CONTINUING MEDICAL EDUCATION

NORFLOXACIN
(A fluoroquinolone antibacterial agent)

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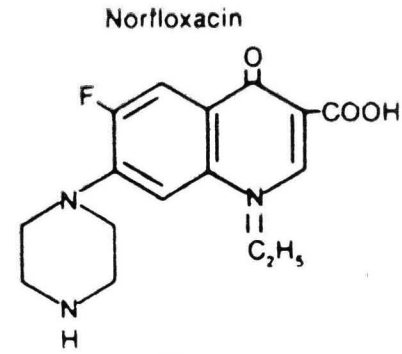
The new fluoroquinolone antibacterials have received increasing clinical attention in recent years.[1-3] The physicians treating infectious disease have viewed these orally absorbed, synthetically derived agents with special interest, despite the recent development of numerous beta-lactam antibiotics (including penicillins, cephalosporins, carbapenems and monobactams). The newer quinolones have a broad antibacterial spectrum that includes gentamicin-susceptible and gentamicin resistant strains of *Pseudomonas aeruginosa*, other multi-resistant, Gram-negative bacteria and both penicillinase-producing and non-penicillinase-producing Gram-negative cocci.[4] Furthermore, their mechanism of anti-microbial activity is different from other anti-biotics. Norfloxacin, one of these fluoroquinolone antibacterials, was originally synthesized in 1980 in Japan, where the first documentation of its broad spectrum of antibacterial activity was made.[5]

Out of the various fluoroquinolone anti-bacterials, norfloxacin is found to be specifically suitable for the treatment of urinary tract infections (UTIs) and uncomplicated gonorr-hoea, due to its unique pharmacodynamic and pharmacokinetic properties.

Chemistry

Norfloxacin (1-ethyl-6-fluoro 1, 4-dihydro -4-oxo - 7 - (1-piperazinyl)-3-quinolinecarboxylic acid) is a pyridine betacarboxylic acid, chemically related to nalidixic acid, however it has a wider antibacterial spectrum and greater potency. The structural formula of norfloxacin is as per fig. 1.



(Fig. 1)

The piperazinyl ring is believed to confer anti-*pseudomonas* activity to norfloxacin, while the 6-flourine atom is thought to contribute to the electron stability of the molecule and to its greater potency.[6]

Pharmacodynamics

Antibacterial activity : Most Gram-negative pathogens including *E. coli*, *Klebsiella*, *Entero-bactor*, *Proteus* and *Citrobacter* species are susceptible to norfloxacin and are inhibited by concentrations of 2 mg/L or less. Some strains of *Acinetobacter*, *Providencia* and *Serratia* species are less susceptible. *H. influenzae*, *N. gonorrhoeae* and *N. meningitidis* are also susceptible to

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Table I. Minimum inhibitory concentrations (MIC) range of norfloxacin against urinary pathogens.[7-9]

Organism (Number of isolates tested)	MIC range (mcg/ml)
E. coli (200)	0.125 — 2
Klebsiella SPP (100)	0.125 — 8
Enterobacter SPP (50)	0.125 — 1
P. mirabilis (50)	0.125 — 2
Proteus SPP (50)	0.125 — 8
Citrobacter SPP (23)	0.125 — 1
P. aeruginosa (48)	0.5 — 16
S. marcescens (10)	0.125 — 2
Enterococca (50)	1 — 8
S. aureus (22)	0.5 — 8
S. epidermidis (50)	0.5 — 8
N. gonorrhoeae	
(a) Beta-lactamase negative (50)	0.06
(b) Beta-lactamase positive (58)	0.1 — 0.5

norfloxacin. The gastro-intestinal pathogens such as *Salmonella*, *Shigella* and *Campylobacter* species are also susceptible to norfloxacin.[4] Norfloxacin is also effective against *Staphylococci* including *S. saprophyticus*. Table I depicts the minimum inhibitory concentration (MIC) range of norfloxacin against urinary pathogens. The high concentration of norfloxacin (500 times the MIC) achieved in urinary tract makes it a very valuable and effective antibacterial agent in UTI. The reduction of anti-bacterial activity of norfloxacin in urine could be the effect of pH. The activity of norfloxacin decreases considerably with decreasing pH below 5.5.[4] Optimum activity of norfloxacin is thought to occur between pH 7.5 and 8.[7-8]

