CHAPTER II

REVIEW OF CIPROFLOXACIN

1. <u>Physicochemical Properties</u> (McEvoy, ed., 1989; The United States Pharmacopoeial convention, Inc. 1990)
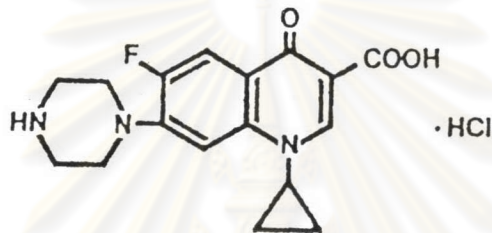

Figure 1 structural formula of ciprofloxacin

Chemical name   3-Quinolone carboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride

Ciprofloxacin likes other fluoroquinolone (Norfloxacin, Ofloxacin), contains a piperazine group at position 7 of the 4-quinolone nucleus which results in antipseudomonal activity. The drug also contains a cyclopropyl group at position 1, which enhances antimicrobial activity.

Empirical formula $C_{17}H_{18}FN_3O_3.HCl.H_2O$

Molecular weight   385.82

Description   faintly yellowish to yellow crystalline powder

Solubility   36 mg/ml in water at 25° C

pKa   6, 8.8

2. Mechanism of Action

Ciprofloxacin usually is bactericidal in action (McEvoy, ed., 1989). The primary antibactericidal activity is the inhibition of bacterial DNA gyrase (topoisomerase II). This particular enzyme is crucial to bacterial growth and reproduction (White, 1986). The target of ciprofloxacin appears to be the A subunit of this enzyme, which introduce staggered single strand DNA incisions on the bacterial chromosome and then reseal the DNA (McEvoy, ed., 1989 ; Smith, 1984). There is some evidence that ciprofloxacin may also interact with the B subunits of the enzymes (McEvoy, ed.). Results of some studies suggest that, rather than binding to this toporisomerase, quinolones may bind to specific sites on the DNA molecules and then prevent the enzyme from functional properly (McEvoy, ed.).

Some authors have shown a correlation between inhibition of gyrase-dependent supercoiling and MIC values for various quinolones. However such a correlation was not always found (Campoli-Richards et al., 1988). Thus mechanisms other than DNA gyrase inhibition may also be involved in determining the potency of these drugs. Differences in the ability of quinolones to permeate bacteria may be important, too (Campoli-Richards et al.).

3. In Vitro Activity

Ciprofloxacin has a broad spectrum of activity. In vitro on a weight basis, ciprofloxacin generally is at least 2 times more active against susceptible organisms than norfloxacin.

Ciprofloxacin is active in vitro against most gram-negative aerobic bacteria, including Enterobacteriaceae and *Pseudomonas aeruginosa*. Ciprofloxacin also is active in vitro against many gram-positive aerobic bacteria, including penicillinase-producing, nonpenicillinase-producing and methicillin-resistant Staphylococci, although many strains of streptococci are relatively resistant to the drug. The drug generally is less active against gram-positive than gram-negative bacteria. Many of obligately anaerobic bacteria are resistant to ciprofloxacin. Ciprofloxacin also have some activity in vitro against Chlamydia, Mycoplasma, Mycobacterium, Plasmodium, and Rickettsia. Ciprofloxacin is inactive against fungi (McEvoy, ed., 1989; Campoli-Richards et al., 1988).

4. Bioavailability and Pharmacokinetics of Oral Ciprofloxacin

Absorption :

Ciprofloxacin hydrochloride is rapidly and well absorbed from the GI tract following oral administration with a range of absorption rate of 1.54-3.37 hour^{-1}. Peak serum concentration occured between 1.0-1.25 hours after each dose and ranged from 1.04-1.59 mcg/ml. (Bergan et al., 1986; Borner et al., 1986; Brittain et al., 1985). The mean peak concentrations increased in proportion to dose within the normal therapeutic dose range. The total area under the plasma concentration-time curves (AUC) were also proportional to dose (Tartoaglione et al., 1986). As the oral dose increased a slight increase was observed in the apparent time lag (T_{lag}) before absorption from approximately 0.3 hours after 100 mg to approximately 0.5 hours after 1000 mg.

Present of food in the GI tract decreases the rate but not the extent of absorption of the drug (McEvoy, ed., 1989). Antacids containing magnesium hydroxide and/or aluminium hydroxide with ciprofloxacin leads to a reduction in the bioavailability of the quinolone with little effect on the absorption rate (McEvoy, ed.; Campoli-Richards et al., 1988).

