Quinolones: A Practical Review of Clinical Uses, Dosing Considerations, and Drug Interactions

Shawn M. Borcherding, PharmD; Robert Stevens, PharmD; Richard A. Nicholas, MD; Cheryl R. Corley, PharmD; and Timothy Self, PharmD
Cincinnati, Ohio; Memphis, Tennessee; and Denver, Colorado

A review of the literature on quinolones reveals numerous clinically relevant points regarding indications, dosing considerations, and drug interactions. Quinolones are useful in the treatment of several infectious diseases. Unfortunately, indiscriminate use of these valuable antimicrobials has resulted in increased patterns of resistance. It is important to consider carefully the site of infection and the potential pathogens in each patient before dosing. Quinolones have excellent oral absorption, with peak serum concentrations approaching those achieved with intravenous administration. When prescribing quinolones, the dose should be based on estimated creatinine clearance. Quinolones are associated with several clinically significant drug interactions. Some of these agents are well-documented inhibitors of hepatic metabolism of theophylline, caffeine, and warfarin. It has been well documented that divalent and trivalent cations in antacids, sucralfate, and some other products significantly reduce the absorption of quinolones. Avoidance or proper management of these interactions is required to ensure optimal safety and efficacy.

Key words. Quinolones; drug interactions; ciprofloxacin; enoxacin; norfloxacin; ofloxacin. (*J Fam Pract 1996; 42:69-78*)

Fluoroquinolones represent a significant advance in the antimicrobial armamentarium. Several fluoroquinolones have been approved by the Food and Drug Administration (FDA), and, based on the numerous agents being investigated in ongoing trials, more quinolones are expected to be approved in the future. The goal of this review is to highlight the clinical uses of the quinolones and to emphasize factors to consider when prescribing these agents. A review of several clinically significant drug interactions with quinolones is also presented.

The primary mechanism of action of quinolone antibiotics is inhibition of the bacterial enzyme DNA gyrase.[1] This enzyme is present in all bacteria and is essential for their survival. Inhibition of this enzyme by a quinolone results in a bactericidal outcome. These agents demonstrate a postantibiotic effect against many gram-positive and gram-negative organisms.[2] This inherent antimicrobial activity enables continued suppression of bacterial replication after exposure to subinhibitory concentrations of quinolones.

Overview of Clinical Uses of Quinolones

Quinolones have many advantages that make them attractive agents for the treatment of selected infectious diseases. Quinolones possess many ideal properties of an antibiotic: bactericidal activity; broad spectrum of activity; favorable pharmacokinetic profile, including excellent bioavailability after oral administration for most agents (Table 1); good tissue penetration; and an acceptable safety profile. For these reasons, however, quinolones are often used without judicious thought regarding the site of infection and potential pathogens in an individual patient. Indiscriminate use of quinolones has resulted in increased

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From the Department of Medical Affairs, Regulatory and Clinical Development, The Procter & Gamble Co, Cincinnati, Ohio (S.M.B.); the Department of Clinical Pharmacy, University of Tennessee (R.S., T.S.) and the Clinical Pharmacy Resident Program at the University of Tennessee Bowld Hospital (C.R.C.), Memphis; and the Department of Family Medicine, University of Colorado, Denver (R.A.N.). Requests for reprints should be addressed to Timothy Self, PharmD, Department of Clinical Pharmacy, University of Tennessee, 26 S. Dunlap St, Memphis, TN 38163.

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Table 1. Clinical Pharmacokinetics of Quinolones

