Urol Res (1989) 17:117–124

Urological Research

Invited review

Quinolones in urology*

K. T. Nielsen and P. O. Madsen

Urology Section, V. A. Hospital and Department of Surgery, University of Wisconsin, Madison, Wisconsin, USA

Accepted: November 8, 1988

Summary. The new quinolones have broad antimicrobial spectra covering all aerobic gram-negative and gram-positive bacteria encountered in urinary tract infections. All are administered orally, some also parenterally, low degree of resistance, few side effects and bacteriological and clinical cure rates similar to or higher than traditional antimicrobials make them especially suitable for treatment of complicated urinary tract infections including bacterial prostatitis. Non-critical use of quinolones in simple infections where standard drugs may be equally effective and safe should be discouraged.

Key words: Quinolone – Urinary tract infection – Bacterial prostatitis – Prophylaxis

Introduction

During the last decade, the synthetically made quinolone antimicrobials have gained much interest and clinical application due to their broad antimicrobial spectrum, excellent pharmacokinetics and low degree of resistance and side-effects. Nalidix acid and oxolinic acid, pipemidic acid and cinoxacin constitute the first and second generation of the quinolones. The third generation, the fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, enoxacin, pefloxacin, fleroxacin) is the scope of this review.

Structure and mode of action

The basic chemical structure of the fluoroquinolones is shown in Fig 1. Manipulations of the side groups at different positions changes the properties of the molecule [32, 54]. Antimicrobial activity depends on a 2-carbon fragment at position 1 and on the ketone and carboxylic acid groups in position 3 and 4. The fluorine atom at position 6, which is the hallmark of the fluoroquinolones, increases the antibacterial activity of the molecule up to 30-fold regardless of all other side chains. Further, the addition of a piperazin ring at position 7 has enhanced the antibacterial activity apparently by improving the penetration of the molecule. Absorption is increased by substituting the H-atom at position 2 with a N-atom while tissue distribution can be slightly improved by placing a NH_2 group at position 5.

The antibacterial activity of the quinolones is caused by binding and thus blocking of the DNA gyrase enzyme in the bacteria thus preventing negative supercoiling of the DNA molecule and normal function of the bacteria. Human cells contain a slightly different gyrase enzyme which is not attacked by the quinolones.

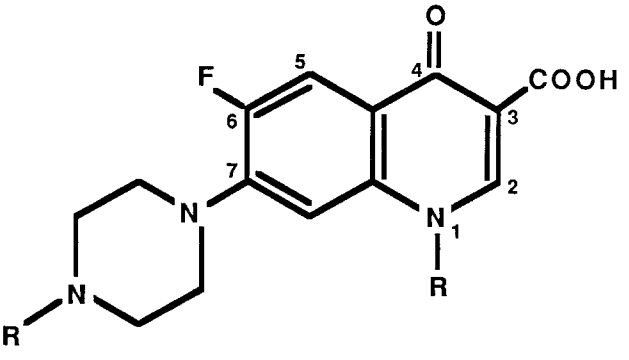

Fig. 1. Basic structure of the fluoroquinolone antimicrobial (R indicates side group)

* Supported in part by the Veterans Administration

Table 1. Comparison between the in-vitro antimicrobial activity of six fluoroquinolones. Minimal inhibitory concentration for 90% of the strains (MIC_{90}) is listed

	MIC_{90} (mcg/ml)					
	CIPRO	NORF	ENOX	OFLOX	PEFLOX	FLEROX
E. coli	0.03	0.12	0.40	0.20	0.25	2.0
Kleb. pneum.	< 0.12	1.6	3.1	0.20	2.0	2.0
Proteus mirabilis	< 0.12	0.10	0.80	0.20	0.50	0.5
Serratia marcescens	1.0	3.1	6.3	6.3	1.0	2.0
Pseudomonas aerug.	0.50	3.1	2.0	3.1	2.0	2.0
Enterobacter	< 0.12	0.40	0.40	1.0	-	2.0
Shigella species	0.02	0.03	0.20	<0.10	0.06	-
Bacteroides fragilis	2.00	128	50	6.3	16	16
Staph aureus	1.0	6.3	3.1	0.40	0.50	1.0
Strep faecalis	2.0	12	12	1.6	-	-
Neisseria gonorrhea	0.01	0.06	0.25	0.06	-	0.015
Chlamydia trachomatis	1.0	16	16	4.0	-	6.25
Ureaplasma urealyticum	32	32	64	8.0	-	-

From Refs. [29, 30, 67]
CIPRO = ciprofloxacin; NORF = norfloxacin; ENOX = enoxacin; OFLOX = ofloxacin; PEFLOX = pefloxacin; FLEROX = fleroxacin

