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**PHA 302(PHARMACOLOGY)**

**300LEVEL**

**TETRACYCLINES**

These are a class of antibiotics having a nucleus of four cyclic rings.

All are obtained from soil actinomycetes.The first to be introduced was chlortetracycline in 1948 under the name aureomycin (because of the golden yellow color of S.aureofaciens colonies producing it).It contrasted markedly from penicillin and streptomycin (the other two antibiotics available at that time)in being active orally and in affecting a wide range of micro-organisms- hence called ‘broad-spectrum antibiotic’.Oxytetracycline soon followed;others were produced later,either from mutant strains or semi-synthetically.

All tetracyclines are slightly bitter solids which are weakly water soluble, but their hydrochlorides are more soluble. Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences). The subsequently developed members have high lipid solubility, greater potency and some other differences. The tetracyclines still available in India for clinical use are:

Tetracycline DemeclocyclineOxytetracycline DoxycyclineMinocycline

Many others like Chlortetracycline, Methacycline,Rolitetracycline, Lymecycline are no longer

commercially available.

***Mechanism of action***

The tetracyclines are primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism. Subsequent to such binding, attachment of aminoacyl-t-RNA to the mRNA-ribosome complex is interferred . As a result, the peptide chain fails to grow.The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly. In gramnegative bacteria tetracyclines diffuse throughporin channels as well. The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency). The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less sensitive to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.

***Pharmacokinetics***The older tetracyclines are incompletely absorbed from g.i.t.; absorption is better if taken in empty stomach. Doxycycline and minocycline are completely absorbed irrespective of food.Tetracyclines have chelating property—form insoluble and unabsorbable complexes with calcium and other metals. Milk, iron preparations, nonsystemic antacids and sucralfate reduce their absorption. Administration of these substances and tetracyclines should be staggered, if they cannot be avoided altogether.Tetracyclines are widely distributed in the body (volume of distribution > 1 L/kg). Variable degree of protein binding is exhibited by different members. They are concentrated in liver, spleen and bind to the connective tissue in bone and teeth. Intracellularly, they bind to mitochondria. Minocycline accumulates in body fat. The CSF concentration of most tetracyclines is about 1/4 of plasma concentration, whether meninges are inflamed or not.Most tetracyclines are primarily excreted in urine by glomerular filtration; dose has to be reduced in renal failure; doxycycline is an exception to this. They are partly metabolized and significant amounts enter bile—some degree of enterohepatic circulation occurs. They are secreted in milk in amounts sufficient to affect the suckling infant.Enzyme inducers like phenobarbitone and phenytoin enhance metabolism and reduce the t½ of doxycycline.

***Administration***

Oral capsule is the dosage form in which tetracyclines are most commonly administered. The capsule should be taken ½ hr before or 2 hr after food. Dry syrups and other liquid oral preparations have been banned and discontinued to discourage use in children.Tetracyclines are not recommended by i.m. route because it is painful and absorption from the injection site is poor. Slow i.v. injection may be given in severe cases, but is rarely required now.A variety of topical preparations (ointment, cream, etc.) are available, but should not be used, because there is high risk of sensitization.However, ocular application is not contraindicated.

***Adverse effects*Irritative effects:** Tetracyclines can cause epigastric pain, nausea, vomiting and diarrhoea by their irritant property. The irritative diarrhoea is to be distinguished from that due to superinfection. Esophageal ulceration has occurred by release of the material from capsules in the esophagus during swallowing, especially with doxycycline. Intramuscular injection of tetracyclines is very painful; thrombophlebitis of the injected vein can occur, especially on repeated use.

**Dose related toxicity*1. Liver damage :***Fatty infiltration of liver and jaundice occurs occasionally. Oxytetracycline and tetracycline are safer in this regard. Tetracyclines are risky in pregnant women; can precipitate acutehepatic necrosis which may be fatal.

***2. Kidney damage:*** It is prominent only in the presence of existing kidney disease. All tetracyclines, except doxycycline, accumulate and enhance renal failure. A reversible Fancony syndrome like condition is produced by outdated tetracyclines due to proximal tubular damage caused by degraded products—epitetracycline, anhydrotetracycline and epianhydrotetracycline. Exposure to acidic pH, moisture and heat favours such degradation.

***3. Phototoxicity:*** A sunburn-like or other severe skin reaction on exposed parts is seen in some individuals. A higher incidence has been noted with demeclocycline and doxycycline. Distortionof nails occur naturally.

***4. Teeth and bones :***Tetracyclines have chelating property. Calcium-tetracycline chelate getsdeposited in developing teeth and bone. Given from midpregnancy to 5 months of extrauterinelife, the deciduous teeth are affected: brown discolouration, ill-formed teeth, more susceptibleto caries. Tetracyclines given between 3 months and 6 years of age affect the crown of permanentanterior dentition. Repeated courses are more damaging.Given during late pregnancy or childhood, tetracyclines can cause temporary suppression of bone growth. The ultimate effect on stature is mostly insignificant, but deformities and reduction in height are a possibility with prolonged use.