Quinolone (Trade Name)	Oral Absorption, %	Normal T ½, h		Renal Excretion of Unchanged Drug, %	Concentration			Usual Dose (mg) and Dosing Interval (h) Adjusted for CrCl (mL/min)		
		Normal	Anuric		Dose, mg	Serum, mg/L	Urine, mg/L	>50	50–10	<10 (Anuric)
Ciprofloxacin* (Cipro)	50–85	3–5	5–10	30–50	500 po 750 po 400 iv	1.6–2.9 2.5–4.3 4.6	350 — —	250–750 po q12 200–400 iv q8–12	250–500 po q12 200–400 iv q12–24	250–500 po q24 200–400 iv q24
Enoxacin* (Penetrex)	80–90	5–7	40	>90	400 po	2.8–3.6	250–300	200–400 po/iv q12	100–200 po/iv q12†	100–200 po/iv q12
Lomefloxacin (Maxaquin)	>95	7–8.5	38–44	>90	200 po 400 po	2.1 3–4.7	170 —	400 po q24	200‡ po q24	200‡ po q24
Norfloxacin*§ (Noroxin)	30–40	2.3–4	7.6	30	400 po	1.3–1.9	≥200	400 po q12	400 po q24†	400 po q24
Ofloxacin* (Floxin)	85–100	4–8	17–36	>90	200 po 400 po 400 iv	1.5–2.7 2.9–5.6 4.0	— 200 —	200–400 po/iv q12	200–400 po/iv q24	100–200 po/iv q24

**Avoid taking with meals if possible because of decreased absorption.*
†For CrCl ≤ 30 mL/min; if CrCl > 30 mL/min, use normal dose.
‡After initial loading dose of 400 mg po.
§Primary use is for urinary tract infections.
T½ denotes half-life; CrCl, creatinine clearance; po, by mouth; q, every; iv, intravenous.

patterns of resistance, which is especially problematic for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This potential problem underscores the importance of the physician being familiar with the appropriate clinical applications of these useful antibiotics. Table 2 lists common clinical uses for quinolones, and Table 3 provides a breakdown of costs.

Clinical experience with quinolones is almost exclusively limited to the adult population, as no quinolone has yet been approved by the FDA for use in children. This restriction is based primarily on arthropathies observed in young experimental animals. However, in more than 1000 pediatric patients who have received ciprofloxacin, there have been no definite arthropathies.[3] Most of these children were patients with cystic fibrosis who received ciprofloxacin because other therapeutic options were not feasible because of such problems as drug resistance to other antibiotics. The lack of a reliable early marker for joint damage restricts the use of quinolones in pediatric patients to a select group of children for whom there is no alternative.

Table 2. Clinical Uses of Quinolones

Sexually transmitted diseases[4]
Urinary tract infections[4–6]
Prostatitis[4–6]
Gram-negative pneumonias[9,10]
Osteomyelitis[4,11,12]
Skin and soft tissue infections[13]
Traveler's diarrhea[4,14,15]
Prevention of spontaneous bacterial peritonitis[4]

Urinary Tract Infections

Urinary tract infections (UTIs) are the main indication for quinolones. Numerous clinical trials have documented the efficacy of quinolones for UTIs of all types. In the

Table 3. Cost of Oral Quinolone Therapy

Quinolone	Regimen	Cost* per Dose, $	Cost* per 7 Days, $
Ciprofloxacin	250 mg bid	2.70	37.80
	500 mg bid	3.13	43.82
	750 mg bid	5.43	76.02
Enoxacin	200 mg bid	2.73†	38.22
Lomefloxacin	400 mg daily	6.11	42.77
Norfloxacin	400 mg bid	2.54	35.56
Ofloxacin	200 mg bid	3.06	42.84
	300 mg bid	3.64	50.96
	400 mg bid	3.84	53.76

**Average wholesale price, 1995.*
†Enoxacin 400 mg is the same price.
bid denotes twice daily.

treatment of uncomplicated and complicated UTIs, cure rates can exceed 90% and 80%, respectively.[4]

There is little variation among quinolone agents with respect to efficacy in the treatment of UTIs.[4] Dosing schemes for the 3 to 7 days of therapy required for uncomplicated UTIs include ciprofloxacin 100 to 250 mg, enoxacin 200 mg, norfloxacin 200 to 400 mg, and ofloxacin 100 to 200 mg, each of which is administered twice daily, and lomefloxacin 400 mg, administered once daily. The regimens for complicated UTIs include ciprofloxacin 100 to 500 mg, enoxacin 400 mg, norfloxacin 400 mg, and ofloxacin 100 to 200 mg twice daily, and lomefloxacin 400 mg once daily for 7 to 14 days.