In vitro antibacterial activity

The fluoroquinolones are active against all aerobic gram-positive and gram-negative bacteria including several Pseudomonas strains and beta-lactam resistant bacteria [70]. Ciprofloxacin is the most active drug in vitro followed by norfloxacin, ofloxacin, fleroxacin, pefloxacin and enoxacin [44] but this difference may be clinically insignificant due to the high serum concentrations obtained. Gram-positive cocci are usually less sensitive, but ciprofloxacin and ofloxacin both reach sufficiently high serum concentrations to be effective against these bacteria. Anaerobic bacteria are resistant to quinolones while Chlamydia trachomatis and Ureaplasma urealyticum are relatively resistant [7]. The MIC's for the common uropathogens are several times below the obtainable serum concentrations of the fluoroquinolones since a serum concentration of the quinolone of 1–4 times the minimal inhibitory concentration (MIC) is bactericidal [70] (Table 1). The in vitro antibacterial activity of the fluoroquinolones is decreased in the presence of urine and if the pH of the urine is decreased below 7.0 [24] but whether this is of any clinical importance is doubtful in the face of peak urine concentration above 100 mcg/ml for all fluoroquinolones after a single oral dose. However, when bacteria are challenged in vitro with these very high concentrations, a paradox effect leading to a decrease in bactericidal effect may be observed [15]. This is thought to be caused by a second action of the quinolones which causes inhibition of DNA synthesis and thus interferes with the lethal action on the DNA molecule [57]. We found discrepancy between in vitro activity expressed by MIC and in vivo activity for ciprofloxacin in the treatment of experimental rat prostatitis when the ratio between ciprofloxacin concentration in the prostatic tissue and MIC was above 500. The cure rate was lower in this group of rats compared to rats treated with temafloxacin and difloxacin where the serum/MIC ratio was <90 [47].

The incidence of mutational resistance to quinolones is low, one or fewer instances per 10^{11} colonies [46]. Plasmid transferred resistance does not seem to occur although a case of plasmid mediated resistance to nalidix acid in Shigella dysenteria has recently been published [41]. Cross resistance among the fluoroquinolones is common [63] but does not extend to non-quinolone antimicrobials.

Pharmacokinetic

Some fluoroquinolones can be administered both orally and intravenously. The intestinal absorption is rapid but variable and food and magnesium containing antacids will delay the absorption [35]. Peak serum concentration (C_{max} after a 400–500 mg oral dose of norfloxacin and ciprofloxacin range from 1–3 mcg/ml while enoxacin, ofloxacin, fleroxacin and pefloxacin reach peak concentrations around 4 mcg/ml (Table 2). The quinolones are partially metabolized in the liver and excreted in urine and bile. The peak urine concentration of all fluoroquinolones is many times the MIC for common uropathogens. Several metabolites, some of which have antibacterial activity, have been identified in the urine: 73% of ofloxacin and 67% of

Table 2. Pharmacokinetic parameters for six fluoroquinolones following a single oral dose (mean values as listed by authors)

	Oral dose (mg)	C_{max} (mcg/ml)	$T^1/_2$ (h)	24 h urine rec (%)	Ref.
Ciprofloxacin	500	2.3	3.9	30.6	14
Norfloxacin	400	1.6	7.4	30.0	60
Enoxacin	600	3.7	6.2	67.3	68
Ofloxacin	400	3.5	4.9	73.6[a]	37
Fleroxacin	400	3.7	13.5	50.3	49
Pefloxacin	400	3.9	11.5	10.0	69

[a]Following an oral dose of 200 mg
C_{max} = peak serum concentration; $T^1/_2$ = half life in serum

Table 3. Concentration of six fluoroquinolones in human prostatic secretion and tissue (mean values as listed by authors)

	PS (mcg/ml)	PS/P	PT (mcg/g)	PT/P
Ciprofloxacin	0.16	0.26	3.2	2.05
Norfloxacin	0.14	0.12	2.2	1.86
Enoxacin	0.39	0.39	4.9	2.48
Ofloxacin	1.34	1.10	4.08	1.12
Fleroxacin	1.00	0.28	4.24	1.10
Pefloxacin	8.7[a]	no data	no data	no data

Data compiled from Refs. [11, 34, 45, 59]
[a] Drug concentration in split ejaculate 1
PS = prostatic secretion; PT = prostatic tissue; P = plasma

enoxacin are recovered unchanged in the urine following oral administration while approximately one-third of an oral dose of norfloxacin and ciprofloxacin are excreted unchanged in the urine [30].

Ciprofloxacin [8], norfloxacin [29] and enoxacin [18] are recovered in the feces in high concentration and all three quinolones decreased the number of aerobic bacteria while ciprofloxacin completely eradicated coliform bacteria leaving the anaerobic flora unaffected. One week after cessation of quinolone administration, the fecal flora had returned to normal.