Distribution :

Ciprofloxacin widely distributed into body tissues and fluids. Compared with serum concentrations in the same patients, the peak concentration of ciprofloxacin was very high in various tissues and fluids such as bile, kidney, gallblader and liver tissues. The high intracellular concentration resulting from ion trapping (McEvoy, ed. 1989; Campoli-Richards, 1988).

Ciprofloxacin is 16.4-28.1% bound to serum proteins in independent of both concentration and pH (Joos et al 1985).

It is not known whether ciprofloxacin crosses the placenta or is distributed into human milk. The drug is distributed into the milk of rats (McEvoy, ed., 1989).

Elimination :

Ciprofloxacin is slightly showed first-pass effect (McEvoy ed., 1989; Campoli-Richards, 1988). The drug is partially metabolized in the liver by modification of the piperazinyl group to at least 4 metabolites such as desethyleneciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3) and N-formylciprofloxacin (M4).

The serum elimination half-life of ciprofloxacin in adults with normal renal function is 2.79- 5.33 hours. It is independent of dose or duration of administration (Campoli-Richards et al., 1988).

Ciprofloxacin and its metabolites are excreted in urine and feces. Unchanged ciprofloxacin is excreted in urine by both glomerular filtration and tubular secretion (Tartaglione et al., 1986). The amount of drug excreted in urine within 24 hours as unchanged drug and metabolites were 15-50% and 10-15%, respectively, 20-40% of the drug is excreted in feces as unchanged drug and metabolites within 5 days. Most of unchanged drug in feces appears to result from biliary excretion.

5. Therapeutic Indications

Urinary Tract Infections :

The quinolones class of antibiotics has previously been used for the treatment of urinary tract infections. Ciprofloxacin represents a distinct advance because of its excellent activity, particularly against problem gram-netative bacilli often resistant to β-lactam and aminoglycoside antibiotics (Ramirez et al., 1985).

The study in female patients with uncomplicated urinary tract infections for 5 days showed that ciprofloxacin is a useful drug in the short term treatment (Boerema, Willems and Grob, 1989). In comparative studies, ciprofloxacin versus co-trimoxazole in the treatment of patients with complicated urinary tract infections showed no differences in efficacy between two drugs (Boerema,

Willems and Verheggen, 1989; Williams and Grureberg, 1986), also in geriatric patients (Newsom, Murphy and Matthews, 1986).

Some clinicians suggest that ciprofloxacin be reserved for the treatment of complicated UTIS especially those caused by multidrug-resistant bacteria, and that the drug generally not be used in the treatment of uncomplicated UTIS unless more commonly employed urinary anti-infectives are likely to be ineffective or other equally effective, less expensive anti-infective agents are contraindicated or not tolerated (McEvoy. ed., 1989).

Lower Respiratory Tract Infection

Ciprofloxacin is used in adults for the treatment of lower respiratory tract infections and the drug has been most effective in the treatment of respiratory tract infections caused by *Haemophilus Influenza* or *Bacteroid catarrhalis* (McEvoy, ed., 1989). However it should not be currently considered as the agent of first choice for Pneumonia acquired in the community (Neu, 1987).

Bronchopulmonary infection, especially *Ps. aeruginosa*, is the major cause of morbidity and mortality in cystic fibrosis patient. Oral ciprofloxacin used alone appears to be effective as parenteral regimens using azlocillin and either gentamicin or tobramycin for the short term treatment of acute exacerbations of *Ps. aeruginosa* infections in cystic fibrosis patients (Bosso, Black and Matsen, 1987; Hodson et al., 1987). However this drug should not be advocated for long term use, it should be alternated with other antibiotics because continued use

of ciprofloxacin in this disease has resulted in major increases in MICS (Neu, 1987).

Skin and Soft Tissue Infections

There are many agents available to treat streptococcal skin infections but with gram-negative species it would be useful to have agents to replace the parenteral drugs such as aminoglycosides or cephalosporins. The results obtained from the comparative studies suggest that oral ciprofloxacin in the 750 mg dose twice a day was as effective as parenteral cefotaxime for the treatment of skin and skin structure infections (Ramirez-Ronda, Saavedra and Rivera-Vazquez, 1987; Self et al., 1987).

Gastro intestinal infections :

There has been increased resistance of Samonella, Shigella and other pathogens to many of the antimicrobial agents used to treat diarrheal disease. Quinolones have excellent antibacterial activity against all of the diarrheal pathogens (Neu, 1987).