Single-dose treatment using a quinolone for uncomplicated UTIs has been studied in several trials, but cure rates were generally less than the standard 3- to 7-day regimen. Recurrent cystitis can be prevented when a quinolone is used for long-term prophylaxis in women with chronic UTIs.[5] Norfloxacin 200 mg daily is the agent used most often for UTI prophylaxis.

A limited number of therapeutic trials are reported on the use of quinolones for treatment of prostatitis. Norfloxacin 400 mg twice daily, ciprofloxacin 500 mg twice daily, and ofloxacin 100 to 200 mg two to three times a day were studied for up to 3 months, with bacteriologic cure rates ranging from 54% to 91%.[6] Quinolones appear to be effective agents for prostatitis, but more controlled trials are needed to ascertain their niche for treating this infection.

Sexually Transmitted Diseases

Quinolones are potent agents to use against *Haemophilus ducreyi* (chancroid) and penicillin-sensitive and penicillin-resistant *Neisseria gonorrhoeae*. They demonstrate moderate activity against *Chlamydia trachomatis* and have limited activity against *Mycoplasma hominis* and *Ureaplasma urealyticum*, which are common causes of nongonococcal urethritis.

Single oral doses of quinolones are highly effective in treating uncomplicated gonococcal urethritis, proctitis, pharyngitis, and cervicitis.[4] The single doses used for treating these infections include norfloxacin 800 mg, ciprofloxacin 100 to 500 mg, ofloxacin 200 to 600 mg, and enoxacin 200 to 600 mg. Cure rates range from 94% to 100%. Insufficient data exist to recommend the use of quinolones to treat disseminated gonococcal infections. Quinolones administered either as a single dose or for 3 days is effective in curing chancroid, but longer treatment (5 to 10 days) is required to eradicate chlamydial infections. It should be noted that norfloxacin is ineffective in chlamydial infections perhaps in part because of the drug's marginal bioavailability compared with other quinolones (Table 1).

Respiratory Tract Infections

Pulmonary infections encompass a broad topic because of the different array of pathogens, anatomical sites, and clinical settings. Major categories include upper respiratory tract infections, acute exacerbation of chronic bronchitis, and community-acquired and nosocomially acquired pneumonias. Quinolones have inferior activity against streptococci and should not be used as primary therapy for common upper respiratory tract infections. Quinolones are alternatives for treatment of acute exacerbation of chronic bronchitis in patients with obstructive pulmonary disease who are intolerant of or have developed resistance to first-line antibiotics. These acute episodes typically benefit from antibiotics with activity against *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis.*

Community-acquired pneumonia can be a major medical problem in that there is an approximate 10% mortality rate among patients requiring hospitalization for this infection. Therefore, empiric antibiotic selection is important and should be based on local surveillance reports that take into account the typical pathogens causing pneumonia and their susceptibility patterns. Of major concern are the reports of therapeutic failure with subsequent serious life-threatening infectious complications caused by *S pneumoniae*, including sepsis occurring while patients were being treated with ciprofloxacin.[7,8] The inferior activity of currently available quinolones against *S pneumoniae* is the primary reason why these antibiotics should neither be considered as drugs of choice nor used as initial monotherapy for community-acquired pneumonia.

Gram-negative bacilli account for more than one half of the causative pathogens associated with nosocomial pneumonia, which constitutes approximately 15% of all hospital-acquired infections. It is paramount that empiric antibiotic therapy include coverage against gram-negative bacilli, including *P aeruginosa*. Most of the clinical experience in this area is with ciprofloxacin, which showed a higher bacteriologic eradication and a higher clinical response rate when compared with imipenem-cilistatin in one clinical trial.[9] Failure to obtain efficacy was common in patients infected with *P aeruginosa*.[9,10] It appears that intravenous ciprofloxacin or ofloxacin can be used to treat nosocomial pneumonia caused by gram-negative bacilli, but an aminoglycoside should be added for suspected or documented *P aeruginosa* infection.