Tissue distribution

Special attention has focused on the distribution of the fluoroquinolones in prostatic tissue and secretions. The low degree of protein binding and minimal ionization at plasma pH make a large percentage of the drugs available for passive diffusion into the prostate. This is in contrast to other antimicrobials such as ampicillin and cephalosporins. Several human studies have determined the concentration of quinolones in prostatic tissue obtained during postatectomies and following administration of the drugs. However one major shortcoming of these studies is the lack of steady state. It is therefore unknown at the time of tissue and serum sampling if the quinolone concentrations are changing in one or both of the compartments. With this reservation in mind, the investigated quinolones all concentrated in the prostatic tissue (Table 3). Ciprofloxacin and enoxacin reached the highest tissue/serum ratio between 2 and 2.5 while the ratio for norfloxacin was around 1.8 and for ofloxacin and fleroxacin 1.1. We have evaluated the distribution of fluoroquinolones in prostatic tissue and fluid using a dog model during steady state conditions [16, 20, 31, 38] and found prostatic secretion/plasma ratios somewhat lower: enoxacin reaching the highest ratios (appr 1.5) followed by fleroxacin (1.1), ciprofloxacin (0.7) and norfloxacin (0.5). Results obtained in the dog can, however, not be applied directly to humans since the pH of dog prostatic secretion is lower than that of humans.

Clinical studies in urinary tract infections

Numerous clinical trials have studied the efficacy of fluoroquinolones in the treatment of urinary tract infections (UTI). Comparison between the studies is difficult because of different criteria for patient enrollment, wide variations in definition of bacteriological and clinical cure and length of follow-up. Furthermore several studies are manufacturer controlled and designed as open and non-randomized trials.

Uncomplicated urinary tract infections

Antimicrobial treatment of uncomplicated UTI, i.e infection in a urinary tract with no anatomical abnormalities, can effectively and safely be performed using single dose treatment with conventional drugs like

trimethoprim combined with a sulfonamid or amoxicillin. However in patients allergic to these antimicrobials or with infection caused by 8 resistant bacteria, the fluoroquinolones are an excellent second choice and can be administered in low dosages.

Two dosages of norfloxacin, 200 mg and 400 mg, were compared to trimethoprim-sulfametoxazole (TMP-SMX) 160/800 mg in a double blind randomized study involving 9 primary care centers and 886 patients with UTI [62]. All antimicrobials were administered orally twice daily for seven days and less than 15% of the patients in each group had complicated UTI. Bacteriological cure ranged from 97.5 to 98.6%, 3 to 13 days after treatment, decreasing to 87.9 to 88.8% at 5 $^1/_2$ week follow-up in all three groups. 5.1% of the patients treated with TMP-SMX discontinued therapy because of adverse reactions compared to 1.5% receiving 200 mg norfloxacin. Enoxacin, 400 mg, administered as a single dose to 29 women achieved a bacteriological cure rate of 69% compared to 85% of 26 patients cured receiving a single dose of trimethoprim 600 mg [2] in a double-blind trial while an open study on a single dose of enoxacin, 400 mg, sterilized the urine in 92.5% of the patients at 1 week follow-up compared to 65% of the patients receiving a single oral dose of 3 g amoxicillin. Similar results showing no differences between standard therapy and ciprofloxacin and ofloxacin treated patients have been reported [13, 21]. Although the risk of generating resistant bacteria is minimal using short-term therapy and especially single-dose treatment, one should probably restrict the use of the fluoroquinolones to difficult to treat urinary tract infections.

