicity was demonstrated in rats which recovered due to oral administration of coconut water within two weeks.

**Toxicity for newborn infants**:

* Newborn infants lack an effective glucoronic acid conjugation
* Mechanism for the degradation and detoxification of chloramphenicol.
* Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse.

**Adverse Reactions**

* Gastrointestinal disturbances: Adults occasionally develop nausea, vomiting, and diarrhea.
* Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.
* Bone marrow disturbances*: Chloramphenicol commonly causes a dose-related reversible* suppression of red cell production at dosages exceeding 50 mg/kg/d after 1-2 weeks.
* Aplastic anemia is a rare consequence of chloramphenicol administration by any route. It is an idiosyncratic reaction unrelated to dose, though it occurs more frequently with prolonged use. It
* Tends to be irreversible and can be fatal.

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol.