Chapter 3

Drug Profile

3.0 DRUG PROFILE

3.1 Amoxicillin trihydrate

Amoxicillin is official in Indian Pharmacopoeia (IP, 2007), United States Pharmacopeia (USP, 2007) and British Pharmacopoeia. It is white or almost white crystalline powder. It is slightly soluble in water, in ethanol and in methanol. It is practically insoluble in chloroform and in fixed oils. It is soluble in dilute solution of acids and alkali hydroxides (IP, 2007).

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically, it is (2*S*,5*R*,6*R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. It may be represented structurally as:

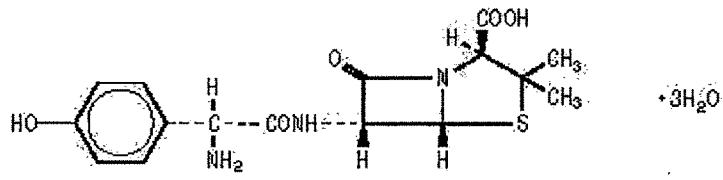

Fig 3.1 Structure of Amoxicillin

Molecular formula of amoxicillin is $C_{16}H_{19}N_3O_5S$. $3H_2O$ and the molecular weight is 419.45.

Amoxicillin is stable in the presence of gastric acid and is rapidly absorbed after oral administration. Amoxicillin diffuses readily into most body tissues and fluids, with the exception of brain and spinal fluid, except when meninges are inflamed. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid. In blood serum, amoxicillin is approximately 20% protein-bound. Amoxicillin may be taken every 8 hours or every 12 hours, depending on the strength of the product prescribed. Orally administered doses of amoxicillin result in average peak blood levels 1 to 2 hours after administration (Sweetman, 2005)

Mode of action:

Amoxicillin is bactericidal in action against susceptible micro-organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide.

Amoxicillin is a penicillin-type antibiotic used to treat a wide variety of bacterial infections. It works by stopping the growth of bacteria. This antibiotic treats only bacterial infections. It does not not work for viral infections (e.g., common cold, flu). Unnecessary use or overuse of any antibiotic can lead to its decreased effectiveness. It is indicated in the treatment of infections due to susceptible (only β-lactamase- negative) strains of the designated microorganisms responsible for infections of the ear, nose, throat, genitourinary tract, skin and skin structure, and lower respiratory tract. It is also indicated for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence. (www.rxlist.com)

Cooreman et al measured amoxicillin concentration in gastric mucosa after its oral administration. After 60 min of oral administration of amoxicillin in the form of tablet, amoxicillin concentration in mucus was found below minimum bactericidal concentration. Results of this study show that incomplete elimination and high recolonization rate of H.pylori may be due to insufficient (subbactericidal) local concentrations at the desired site of action of amoxicillin that is highly effective in vitro against H.Pylori (Cooreman et al., 1993).

Systemic distribution of amoxicillin is of little importance for its activity against H. pylori. The MICs for 50% and 90% of H. pylon strains are 0.06 and 0.12 μg/ml, respectively and the MBC_{90} is 0.25 μg/ml (Cooreman et al., 1993). At concentrations above 0.03 μg/ml there was no regrowth and H.pylori did not show resistance (Sorberg et al., 1998). Amoxicillin MIC for different H.Pylori strains vary from 0.06 μg/ml to 2.0 μg/ml (Hasan et al., 1999).

Shah et al (Shah et al., 1999) have reported that the permeability coefficient of amoxicillin was 5.5×10^{-6} cm per second through gastric fluid and 2.3×10^{-6} cm per second through gastric mucin. Assuming that the permeability coefficient of amoxicillin is approximately the same in gastric mucus, the drug would penetrate a 200-μm layer in 2.4 hours. (Umamaheshwari et al., 2004).

3.2 Levofloxacin hemihydrate

Levofloxacin is official in Indian Pharmacopoeia. It is yellowish white to yellowish powder. It is slightly soluble in methanol, sparingly soluble in acetic acid and chloroform and soluble in dilute sodium hydroxide solution. (IP, 2007).

Levofloxacin is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically it is a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

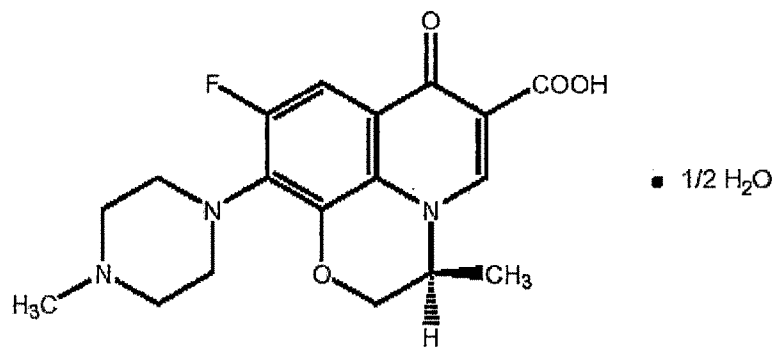

Fig 3.2 Structure of Levofloxacin

The empirical formula is $C_{18}H_{20}FN_4.½\ H_2O$ and the molecular weight is 370.38. The molecule exists as a zwitterion at the pH conditions in the small intestine. Solubility of levofloxacin is approximately 100 mg/ml from pH 0.6 to 5.8. Levofloxacin is considered soluble to freely soluble in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/ml) and is considered freely soluble in this range. Above pH 6.7, the solubility decreases and reaches a minimum value of about 50 mg/mL at a pH of approximately 6.9.

Pharmacokinetics

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of levofloxacin is approximately 99%, demonstrating complete oral absorption.

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L It reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. It is mainly bound to serum albumin and its binding to serum proteins is independent of the drug concentration. Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. It undergoes limited metabolism and is primarily excreted as unchanged drug in the urine. Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life ranges from approximately 6 to 8 hours following single or multiple doses given orally or intravenously.

Mechanism of action

Like other fluoroquinolone anti-infectives, levofloxacin inhibits DNA synthesis in susceptible organisms via inhibition of type II DNA topoisomerases (DNA gyrase, topoisomerase IV).

Levofloxacin plus rabeprazole combination is as effective as triple drug treatment (amoxicilin, clarithromycin and rabeprazole) in eradicating H.pylori infection. It has the advantage of using only 2 drugs which might increase adherence to treatment, and an antibiotic with less known resistance (Prado and Loy-Gerala, 2006). After first and second line therapy failure, one week triple regimen with omeprazole, amoxicillin and levofloxacin was tried and H. pylori eradication was obtained in 90% of the subjects (Bytzer and Morain, 2005).

3.3 Clarithromycin

Clarithromycin is official in Indian Pharmacopoeia (IP, 2007), United States Pharmacopeia and British Pharmacopoeia. It is a white to off-white crystalline powder.It is practically insoluble in water, slightly soluble in methanol and soluble in acetone and methylene chloride (IP, 2007).

Clarithromycin is a semi-synthetic macrolide antibiotic. Chemically, it is 6- 0-methylerythromycin. The molecular formula is $C_{38}H_{69}NO_{13}$, and the molecular weight is 747.96. The structural formula is:

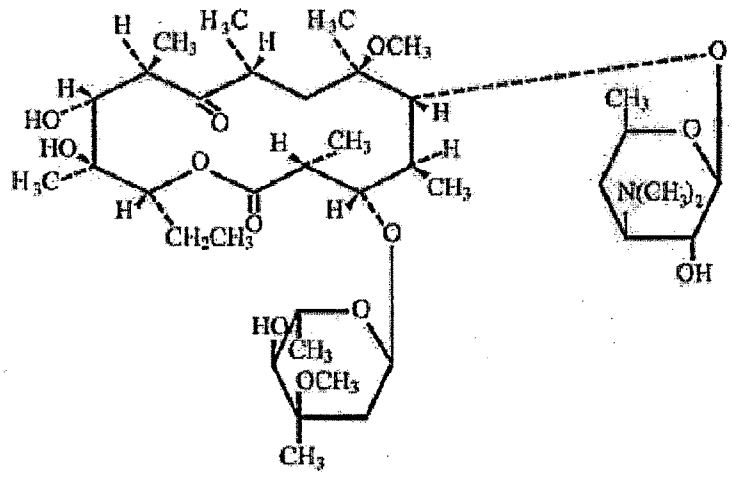

Fig 3.3 Structure of Clarithromycin

Pharmacokinetics

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. Food slightly delays the onset of clarithromycin absorption, increasing the peak time from approximately 2 to 2.5 hours. Food also increases the clarithromycin peak plasma concentration by about 24%, but does not affect the extent of clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve. Therefore, clarithromycin tablets may be given without regard to food. The elimination half-life of clarithromycin is about 5 to 7 hours and elimination half life of the principal metabolite, 14-OH clarithromycin, is 7 to 9 hours.

Mechanism of action

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis. Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms as well as most Mycobacterium avium complex microorganisms.

Clarithromycin MIC for different H.Pylori strains vary from 0.03 μg/ml to 4.0 μg/ml (Hasan et al., 1999; Sorberg et al., 1998).