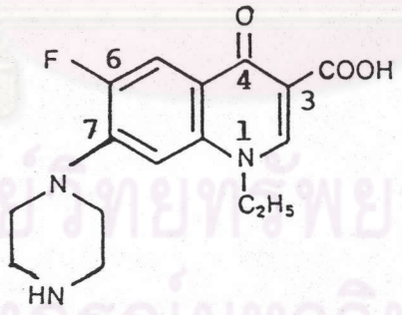
CHAPTER II

REVIEW OF LITERATURE

1. Physicochemical Properties

Norfloxacin is a quinolone carboxylic acid derivative. Its chemical name is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. In comparison with nalidixic acid, norfloxacin has a quinolone ring instead of a 1,8 napthyridine molecule. The addition of a 1-piperazinyl group at the 7 position of the quinolone ring confers antipseudomonal activity. (Marble and Bosso, 1986; McEvoy, ed., 1989). This activity is improved when a fluorine atom is added at the 6 position of the quinolone ring . (Figure 1)



1-ETHYL-6-FLUORO-1,4 DIHYDRO-4-OXO-7-
(1-PIPERAZINYL)-3-QUINOLINE-CARBOXYLIC ACID

NORFLOXACIN

Figure 1 Structural formula of norfloxacin

Empirical formula : $C_{16}H_{18}FN_3O_3$

Molecular Weight : 319.34

Description : Norfloxacin occurs as a white to pale yellow, crystalline powder

Solubility : Norfloxacin is very slightly soluble in water and in alcohol , having solubilities of approximately 0.28 mg/ml and 1.9 mg/ml, respectively,at 25 °C. Although the drug is relatively insoluble in aqueous solutions with neutral pH, it is generally soluble in solutions with acidic or basic pH. Solubility of norfloxacin in urine depends on pH and temperature. The drug is least soluble in urine at pH 7.5 , the maximum solubilities at 25 °C and 37 °C are approximately 0.45 and 1.2 mg/ml, respectively. At 37 °C, the solubility of the drug in urine is greater than 40 mg/ml at pH 5.5 or less. As the pH is increased to 6.5, 7 and 8, the solubility of the drug is decreased to be 2.8, 1.5 and 1.9 mg/ml, respectively. Norfloxacin has a pK_a values of 6.34 and 8.75.

2. Mechanism of Action

Norfloxacin is usually bactericidal in action. Unlike penicillins and cephalosporins , it exerts its action intracellularly in bacteria (Crumplin, Kenwright and Hirst, 1984). It is thought to specifically inhibit the A-Subunit of the enzyme DNA gyrase , which appears to

be essential for DNA replication (Crumplin et al., 1984). Result of some studies suggest that, rather than binding to this enzyme ,the drug may bind to specific sites on the DNA molecule and then prevent the enzyme from functioning properly (McEvoy, ed., 1989).

Alternative theories, regarding the mechanism of antibacterial action of the fluoroquinolones have also been postulated. Zweerink and Edison (1986) studied the activity of fluoroquinolones, including norfloxacin, on M. luteus DNA gyrase. They noted that the potency of the fluoroquinolones as DNA gyrase inhibitors did not always correlate with their antimicrobial potency. This suggested that other factors, such as penetration of the drug into the bacterial cell, were important for fluoroquinolone activity.

3. **In Vitro Activity**

Norfloxacin has a broader spectrum of activity. It is active in vitro against most gram-negative aerobic bacteria, including *Enterobacteriaceae* and *Pseudomonas aeruginosa*. The drug is also active in vitro against many gram-positive aerobic bacteria, including penicillinase-producing, non penicillinase-producing , and methicillin-resistant staphylococci, although many strains of streptococci are relatively resistant to the drug. Obligately anaerobic bacteria are generally resistant to norfloxacin. The drug has some activity

against Chlamydia, Mycoplasma, and some Mycobacterium, but it is inactive against fungi and viruses (Holmes, Brodgen and Richards, 1985; McEvoy, ed., 1989).