In comparative placebo controlled studies, 5 days' administration of ciprofloxacin 500 mg twice daily was evaluated for efficacy in acute diarrhea. Both ciprofloxacin and co-trimoxazole were effective in treating mild to moderate and moderate to severe disease and both were well tolerated (Ericsson, 1987; Pichler et al., 1987; Dupont, 1987).

Sexually Transmitted Diseases :

A single 100, 250, 500 mg oral dose of ciprofloxacin has been effective when used alone in men for the treatment of uncomplicated urethral gonorrhea caused by penicillinase and non-penicillinase-producing *Neisseria gonorrhoeae* (Aznar et al, 1986; Loo, Ridgway and Oriel, 1985; Shahmanesh et al., 1986). Single dose ciprofloxacin in therapy for gonorrhea generally is ineffective in the treatment of coexisting chlamydial or mycoplasmal infections and generally does not prevent postgonococcal urethritis (Loo, Ridgway and Oreil, 1985; Fong et al.,1987; Roddy, Handsfield and Hook, 1986; Shahmanesh et al., 1986).

Comparative trial of single dose ciprofloxacin and ampicillin plus probenecid showed the equal efficacy against uncomplicated gonococcal urethritis (Roddy, Handsfield and Hook, 1986). The efficacy of ciprofloxacin 750 mg twice daily for 7 days was compared with that of doxycycline 100 mg twice daily for 7 days in the treatment of nongonococcal urethritis. The cure rates of *Ureaplasma urealyticum* were more favorable trend in the ciprofloxacin group but in patients with chlamydial infections, ciprofloxacin was less effective than doxycycline (Fong et al., 1987).

Ciprofloxacin has been used successfully to treat chancroid caused by *Hemophilus ducreyi*. If resistance to trimethoprim-sulfamethoxazole becomes widespread, ciprofloxacin may become a first-line therapy for chancroid (Naamara et al., 1987)

Bone and Joint Infections :

Ciprofloxacin is used in adults for the treatment of bone and joint infections, including osteomyelitis, caused by susceptible organism (McEvoyed, 1989; Neu, 1987). The availability of a quinolone is a major advance in the treatment of methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Ps.* aeruginosa osteomyelitis of the sternum and lower extremities. Clindamycin, metronidazole, penicillin, or amoxicillin and clavulanate potassium has seen given concomittantly with ciprofloxacin if there was a possibility that one of the causative organisms was resistant to ciprofloxacin (McEvoy ed., 1989).

6. Review of Safety Study, Adverse Reaction and Precaution

The incidence of side effects related to treatment with ciprofloxacin is low. In general, this drug appears to be safe and well tolerated with an overall incidence of adverse effect of 5-25% which most are mild to moderate. Therapy had to be discontinued in less than 2% of patient (McEvoy, ed., 1989; Smith, 1987).

Adverse gastrointestinal symptoms occur most commonly up to 10% of patients. The GI symptoms are comprised of nausea, vomitting, diarrhoea and abdominal pain, but are generally mild and transient.

CNS effects such as anxiety, nervousness, insomnia, euphoria and tremor are reported by 1-4% of patients receiving the drug but are usually also mild (McEvoy,

ed., 1989; Smith, 1987). These adverse effects are reversible when therapy is discontinued.

Ciprofloxacin is not recommended for use in children because it inhibits the growth of juvenile cartilage as well as causing cartilage alteration and arthropathy in animal (Campoil-Richards et al., 1988; McEvoy, ed., 1989; White, 1986). Also in pregnant or lactating women, ciprofloxacin is not recommended because of finding of arthropathy in immature animals (Campoli-Richards, 1988).

7. <u>Dosage</u> (Campoli-Richards et al., 1988; McEvoy, ed., 1989)

For the treatment of urinary tract infections, the usual adult oral dosage of ciprofloxacin for mild to moderate infections is 250 mg and for complicated infections is 500 mg, every 12 hours.

The usual adult dosage for mild to moderate lower respiratory tract, skin and skin structure, or bone and joint infections is 500 mg every 12 hours. If infections are severe or complicated, a dosage of 750 mg every 12 hours may be needed.

For infectious diarrhoea, the usual adult oral dosage is 500 mg every 12 hours.

In general, treatment is usually continued for at least 2 days after the sign and symptoms of infection have disappeared, with 7 to 14 days being the most common duration of therapy.

Dosage adjustment for altered renal function is usually not required unless creatinine clearance is 20 ml/min or less.