Complicated urinary tract infections

Complicated UTI is defined as infection in an anatomically abnormal urinary tract. In general, all fluoroquinolones achieve cure rates equal to or higher than the standard drugs. No clinical significant differences were demonstrable when norfloxacin, 400 mg twice daily, was compared to TMP-SMX 160–800 mg twice daily in 3 studies using a 10 days treatment period [27, 29, 48]. Cure rates between 94–97% were obtained for norfloxacin while 90–95% of TMP-SMX treated patients were cured. Norfloxacin, 400 mg twice daily, was compared to amoxicillin, 250 mg three times daily, both administered for 7 days in 40 elderly patients with complicated UTI [36]. Cure rates at 5 to 9 days follow-up were 95% for norfloxacin and 75% for amoxicillin; no long-term follow-up was performed. However amoxicillin has relatively limited activity against gram-negative bacteria and is therefore not ideal for treatment of UTI. Comparison between norfloxacin, 400 mg, and cinoxacin 500 mg, both given twice daily for 10 days, cured 93% and 83% of the patients, respectively [53]. However, direct comparison between the two treatments is difficult since 70 patients were treated with cinoxacin while only 15 patients were enrolled in the norfloxacin group. Three oral dosages regimens of ciprofloxacin, 250, 500 and 750 mg twice daily for 7 days were compared in the treatment of complicated UTI in 110 patients [23]. The cure rates (range 84–87%) were similar in the three groups, five to nine days after treatment, suggesting that 250 mg ciprofloxacin twice daily is sufficient therapy. Long-term cure rates of 64 to 67% at 4–6 weeks follow-up were reported in 3 studies [6, 12, 40] using treatment duration of 10–28 days and ciprofloxacin, 250 to 500 mg dosages twice daily. In a multicenter study, ciprofloxacin, 250 mg twice daily, was compared to TMP-SMX 160–800 mg, both administered twice daily for 9 days [1]. Cure rates of 94% and 86% were obtained respectively but in cases where Klebseilla and Enterobacter were the causative organism, this difference disappeared. No difference in cure rates was observed when ciprofloxacin was compared to norfloxacin [43] and ofloxacin [33] in double-blind randomized studies involving patients with uncomplicated and complicated UTI. Treatment results with ofloxacin [5, 13] and enoxacin [44, 51] are generally not different from those obtained with ciprofloxacin and norfloxacin. The newest fluoroquinolones, pefloxacin and fleroxacin, are not yet available for clinical use in the USA but are expected to be marketed within the coming year in West Germany while lomefloxacin and temafloxacin are undergoing investigation. Pefloxacin and fleroxacin are long acting (T1/2 approx 11–12 h) and therefore attain high urine concentrations up to 48 h after administration of a single oral dose. Results from open studies published as abstracts indicate cure rates of 64 to 90% in patients with complicated UTI treated with i.v. or peroral pefloxacin [17, 40, 56]. Clinical studies of fleroxacin are sparse but suggest that cure rates comparable to norfloxacin can be obtained using either 200 or 400 mg dosages [3, 62].

Side effects

The incidence of side effects using fluoroquinolones is about 5%. Gastrointestinal side effects (nausea, vomiting, diarrhea) prevail but are usually mild. Photosensitivity is known to occur with nalidix acid but the incidence for the fluoroquinolones is unknown at present.

Crystalluria has been described in healthy volunteers receiving high doses of norfloxacin (1.2–1.6 g) and having a urine pH of 7.0 to 7.8 and urine drug concentration between 1,200 to 2,300 mcg/ml [60].

Animal studies have shown the fluoroquinolones to accumulate in developing bone and cartilage and damage joints. Pregnant and breastfeeding women should therefore not be treated with fluoroquinolones. The fluoroquinolones, especially enoxacin [65] and to a lesser extent ciprofloxacin [55] and pefloxacin [66], interfer with the hepatic metabolism of theophylline by lowering it's clearance up to 30% leading to possible overdose symptoms. In conclusion, all the mentioned fluorquinolones show low rate of resistance, favorable pharmacokinetics and few side effects which make these antimicrobials an excellent choice in the treatment of patients with complicated UTI, reaching high clinical and bacteriological cure rates.

Bacterial prostatitis

The fluoroquinolones reach prostatic tissue levels 1–2 times the simultaneous plasma concentration and are found in the prostatic secretion in concentrations well above the MIC for most pathogens isolated from patients with chronic bacterial prostatitis. E. coli is the bacteria most frequently isolated but Pseudomonas, Klebsiella, Proteus and Enterobacteriacae species are also seen. Chlamydia trachomatis, Ureaplasma urealyticum and gram positive cocci are less often encountered. Acute bacterial prostatitis is relatively easy to treat using various parenteral antibiotics showing in vitro effect against the isolated microorganism.

In chronic prostatic bacterial infection, the characteristics of the drug determine the drug concentration obtainable in the prostate. A low degree of drug ionization at serum pH, low level of drug binding to serum protein, high lipid solubility, and maybe a small sized drug molecule increases the drug diffusion into the prostatic acini [58]. In the US, carbenicillin indanyl sodium is yet the only antibiotic approved by the Food and Drug Administration for treatment of acute and chronic bacterial prostatitis. However, the diffusion of the drug into the prostate is negligible according to the Henderson-Hasselbach equation since the drug is an acid [58]. The fluoroquinolones, like norfloxacin, ciprofloxacin and enoxacin are amphoteric and have two pKa values. At pH 7.4, approximately 10% of these quinolones are ionized [34] and 15–30% bound to serum proteins leaving a large proportion available for passive diffusion. Once the quinolones have diffused into the prostatic acini, more of the drug will be ionized since the pH of prostatic secretion in patients with chronic bacterial prostatitis is often above 8.0 [19]. This leads to "ion-trapping" of the drugs in the acini. From a theoretical standpoint the fluoroquinolones should be excellent in the treatment of this disease.