Osteomyelitis

When oral ciprofloxacin became commercially available in the late 1980s, it was touted as the magic bullet to treat osteomyelitis. Patients who previously required weeks of parenteral antibiotics were now able to receive effective treatment by taking a pill. This initial enthusiasm has waned over the ensuing years because of the development of resistant pathogens. When ciprofloxacin was first introduced, it was uniformly sensitive to *P aeruginosa* and methicillin-resistant *S aureus.* Nationwide, resistance is now at least 10% and 80%, respectively.[11]

Overall, the clinical success rates for quinolone-treated osteomyelitis range from 75% to 90%.[4] Ciprofloxacin 750 mg twice daily and ofloxacin 400 mg twice daily are the two oral agents that have accumulated the most experience in osteomyelitis. Most failure rates occurred in patients with polymicrobial infections that included *P aeruginosa* as one of the pathogens. Ofloxacin in combination with rifampin was successful in 74% of patients with orthopedic implants infected with *S aureus.*[12]

The available data suggest that oral quinolones are as effective as conventional parenteral antibiotics against susceptible pathogens for therapy of osteomyelitis. Infections involving *P aeruginosa* and *S aureus* pathogens must be closely monitored for emergence of resistant strains. Addition of an aminoglycoside and rifampin, respectively, may be useful in minimizing resistance.

Skin and Soft Tissue Infections

The more common types of skin and soft tissue infections (eg, cellulitis, pyoderma) are typically caused by streptococcal and staphylococcal species for which conventional therapy with penicillin, semisynthetic penicillin, or a cephalosporin remain the therapy of choice. Quinolones should not be used in this setting because of the suboptimal streptococcal activity and the concern with resistant staphylococcal organisms. However, soft tissue infections can be polymicrobial (aerobic and anaerobic gram-positive and gram-negative organisms) in patients with diabetes and peripheral vascular disease, decubitus ulcers, and some surgical wound infections. In some of these subgroups of patients, quinolones have been evaluated as a treatment for these infections with clinical and bacteriologic efficacy rates in the range of 80% to 90%.[13]

Gastrointestinal Infections

Quinolones have excellent in vitro activity against many enteric pathogens, including *Escherichia coli, Aeromonas, Shigella, Salmonella, Campylobacter, Vibrio,* and *Yersinia* species.[4] Furthermore, quinolone drug concentrations in feces are exceedingly high.

Treatment of traveler's diarrhea with norfloxacin 400 mg twice daily for 3 days and ciprofloxacin 500 mg twice daily for 5 days begun shortly after the onset of diarrhea have shortened the duration of loose stools by 1 to 3 days.[4] Prevention of traveler's diarrhea has also been studied with once-daily dosing of norfloxacin 400 mg, ciprofloxacin 500 mg, and ofloxacin 300 mg. Protection rates range from 70% to 90%.[14,15] Routine prophylaxis for traveler's diarrhea, however, is not recommended because of concerns associated with the emergence of drug resistance, expense, toxicity, and superinfection.

Quinolone treatment for 5 to 7 days has been shown to shorten the symptomatic period for diarrhea caused by *Shigella, Salmonella,* and *Campylobacter* species. In patients with diarrhea caused by *Yersinia* and *Aeromonas,* quinolones have eradicated the organisms from the stool, but have not been clearly shown to decrease the duration of illness.[4]

Norfloxacin 400 mg daily is commonly used to prevent spontaneous bacterial peritonitis in patients with ascites. Enteric gram-negative bacilli are the usual pathogens causing spontaneous bacterial peritonitis, and norfloxacin has been shown to reduce its incidence.[4]

Helicobacter pylori is susceptible to quinolones in vitro. However, quinolones have failed to eradicate this organism from gastric mucosa, and failures have been associated with the rapid development of quinolone resistance.[1]

Dosing Considerations

When prescribing a quinolone, major considerations include dosage adjustment for decreased renal function and the excellent oral absorption of these agents. Table 1 summarizes important dosing considerations.