4. Bioavailability and Pharmacokinetics of Oral Norfloxacin

Absorption :

Norfloxacin is rapidly, but incompletely absorbed. Following oral administration , 30 to 40 percent of the norfloxacin dose is rapidly absorbed from the gastrointestinal tract with a mean absorption rate of 3.22 $hour^{-1}$ (range from 1.8-5.54 $hour^{-1}$) (Adhami et al., 1984; Neuman, 1988) Approximately 1-2 hours (T_{max}) after a 400- mg oral dose, peak serum levels of 1.5 to 2.0 µg/ml are achieved (Swanson et al., 1983; Adhami et al., 1984). Although doses of norfloxacin between 200 and 800 mg result in linear increases in the peak serum level and area under the plasma concentration- time curve , dosages greater than 800 mg produce nonlinear increases in these parameters (Swanson et al., 1983). Similarly with higher doses, the T_{max} is slightly delayed. It is not entirely known how the presence of food in the gastrointestinal tract affects absorption of the drug .

Distribution :

The drug is widely distributed throughout the body, achieving high ratios of tissue to serum concentrations in both renal and prostatic tissue . Low protein binding (14 %) and high lipid solubility of norfloxacin result in a large volume of distribution (Adhami et al., 1984; Gilfillan et al., 1984). Extrapolation of volume of distribution data from animal studies to man suggests the values around 25 to 35 L , but the volume of distribution may prove to be much higher (Shimada et al., 1983). The mean serum elimination half-life in normal volunteer ranged from three to seven hours (Swanson et al., 1983; Eandi et al., 1983; Adhami et al., 1984). The variability in the observed serum half-life may be due to the fact that the elimination of norfloxacin is not strictly log-linear with time (Wise, 1984).

Metabolism :

The liver appears to be the primary site of norfloxacin metabolism,whereas the urine is the major route of excretion . Six metabolites of norfloxacin , which contain modifications of the piperazinyl ring and are excreted unconjugated in the urine , several appear to be microbiologically active (Stein, 1987).

Excretion :

Approximately 29 percent of a single 400 mg dose of norfloxacin is recovered in the feces over a 48-hour period (Cofsky, DuBouchet and Landesman, 1984). Renal clearance of norfloxacin is high (272 to 296 ml/min) and urinary drug concentrations range from 100 to 300 times the simultaneous serum concentration (Swanson et al., 1983).

High renal clearance (both glomerular filtration and active tubular secretion) and a long elimination half-life result in sustained therapeutic levels of drug in the urine for 12 to 24 hours following administration of 400 mg oral dose (Stein, 1987). Approximately 30 percent of an oral dose is excreted unchanged in the urine (Swanson et al., 1983; Shimada et al., 1983; Gilfillan et al., 1984). The presence of a reduced glomerular filtration rate increases the elimination half-life. Dosage modification is, therefore, necessary when the glomerular filtration rate falls below 20 ml/minute.

5. **Therapeutic Indications**

Urinary Tract Infections

Norfloxacin appears to share all the potential advantages of nalidixic acid. Its spectrum includes essentially all urinary pathogens ,including *Pseudomonas*

aeruginosa and *Streptococcus faecalis*, which are intrinsically resistant to nalidixic acid (Haase et al., 1983).

In controlled studies in men and women with uncomplicated UTIS 7-10 days of oral norfloxacin therapy was at least as effective as co-trimoxazole but with fewer adverse effects (Guerra et al., 1983; Glamorellou et al., 1983; Goldstein, Alpert and Ginsberg, 1985; Sabbaj, Haogland and Shih, 1985). Oral norfloxacin has also been at least as effective as oral amoxycillin when used in men and women , including geriatric individuals (Vogel et al., 1984). The extended coverage of gram negative such as *Pseudomonas aeruginosa* makes norfloxacin an excellent choice in the treatment of complicated urinary tract infections such as in patients with renal calculi or neurogenic bladders, thus avoiding the use of aminoglycosides with their potential for nephrotoxicity and the need for parenteral treatment and hospitalization (Clair, Robert and Christine, 1987).