Mechanism of action : The fluoroquinolone antibacterials in general and norfloxacin in particular are bactericidal. Norfloxacin acts by inhibiting bacterial DNA synthesis due to inhibition of DNA gyrase.[9] This is achieved in three ways. Firstly, it inhibits the ATP-dependent DNA super-coiling reaction brought about by DNA gyrase. Secondly, it inhibits the relaxation of super-coiled DNA, an activity which is induced by DNA gyrase in the absence of ATP. Thirdly, it blocks the DNA nicking-closing enzyme responsible for DNA elongation which leads to breaks in double-stranded DNA. The reason why it does not produce a similar effect in mammalian cells is that they lack a DNA gyrase.[9]

Bacterial resistance is usually obtained via plasmid mediating drug insusceptibility. The activity of norfloxacin however, is not decreased in the presence of plasmid. Norfloxacin often causes plasmid elimination from bacteria which harbour them[10] and can block the transfer of plasmid.[11] Thus, clinical resistance to norfloxacin has so far been slow to develop though, resistance to norfloxacin can be induced experimentally. Cross-resistance between various members of quinolone derivatives has also been observed.[4]

Pharmacokinetics

The pharmacokinetic profile of norfloxacin is more suitable for making it very useful in UTI. Norfloxacin is absorbed from the gastro-intestinal tract following oral administration. Oral bio-availability has been estimated to be approximately 70%. Peak serum concentrations are attained in one to two hours and have been reported to be 0.75, 1.58, 2.41, 3.15 and 3.87 mcg/ml, with doses of 200, 400, 800, 1200 and 1600 mg respectively. Thus, doses of norfloxacin between 200 and 800 mg result in linear increases in the peak serum levels and area under the plasma concentration time curve, dosages greater than 800 mg produce non-linear increases in these parameters.[12]

The drug is widely distributed throughout the body, it achieves high ratio of tissue to serum concentrations in both renal and prostatic tissues and undergoes metabolic conversion.[13] In urine, the concentrations have been reported to be 200, 478, 697, 992 and 1045 mcg/ml with doses of 200, 400, 800, 1200 and 1600 mg respectively.[14]

Liver appears to be the primary site of norfloxacin metabolism, whereas the urine is the major route of excretion. Six metabolites of norfloxacin are excreted unconjugated in the urine.[15] Approximately 30%of an oral dose is excreted as unchanged norfloxacin in urine. Renal clearance has varied from 16.32 to 17.76 L/hour with doses ranging from 200 to 1600 mg.[12] The elimination half-life of norfloxacin in healthy subjects ranges from 3.5 to 6.5 hours.[4]

The concentrations of norfloxacin (1000 mcg/ml) in the urine are so high that effective MIC concentrations for all the urinary pathogens are maintained for 72 hours after discontinuing the treatment.

Clinical uses and results of trials

Norfloxacin has been primarily studied in acute uncomplicated urinary tract infection (UTI), in chronic and/or complicated UTI, gonococcal infections, gastro-enteritis and other infections.[3,4] Norfloxacin is indicated in cystitis, cystopyelitis and pyelonephritis, as well as UTI after urological surgery, neurogenic bladder or kidney stones. Norfloxacin is also indicated in prophylaxis for infection in neutropenic patients and for the treatment of acute diarrhoeal disease. The relevant clinical trials in gonorrhoea are described below.

Penicillin since its introduction 50 years ago, has been the drug of choice for the treatment of uncomplicated gonococcal infections. Recently, its prominent position has been challenged by the increasing incidence of plasmid encoded penicillinase producing *Neisseria gonorrhoeae*.[16] Foremost among potential contenders for alternate treatment regimens are the new fluoroquinolones, such as norfloxacin. Several clinical trials on norfloxacin have been conducted in the therapy of uncomplicated gonococcal infection.

In an open study,[17] 70 patients with uncomplicated ano-genital *Neisseria gonorrhoeae* infection were evaluated to determine the efficacy and safety of a single oral dose of norfloxacin (800 mg). Norfloxacin eradicated urethral gonorrhoea in all the 31 men evaluated for efficacy. Similarly, endocervical gonococcal infection was eliminated in all the 25 women, and gonococcal eradication from the anal canal was achieved in all the 6 women. Remaining patients were not included in the study for violation of the protocol. The overall cure rate for men and women with genital and ano-rectal infection treated with norfloxacin was 100% (62/62). The MIC of norfloxacin isolated from these patients was 0.05 mcg/ml.

In a recent study,[18] norfloxacin was shown to be as effective as ampicillin and probenecid in the treatment of uncomplicated gonococcal infection in men and women. In this randomised study, three oral treatment regimens were compared. Patients received either two doses of norfloxacin (600 mg twice daily), a single dose of norfloxacin (800 mg)or a single dose ampicillin (3.5 gm+probenecid 1.0 gm) regimen. All the three treatment regimens achieved similar cure rates. It appeared that norfloxacin may be a slightly better treatment for rectal and pharyngeal gonococcal infection than ampicillin and probenecid.