Orally administered quinolones have excellent absorption, with peak serum concentrations near those achieved by the intravenous route.[1,16] These antibiotics should generally be given orally, including to hospitalized patients who are able to tolerate oral medication.[16] Quinolones have wide distribution into tissues. For example, lung tissue concentrations generally exceed levels in the blood.[17]

Although some quinolones have significant hepatic metabolism, each of these agents is dependent to a marked degree on renal elimination.[16] Consequently, a major point in prescribing quinolones is to estimate creatinine clearance and base the dose on that value. Table 1 summarizes guidelines for dosing quinolones based on renal function. Failure to reduce doses in patients with

Table 4. Clinically Significant Quinolone Interactions

Interaction	Drug	Effect	Management
Inhibition of hepatic drug metabolism	Warfarin*	Increased PT; bleeding	Avoid combination if possible; if must use, carefully monitor PT, preferably with INR
	Theophylline	Theophylline toxicity; increased STC	Avoid enoxacin, ciprofloxacin, and norfloxacin with theophylline if possible; use ofloxacin or lomefloxacin or other antimicrobial agent; alternatively, rely on agents other than theophylline; if must use theophylline, monitor STC
	Caffeine	Increased caffeine serum concentrations; nausea, vomiting	Avoid enoxacin and ciprofloxacin, or reduce caffeine intake (ie, if ≥200 mg daily); circumvent interaction with ofloxacin
Decreased oral absorption of quinolones	Antacids	Dramatic decreases (eg, 85%) in quinolone bioavailability if taken concurrently	Space doses; take quinolone at least 2 hours before or more than 6 hours after antacid
	Sucralfate	Dramatic decrease in quinolone bioavailability	Avoid combination; no known management (ie, no studies on adequate spacing of doses)

**Interaction most likely to occur in elderly patients or with higher doses of quinolones.*
PT denotes prothrombin time; INR, international normalized ratio; STC, serum theophylline concentration.

moderate to severe decreases in kidney function results in increased cost of therapy, and far more importantly, increased risks of adverse effects.

To give further emphasis to this important point, the elimination half-life of ciprofloxacin is about 4 hours in patients with normal renal function, but in patients with end-stage renal disease, the half-life is about 8 hours.[18] The half-life of ofloxacin is 4 to 8 hours in patients with normal renal function, but with creatinine clearance of about 40 to 50 mL per minute, the half-life is 15 hours, and with end-stage renal disease, the half-life is about 1.5 days.[18] The half-life of lomefloxacin in patients with normal renal function is 8 hours; however, it is 21 hours in patients with creatinine clearances of 10 to 40 mL per minute, and 38 to 44 hours in patients with creatinine clearances <10 mL per minute.[19] The clinical relevance of dosage adjustment in these patients is obvious.

Adverse Effects

Quinolones are generally well tolerated.[20] While the incidence of adverse effects is low, the most common include nausea and vomiting, dizziness, headache, abdominal pain, and diarrhea. Pseudomembranous colitis also has been reported and should be managed as "antibiotic-associated colitis." As with most medications, very rare severe hypersensitivity reactions can occur with quinolones. Because of several reports of severe reactions to temafloxacin, it is no longer available.[21] Crystalluria has been reported in patients with alkaline urine, but this problem can be avoided by maintaining adequate hydration and urine acidity.

Toxic serum concentrations of quinolones are associated with neurotoxicity.[22] Overdosage, including usual doses in patients with decreased renal function, may cause seizures, confusion, or hallucinations.[22,23] Nonsteroidal anti-inflammatory drugs used concurrently with quinolones may be associated with increased risk of neurotoxicity, but further research is needed to establish this association.[4] Achilles' tendon rupture has recently been associated with quinolone use.[24]

Inhibition of Hepatic Drug Metabolism by Quinolones

Quinolones decrease hepatic metabolism for some drugs through inhibition of the cytochrome P-450 enzyme system.[4] This effect of quinolones can result in serious toxicity for some agents. Table 4 summarizes examples of clinically significant drug interactions associated with quinolones.

Theophylline

Numerous pharmacokinetic studies[25–33] as well as reports of toxicity[34–36] have clearly shown the clinical importance of the effect of several quinolones on theophylline. Enoxacin has the greatest potential to increase serum theophylline concentrations by decreasing theophylline clearance. Trials in patients[25] and healthy subjects[26] have

demonstrated a 50% to 64% decrease in theophylline clearance. Ciprofloxacin also decreases theophylline clearance by 25% to 30%.[25,27,28] While norfloxacin does not have such a dramatic effect on theophylline, it causes a 10% to 15% decline in clearance,[29-30] which can result in clinically important increases in serum theophylline concentrations in some patients. These interactions have been reported to cause theophylline toxicity,[34,35] resulting in adverse events including seizures.[33]