Clinical studies on chronic bacterial prostatitis are difficult to undertake because of the low incidence of the disease. Therefore most studies are open, non-randomized including small patient numbers and unfortunately most of the studies have a short follow-up period which makes it difficult to evaluate the treatment results. 17 patients with symptoms of chronic bacterial prostatitis and failing to show clinical improvement following at least 6 weeks treatment with trimetoprim and/or TMP-SMX were treated with oral ciprofloxacin 500 mg twice daily for two weeks [64]. 12 patients were infected with E. coli while Streptococcus faecalis was isolated in three patients and Pseudomonas aeruginosa and Enterobacter aerogenes in one patient each. During ciprofloxacin treatment all 4 localization specimens were sterile and at 1 year follow-up 5 of 10 evaluable patients orginally infected with E. coli were considered as treatment successes. Recurrent bacterial prostatitis was found in 3 patients while 2 patients had low counts of E. coli in expressed prostatic secretion. Ciprofloxacin treatment of Streptococcus faecalis and Pseudomonas aeruginosa prostatitis was unsuccessful. A similar short term treatment success was reported by Childs [10]. 39 patients with chronic bacterial prostatitis were treated with ciprofloxacin, 500 mg twice daily, for a median period of 29 days. Clinical cure rate was 77% at short term evaluation (<10 weeks) but unfortunately no data on the long-term results (>1 year) were reported. Six patients had treatment failures due to reinfection or relapse caused by Streptococcus (3), Pseudomonas (1), Citrobacter (1) and Klebsiella (1). Other studies published as abstracts have evaluated ofloxacin in 8 patients with acute excaberation of chronic bacterial prostatitis [50] and norfloxacin for long-term prophylaxis in patients with chronic bacterial prostatitis [52]. Following 4 months of continuous suppression therapy with norfloxacin, 400 mg daily, 19 patients were asymptomatic with sterile urine culture. However, after cessation of therapy, 12 patients had relapsing UTI and recurrent symptoms. Long-term, low dosage treatment with fluoroquinolones may be an option in these patients. Standard treatment of chronic bacterial prostatitis using f ex. trimethoprim which also concentrates in the prostate seldom gives cure rates above 30% probably caused by poor drug diffusion into the alkaline prostatic secretion.

Antimicrobial prophylaxis

Prophylactic use of fluoroquinolones during urological surgery are concentrated on transurethral procedures. The quinolones appear suited for prophylactic use because of their broad antibacterial spectrum covering

all common uropathogens. The incidence of postoperative bacteriuria, usually defined as $> 10^5$ colonies/ml, in patients with sterile urine prior to transurethral surgery and not receiving prophylactic antimicorbials varies between 6 and 70%, while approximately 10% of patients undergoing transurethral resection of the prostate (TURP) will have transient bacteremia during surgery which in 1% of the patients leads to septicemia [25]. The value of prophylactic antimicrobials in TURP is usually measured by the incidence of postoperative significant bacteriuria and postoperative fever and length of hospital stay. Oral ciprofloxacin (250 mg) was compared to placebo in 101 patients undergoing TURP [42]. The drug was administered twice daily for 3 days perioperatively with the first dose given preoperatively. Postoperative bacteriuria developed in 38% of patients in the placebo group compared to 6% in the ciprofloxacin group ($p = 0.002$). In adddition, length of hospital stay was shorter among patients receiving prophylaxis. However, no clinical significant differences were reported in a study comparing oral ciprofloxacin, 500 mg every 12 h, in one group starting preoperatively and continued until the day of catheter removal totalling 3 to 4 days of drug administration and in a second group, prolonged by five days after catheter removal totalling 8–9 days drug administration to a third group receiving placebo [26]. Postoperative significant bacteruria was found in 3.4 and 2.5% of the patients with sterile urine preoperatively respectively compared to 19.4% in a placebo group. All cases with bacteriuria resolved spontaneously without treatment and were thus of no clinical importance. The newest fluoroquinolone (fleroxacin, pefloxacin) with long half lifes seem promising for use as single dose prophylaxis and preliminary results showed a single dose of pefloxacin, 800 mg 2 h preoperatively to be as effective as a 2 days course in 50 patients undergoing TURP [9].

The fluoroquinolones are very effective in the treatment of urinary tract infections caused by gram-positive and gram-negative aerobic bacteria. Cure rates comparable to or higher than those obtained by standard antimicrobials are obtained in treatment of uncomplicated and complicated UTI. Bacterial prostatitis can be successfully treated with fluoroquinolones but there is, so far, no dramatic increase in the cure rate compared to traditional drugs and especially long term results are poorly elucidated.