Crider et al,[19] had earlier shown norfloxacin to be highly active in vitro against penicillinase-producing *Neisseria gonorrhoeae*. Ninety two men with culture proved gonococcal urethritis (46% penicillinase-producing and 27% non-penicillinase-producing) were given either 1200 mg of norfloxacin divided into two equal oral doses 4 hours apart (59 patients), or 2 gm of spectinomycin intramuscularly (33 patients). All the patients in both the treatment groups were cured. No adverse reactions were reported in either group. The authors concluded that orally administered norfloxacin is an effective therapy for uncomplicated urethritis caused by penicillin-resistant strains of *N. gonorrhoeae*.

Lately, the incidence of spectinomycin resistance among isolates of penicillinase-producing *N. gonorrhoeae* increased from 3% in 1982 to 11% in the first three months of 1983.[20] The emergence in several areas of non-penicillinase-producing gonococci that are highly resistant to penicillin poses yet another threat. As an oral agent with the inherent advantages of the improved patient acceptance, ease of administration and low toxicity, norfloxacin appears to possess characteristics that could make it the drug of choice for uncomplicated gonococcal infections, particularly in areas where there is a high incidence of resistant strains.[19]

The efficacy and safety of norfloxacin for prevention of bacterial infections in granulocytopenic patients,[21] were compared with those of placebo, vancomycin-polymyxin and trimethoprim-sulfamethoxazole. The study results showed that norfloxacin treatment (400 mg three times a day), which was well tolerated and not associated with any serious systemic adverse effects, prevented acquisition of Gram-negative bacillary infections. Norfloxacin was selected for oral antibiotic prophylaxis in granulocytopenic patients because the antibacterial spectrum of norfloxacin covers most of the aerobic pathogens that may potentially colonize the gastro-intestinal tract, while sparing the anaerobic flora. In norfloxacin treated patients (108), only 5 patients developed Gram-negative bacteremia. However, the incidence of Gram-positive bacteremia was similar in all the groups and was not affected by norfloxacin. Thus, more effective prophylaxis of Gram-positive bacterial infection is needed in granulocytopenic patients.

The clinical efficacy of norfloxacin in gastroenteritis has been assessed in a large multicentered trial conducted by seven investigators in seven countries. 159 patients with acute bacterial gastro-enteritis were treated either with 800 mg of norfloxacin or 320/1600 mg of cotrimoxazole for 5 days. The cure rate was 98% in norfloxacin treated group as compared to 95% in cotrimoxazole treated group.[4]

Isolated reports are available regarding the use of norfloxacin in traveller's diarrhoea, otitis media,[4] chronic sinusitis, acute tonsilitis, respiratory tract infections, etc.[3]

Dosage and administration

For the majority of cases of urinary tract infections, the usual adult dosage is 400 mg twice daily for 7 to 10 days. Three days therapy has been shown to be effective in women with uncomplicated acute cystitis. In chronic UTI, norfloxacin 400 mg twice a day has been administered for 10 to 21 days. In the treatment of chronic relapsing urinary tract infection, the dosage of norfloxacin is 400 mg twice daily for upto 4 weeks; if adequate suppression is obtained within the first 4 weeks, the dosage of norfloxacin may be reduced to 400 mg once daily. A single dose of 800 mg is recommended for the treatment of uncomplicated gonococcal infections. In acute bacterial gastro-enteritis, the usual dosage is 400 mg twice daily for 5 days. A dose of 400 mg twice daily norfloxacin was used for the treatment of acute traveller's diarrhoeal disease. In the prophylaxis of sepsis in profound neutropenia, the recommended dosage is 400 mg 3 times daily for a prolonged duration. However, data for recommending treatment beyond 8 weeks are at present not available.

More than 800 mg of norfloxacin per day is likely to cause crystalluria if satisfactory intake of fluids is not maintained.

Side effects

The incidence of side effects is comparatively lower with norfloxacin. Disorders of the gastro-intestinal tract, nausea and vomiting were the most commonly reported adverse effects with norfloxacin occurring in 2 to 4% of the patients. Reactions, such as light headedness and drowsiness, headache and dizziness were amongst the

more commonly reported central nervous system side effects.

Contraindications

Norfloxacin is contraindicated in patients with known hypersensitivity to the drug or to any chemically related quinolone containing antibacterial agent.

Precautions

Norfloxacin should not be used in children since safety and effectiveness have not been proved. The safety of norfloxacin in pregnant women has not been established. Caution is advised while administering norfloxacin to breast-feeding mothers.

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