***5. Antianabolic effect:*** Tetracyclines reduce protein synthesis and have an overall cataboliceffect. They induce negative nitrogen balance and can increase blood urea.

***6. Increased intracranial pressure*** is noted in some infants.

***7. Diabetes insipidus*** Demeclocycline antagonizes ADH action and reduces urine concentrating ability of the kidney. It has been tried in patients with inappropriate ADH secretion.

***8. Vestibular toxicity*** Minocycline has produced ataxia, vertigo and nystagmus, which subsidewhen the drug is discontinued.

***Hypersensitivity:*** This is infrequent with tetracyclines. Skin rashes, urticaria, glossitis, pruritusani and vulvae, even exfoliative dermatitis have been reported. Angioedema and anaphylaxis areextremely rare. Complete cross sensitization is exhibited by different tetracyclines.

***Superinfection:*** Tetracyclines are the most common antibiotics responsible for superinfections,because they cause marked suppression of the resident flora.Though mouth, skin or vagina may be involved, intestinal superinfection by Candida albicansis most prominent (details see p. 672); pseudomembranous enterocolitis is rare but serious.Higher doses suppress flora more completely— greater chance of superinfection: doses on thelower side of the range should be used whenever possible. The tetracycline should be discontinued at the first sign of superinfection and appropriate therapy instituted.

Doxycycline and minocycline are less liable to cause diarrhoea, because only small amounts reach the lower bowel in the active form.

***Uses***Although tetracyclines are broad-spectrum antibiotics, they should be employed only for thoseinfections for which a more selective and less toxic AMA is not available. Clinical use of tetracyclineshas very much declined due to availability of fluoroquinolones and other efficacious AMAs.***1. Empirical therapy:*** Tetracyclines are often employed when the nature and sensitivity of theinfecting organism cannot be reasonably guessed, but they are not dependable for empiricaltreatment of serious/life-threatening infections.They may also be used for initial treatment of mixed infections, although a combination of β-lactam and an aminoglycoside antibiotic or a third generation cephalosporin or a fluoroquinoloneare now preferred.

***2. Tetracyclines are the first choice drugs:*** despite development of resistance by manorganisms in:

**a) Venereal diseases:**• Chlamydial nonspecific urethritis/endocervicitis:7 day doxycycline treatment is as effective as azithromycin single dose.• Lymphogranuloma venereum: resolves in 2–3 weeks (see Table 54.1).• Granuloma inguinale: due to Calymm. granulomatis: a tetracycline administered for3 weeks is the most effective treatment.

**(b) Atypical pneumonia:** due to Mycoplasma pneumoniae: duration of illness is reduced bytetracycline therapy. Psittacosis is treated in 2 weeks by tetracyclines.

**(c) Cholera:** Tetracyclines have adjuvant value by reducing stool volume and limiting the durationof diarrhoea.

**(d) Brucellosis:** Tetracyclines are highly efficacious; cause rapid symptomatic relief; therapy of choiceis doxycycline 200 mg/day + rifampin 600 mg/day for 6 weeks. Gentamicin may be combinedwith doxycycline in acute cases.

**(e) Plague:** Tetracyclines are highly effective in both bubonic and pneumonic plague. They arepreferred for blind/mass treatment of suspected cases during an epidemic, though streptomycinoften acts faster.

**(f) Relapsing fever:** due to Borrelia recurrentis responds adequately.

**(g) Rickettsial infections:** typhus, rocky mountain spotted fever, Q fever, etc. respond dramatically.

Chloramphenicol is an alternative.

***3. Tetracyclines are second choice drugs:***(a) To penicillin/ampicillin for tetanus, anthrax, actinomycosis and Listeria infections.(b) To ceftriaxone, amoxicillin or azithromycin for gonorrhoea, especially for penicillin resistantnon-PPNG; also in patients allergic to penicillin,but response rate has decreased.(c) To ceftriaxone for syphilis in patients allergic to penicillin; early syphilis can be treated in 2weeks but late syphilis requires 1 month.(d) To penicillin for leptospirosis; doxycycline 100mg BD for 7 days is curative. Weekly doxycycline(200 mg) has been used as prophylactic in subjects at risk during an epidemic.

(e) To azithromycin for pneumonia due to Chlamydia pneumoniae. Oral as well as topicaltetracycline has been used in trachoma.(f) To ceftriaxone/azithromycin for chancroid.(g) To streptomycin for tularemia.

***4. Other situations in which tetracyclines may be used are:***(a) Urinary tract infections: Odd cases in which the organism has been found sensitive.(b) Community-acquired pneumonia, when a more selective antibiotic cannot be used.(c) Amoebiasis: along with other amoebicides for chronic intestinal amoebiasis.(d) As adjuvant to quinine or sulfadoxinepyrimethamine for chloroquine-resistant P. falciparum malaria (see p. 792).(e) Acne vulgaris: prolonged therapy with low doses may be used in severe cases (since Propionibacterium acnes is sensitive to tetracyclines), but simpler treatments are preferred in most cases.(f) Chronic obstructive lung disease: prophylactic use may reduce the frequency of exacerbations,but the risk : benefit ratio is controversial.