References

1. Arcieri G, Griffith E, Gruenwaldt G, Heyd A, O'Brien B, Becker N, August R (1987) Ciprofloxacin: an update on clinical experience. Am J Med 82 [Suppl 4A]:381–386
2. Bailey RR, Gorrie SI, Peddie BA, Davies PR (1987) Double blind, randomized trial comparing single dose enoxacin and trimethoprim for treatment of bacterial cystitis. NZ Med J 100:618–619
3. Bernstein-Hahn L, Barclay CA, Iribarren MA, Casellas JM, Traballi CA, Farinati A (1988) Treatment of complicated urinary tract infections with fleroxacin (Ro 23–6240) a long-acting fluoroquinolone. A dose finding study. 2nd International Symposium on New Quinolones, Geneva, Switzerland
4. Bischoff W (1986) Vergleichende Untersuchung von Enoxacin mit Amoxicillin bei der akuten unkomplizierten Zystitis der Frau. Infection 14 [Suppl 3]:S209–S210
5. Blomer R, Bruck K, Zahlten RN (1986) A summary of clinical phase II and phase III study of ofloxacin (HOE 280) in Europe. Infection 14 [Suppl 2]:S102–S107
6. Boerema J, Boll B, Muytjens H, Branolte J (1985) Efficacy and safety of ciprofloxacin (Bay 0 9867) in the treatment of patients with complicated urinary tract infections. J Antimicrob Chemother 16:211–217
7. Bowie WR, Willetts V, Sibau L (1986) Failure of norfloxacin to eradicate Chlamydia trachomatis in nongonococcal urethritis. Antimicrob Agents Chemother 30:594–597
8. Brumfitt W, Franklin I, Grady D, Hamilton-Miller JMT, Iliffe A (1984) Changes in the pharmacokinetics of ciprofloxacin and fecal flora during administration of a 7-day course to human volunteers. Antimicrob Agents Chemother 26:757–761
9. Charton M, Mombet A, Prapotnich D (1988) Ideal duration of pefloxacin prophylaxis of urinary tract infection following transurethral resection of prostate: a randomized study. 2nd International Symposium on New quinolones, Geneva, Switzerland
10. Childs SJ (1987) Treatment of chronic bacterial prostatitis with ciprofloxacin. Infect Surg 649–651
11. Comhaire FH (1987) Concentration of pefloxacine in split ejaculates of patients with chronic male accessory gland infection. J Urol 138:828–830
12. Cox C (1987) Brief report: ciprofloxacin in the treatment of urinary tract infections caused by Pseudomonas species and organisms resistant to trimethoprim-sulfamethoxazole. Am J Med 82 [Suppl 4A]:288–289
13. Cox CE, Callery SV, Tack KJ (1986) Clinical experience with ofloxacin in urinary tract infection. Infection 14 [Suppl 4]:S303–S304
14. Crump B, Wise R, Dent J (1983) Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob Agents Chemother 2:784–786
15. Crumplin GC, Smith JT (1975) Nalidixic acid: an antibacterial paradox. Antimicrob Agents Chemother 8:251–261
16. Dørflinger T, Madsen PO (1985) Enoxacin concentrations in prostatic tissue, prostatic secretion, interstitial fluid, and other tissues: an experimental study in dogs. J Int Biomed Info Data 6:41–44
17. Dubois J, St-Pierre C, Auger P, Phillips R, Perrier A (1988) Single dose pefloxacin (P) versus a seven day treatment of trimethoprim-sulfamethoxazole (TMP-SMX) in uncomplicated lower urinary tract infection (UTI) in women. 2nd International Symposium on New Quinolones, Geneva, Switzerland
18. Edlund C, Lidbeck A, Kager L, Nord CE (1987) Comparative effects of enoxacin and norfloxacin on human colonic microflora. Antimicrob Agents Chemother 31:1846–1848
19. Fair WR, Cordonnier JJ (1978) The pH of prostatic fluid: a reappraisal and therapeutic implications. J Urol 120:695–698
20. Frimodt-Møller PC, Dørflinger T, Madsen PO (1984) Distribution of ciprofloxacin in the dog prostate and various tissues. Urol Res 12:283–286
21. Garlando F, Rietiker S, Tauber MG, Flepp M, Meier B, Luthy R (1987) Single-dose ciprofloxacin at 100 versus 250 mg for treatment of uncomplicated urinary tract infections in women. Antimicrob Agents Chemother 31:354–356