Gonorrhea and Associated Infections

Norfloxacin has been used alone for the treatment of uncomplicated gonorrhea in adults. In several studies in both men and women, a single 800 mg oral dose of norfloxacin was effective for the treatment of uncomplicated urethral and/or anorectal gonorrhea caused by penicillinase- or nonpenicillinase- producing

Neisseria gonorrhea (Romanowski et al., 1986; Wang et al., 1986). Results of study in men with uncomplicated gonorrhea indicate that oral norfloxacin (two 600 mg doses given 4 hours apart) may be as effective as intramuscular administration of spectinomycin (a single 2-g dose) for the treatment of gonorrhea caused by penicillinase- or non penicillinase-producing *N. gonorrhea* (Crider et al., 1984). Another comparative study shows that single dose norfloxacin has similar cure rate as single dose ampicillin and probenecid (Kalpowitz et al., 1984). However, it has been ineffective when used in men for the treatment of acute nongonococcal urethritis caused by *Chlamydia trachomatis* (McEvoy, ed., 1989).

Prophylaxis of Sepsis in Neutropenic Patients

Norfloxacin was selected for oral antibiotic prophylaxis in granulocytopenic patients because the antibacterial spectrum of the drug covers most of the aerobic pathogens that may potentially colonize the gastrointestinal tract while sparing the anaerobic flora. Comparative study with placebo , vancomycin - polymyxin, and co-trimoxazole showed that norfloxacin treatment was well tolerated and was not associated with any serious systemic adverse effects. Moreover, norfloxacin could prevent acquisition of gram-negative bacillary organisms (Gadebusch et al., 1982).

Gastrointestinal Infections

Several results of clinical trials (Holmes et al.,1985; Marble and Bosso,1986; Wang et al., 1986; McEvoy, ed., 1989) reported herein offer strong evidence that norfloxacin is as effective as co-trimoxazole in the treatment of acute diarrhea and prophylaxis for traveller's diarrhea in adults travelling for relatively short period of time to high-risk area (Johnson et al., 1984).

6. Review of Safety Studies, Adverse Reactions and Precautions

Norfloxacin is an ideal antibacterial agent by killing bacteria while sparing host cells because human cells lack bacterial enzyme, DNA gyrase. There has been no evidence of mutagenic or terratogenic effect in animal. In clinical trials (Guerra et al., 1983; Glamorellou et al., 1983; Crider et al., 1984; Goldstein et al., 1985; Sabbaj et al., 1985) norfloxacin related adverse experiences have been minimal and occur with less frequency than with co-trimoxazole or nalidixic acid. The adverse effects have been observed in only 5-10% of patients receiving the drug and less than 1 percent of patients that the effects have been severe enough to require discontinuation. The most frequently reported side effects have been nausea, dyspepsia , headache and dizziness. It is not recommended for use in pregnant

women and children because it causes arthropathy. (Corrado et al., 1987)

7. **Dosage**

Urinary Tract Infections

For the treatment of complicated or uncomplicated urinary tract infections caused by susceptible organisms, the usual adult dosage is 400 mg twice daily. Therapy should be confirmed for 7-10 days in the treatment of uncomplicated urinary tract infections and for at least 10-21 days in the treatment of complicated urinary tract infections. (Holmes et al., 1985; McEvoy, ed., 1989).

Gastroenteritis

The usual adult dosage is 400 mg twice daily for 5 days.

Dosage in Renal Impairment

In whom creatinine clearance is less than 30 ml/min/1.73 m^2 the recommended dosage is 400 mg daily.

Prophylaxis of Sepsis

In profound neutropenia , the recommended dosage is 400 mg three times daily for the duration of profound neutropenia.