22. Gasser TC, Graversen PH, Madsen PO (1987) Fleroxacin (Ro 23-6240) distribution in canine prostatic tissue and fluids. Antimicrob Agents Chemother 31:1010–1013
23. Gasser TC, Graversen PH, Madsen PO (1987) Treatment of complicated urinary tract infections with ciprofloxacin. Am J Med 82 [Suppl 4A]:278–279
24. Gasser TC, Larsen EH, Dørflinger T, Madsen PO (1986) The influence of various body fluids and pH on E. coli MIC of quinolone derivatives. In: Weidner W, Brunner H, Krause W, Rothauge CF (eds)Therapy of prostatitis. Zuckwerdt, München Bern Wien San Francisco, pp 50–53
25. Grabe M (1987) Antimicrobial agents in transurethral prostatic resection. J Urol 138:245–252
26. Grabe M, Forsgren A, Bjork T, Hellsten S (1987) Controlled trial of a short and a prolonged course with ciprofloxacin in patients undergoing transurethral prostatic surgery. Eur J Clin Microbiol 6:11–17
27. Guerra JG, Falconi E, Palomino JC, Benavente L, Antunez de Mayolo E (1983) Clinical evaluation of norfloxacin versus cotrimoxazole in urinary tract infections. Eur J Clin Microbiol 2:260–265
28. Guibert J, Destree D, Konopka C, Acar J (1986) Ciprofloxacin in the treatment of urinary tract infection due to enterobacteria. Eur J Clin Microbiol 5:247–248
29. Haase DA, Harding GKM, Thomson MJ, Kennedy JK, Urias BA, Ronald AR (1984) Comparative trial of norfloxacin and trimethoprim-sulfa-methoxazole in the treatment of women with localized, acute, symptomatic urinary tract infections and antimicrobial effect on periurethral and fecal microflora. Antimicrob Agents Chemother 26:481–484
30. Hooper DC, Wolfson JS (1985) The fluoroquinolones: pharmacology, clinical uses, and toxicities in humans. Antimicrob Agents Chemother 28:716–721
31. Jensen KM-E, Madsen PO (1983) Distribution of quinolone carboxylic acid derivatives in the dog prostate. Prostate 4:407–414.
32. Klopman G, Macina OT, Levinson ME, Rosenkranz HS (1987) Computer automated structure evaluation of quinolone antibacterial agents. Antimicrob Agents Chemother 31:1831–1840
33. Kromann-Andersen B, Sommer P, Pers C, Larsen V, Rasmussen F (1986) Clinical evaluation of ofloxacin versus ciprofloxacin in complicated urinary tract infections. Infection 14:305–306
34. Larsen EH, Gasser TC, Dørflinger T, Madsen PO (1986) The concentration of various quinolone derivatives in the human prostate. In: Weidner W, Brunner H, Krause W, Rothauge CF (eds) Therapy of prostatitis. Zuckwerdt, München Bern Wien San Francisco, pp 40–44
35. Ledergerber B, Bettex J-D, Joos B, Flepp M, Luthy R (1985) Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin. Antimicrob Agents Chemother 27:350–352
36. Leigh DA, Smith EC, Marriner J (1984) Comparative study using norfloxacin and amoxycillin in the treatment of complicated urinary tract infections in geriatric patients. J Antimicrob Chemother 13 [Suppl B]:79–83
37. Lode H, Hoffken G, Olschewski P, Sievers B, Kirch A, Borner K, Koeppe P (1987) Pharmacokinetics of ofloxacin after parenteral and oral administration. Antimicrob Agents Chemother 31:1338–1342
38. Madsen PO, Baumueller A, Hoyme U (1978) Experimental models for determination of antimicrobials in prostatic tissue, interstitial fluid and secretion. Scand J Inf Dis [Suppl 14]:145–150
39. Maeda H, Fujii A, Nakata K, Arakawa S, Kamidono S (1988) In vitro activities of T-3262, NY-198, Fleroxacin (AM-833; RO 23-6240), and other new quinolone agents against clinically isolated Chlamydia trachomatis strains. Antimicrob Agents Chemother 32:1080–1081
40. Magyar T, Graber H, Arr M, Ludwig E, Ternovszky E (1988) Comparative trial with pefloxacin and ofloxacin in severe urinary tract infections. 2nd International Symposium on New Quinolones, Geneva, Switzerland
41. Munsho MH, Sack DA, Haider K, Ahmed ZU, Rahaman MM, Morshed MG (1987) Plasmid-mediated resistance to nalidixic acid in Shigella dysenteriae type 1. Lancet II:419–421
42. Murdoch DA, Badenoch DF, Gatchalian ER (1987) Oral ciprofloxcin as prophylaxis in transurethral resection of the prostate. Br J Urol 60:153–156
43. Naber KG, Bartosik-Wich B (1986) Ciprofloxacin versus norfloxacin in the treatment of complicated urinary tract infections: in vitro activity, serum and urine concentrations, safety and therapeutic efficacy. In: Neu HD, Weuta H (eds) First international ciprofloxacin workshop. Excerpta Medica, Leverkusen Amsterdam, p 314–317
44. Naber KG, Sörgel F, Gutzler F, Bartosik-Wich B (1986) In vitro activity, pharmacokinetics, clinical safety and therapeutic efficacy of enoxacin in the treatment of patients with complicated urinary tract infections. Infection 14 [Suppl 3]:S203–S208
45. Naber KG, Sörgel F, Schumacher H, Nausch I, Mahr G (1987) True penetration of quinolones into prostatic fluid of man determined by a new method. 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, USA
46. Neu HC (1987) New antibiotics: areas of appropriate use. J Infect Dis 155:403–417
47. Nielsen KT, Madsen PO (1988) Temafloxacin (A63004), difloxacin (A56619) and ciprofloxacin treatment of acute prostatitis. An experimental model in rats. 2nd International Symposium on New Quinolones, Geneva, Switzerland
48. Panichi G, Pantosti A, Testore GP (1983) Norfloxacin (MK-0366) treatment of urinary tract infections in hospitalized patients. J Antimicrob Chemother 11:589–593
49. Panneton A-C, Bergeron MG, LeBel M (1988) Pharmacokinetics and tissue penetration of fleroxacin after single and multiple 400 and 800 mg dosage regimens. Antimicrob Agents Chemother 32:1515–1520
50. Remy G, Rouger C, Chavanet P, Bernard E, Dellamonica P, Portier H (1986) Clinical evaluation of ofloxacin in prostatitis. 2nd International Symposium on New Quinolones, Geneva, Switzerland
51. Roe CJ, Becker GJ, Whitworth JA, Kincaid-Smith P (1987) Enoxacin in the treatment of complicated urinary tract infections. Aust NZ J Med 17:81–82
52. Rugendorf EW (1988) Low-dose norfloxacin suppressive treatment of chronic bacterial prostatitis. 2nd International Symposium on New Quinolones, Geneva, Switzerland
53. Sabbour MS, El Bokl MA, Osman LM (1984) Experiences on the efficacy and safety of nalidixic acid, oxolinic acid, cinoxacin and norfloxacin in the treatment of urinary tract infections (UTI). Infection 12:377–380
54. Schentag JJ, Domagala JM (1985) Structure-activity relationships with the quinolone antibiotics. Res Clin Forum 7:9–13
55. Schwartz J, Jauregui L, Lettieri J, Bachmann K (1988) Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. Antimicrob Agents Chemother 32:75–77
56. Seddik M, Youcef Khodja S, Charif N, Chouider S (1988) Pefloxacin in the treatment of nosocomial complicated urinary tract infections. 2nd International Symposium on New Quinolones. Geneva, Switzerland
57. Smith JT (1984) Awakening the slumbering potential of the 4-quinolone antibacterials. Pharmacol J:299–305
58. Stamey TA, Meares EM, Winningham DG (1970) Chronic bacterial prostatitis and the diffusion of drugs into prostatic fluid. J Urol 103:187–194
59. Suzuki K, Naide Y (1983) Clinical evaluation of DL-8280 in bacterial prostatitis. 13th International Congress of Chemotherapy, Vienna, Austria

60. Swanson BN, Boppana VK, Vlasses PH, Rotmensch HH, Ferguson BK (1983) Norfloxacin disposition after sequentially increasing oral doses. Antimicrob Agents Chemother 23:284–288
61. Taufer M, Pummer K, Primus G (1988) Fleroxacin (RO 23-6240) vs norfloxacin in therapy of complicated UTI. A randomized, multidose, double blind study. 2nd International Symposium on New Quinolones, Geneva, Switzerland
62. The Urinary Tract Infection Study Group (1987) Coordinated multicenter study of norfloxacin versus trimethoprim-sulfamethoxazole treatment of symptomatic urinary tract infections. J Infect Dis 155:170–177
63. Traub WH (1985) Incomplete cross-resistance of nalidixic acid and pipemidic acid-resistant variants of Serratia marcescens against ciprofloxacin, enoxacin, and norfloxacin. Chemotherapy 31:34–39
64. Weidner M, Schiefer HG, Dalhoff A (1987) Treatment of chronic bacterial prostatitis with ciprofloxacin. Results of a one-year follow-up study. Am J Med 82 [Suppl 4A]:280–283
65. Wijnands WJA, van Herwaarden CLA, Vree TB (1984) Enoxacin raises plasma theophylline concentrations. Lancet II:109
66. Wijnands WJA, Vree TB, van Herwaarden CLA (1986) The influence of quinolone derivatives on theophylline concentration. Br J Clin Pharmacol 22:677–683
67. Wise R, Andrews JM, Ashby JP, Matthews RS (1988) In vitro activity of lomefloxacin, a new quinolone antimicrobial agent, in comparison with those of other agents. Antimicrob Agents Chemother 32:617–722
68. Wise R, Lockley R, Dent J, Webberly M (1984) Pharmacokinetics and tissue penetration of enoxacin. Antimicrob Agents Chemother 26:17–19
69. Wise R, Webberley JM, McLeod A, Andrews JM, Ashby JP (1987) Pharmacokinetics and tissue penetration of orally administered pefloxacin. 15th International Congress of Chemotherapy, Istanbul, Turkey
70. Wolfson JS, Hooper DC (1985) The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob Agents Chemother 28:581–586

Dr. P. O. Madsen
Chief, Urology Section
V. A. Hospital
2500 Overlook Terrace
Madison, Wisconsin 53705
USA