Examination of cases reported to the FDA revealed a mean percentage increase in serum theophylline concentrations of 114% when ciprofloxacin or norfloxacin were given concomitantly with theophylline.[34] Fourteen of 39 patients receiving ciprofloxacin and theophylline experienced a seizure, and three of nine patients on concurrent norfloxacin and theopylline had this same adverse event.[34] Analysis of reports to the FDA further revealed that the elderly are at increased risk for this interaction. Although this summary of reports to the FDA was published before enoxacin was released in the United States, adverse effects due to this interaction have been reported outside this country.[35,36]

Fortunately, not all quinolones cause a rise in serum theophylline concentrations. Both ofloxacin[25,26,31] and lomefloxacin[32,33] have been shown to have only negligible effects on theophylline clearance. Therefore, when quinolones must be used concomitantly with theophylline, it is far preferable to use ofloxacin or lomefloxacin if either of these agents is appropriate for the infection being treated.

Caffeine

Since caffeine is a xanthine like theophylline, it is no surprise that the same quinolones that decrease the metabolism of theophylline with resultant increases in serum concentrations have a similar effect on caffeine. For example, enoxacin 400 mg twice daily combined with caffeine 200 mg daily (eg, two cups of coffee) commonly produced side effects such as nausea and vomiting.[37] Ciprofloxacin can also decrease the clearance of caffeine but to a lesser extent than enoxacin.[38] Norfloxacin, lomefloxacin, and ofloxacin do not cause this problem.[1,38,39]

Warfarin

The most compelling evidence for a clinically significant interaction to date is a series of case reports of increased prothrombin times (PT) after quinolones were added to stable warfarin regimens.[40-50] In these 10 reports, most of the patients (12 of 14) were older than 60 years of age, and the effect on warfarin was detected as early as 2 days or as late as 16 days after initiation of quinolone therapy. In a series of 18 cases reported to the FDA, five patients were described in detail because of thorough documentation.[43] Three of the five patients had hemorrhagic complications associated with the rise in PT.[43] Hemorrhagic complications attributed to this interaction have been reported in other cases as well.[40,41,46,48] Ciprofloxacin,[40-45] norfloxacin,[43,46] ofloxacin,[47,48] nalidixic acid,[49] and enoxacin[50] are the quinolones that have been reported to be associated with an increase in warfarin effect.

The study by Toon et al[50] provides further evidence that quinolones inhibit the metabolism of warfarin. In this report, enoxacin decreased the clearance of the R-stereoisomer of warfarin in six healthy male volunteers but did not affect the hypoprothrombinemic effect of warfarin. Although the R-stereoisomer of warfarin is less pharmacologically active than the S-stereoisomer, this investigation provides a reasonable explanation for increased warfarin effect in at least some patients as a result of decreased warfarin clearance. It is pertinent to note that cimetidine also inhibits the R-stereoisomer of warfarin and it is well documented to cause increased warfarin response in some patients.[51,52] In contrast to enoxacin, norfloxacin altered neither warfarin's pharmacokinetics nor its anticoagulant effects in another trial of healthy subjects.[53] Caution is advised, however, in extrapolating these results from healthy volunteer subjects to patients with underlying diseases and organs impaired for drug clearance.

In a study of nine male patients with a mean age of 62 ± 12 years, ciprofloxacin 500 mg twice daily for 7 days did not affect the mean response to warfarin.[54] However, one patient had a 22% increase in PT. These authors correctly point out that their study does not rule out an interaction in some patients on higher approved doses (eg, 750 mg twice daily). In a similar study, ciprofloxacin 500 mg twice daily for 10 days did not affect mean response to warfarin.[55]

Based on reports to date, we believe further study is warranted to examine how quinolone dose affects warfarin. For example, in the FDA report, the two patients who were receiving ciprofloxacin 1000 mg daily (presumably 500 mg twice daily) were both >80 years of age.[43] Since ciprofloxacin is renally eliminated and doses should be adjusted per creatinine clearance, it is likely that these two elderly patients had higher serum concentrations of ciprofloxacin than would a young or middle-aged individual taking the same dose. Studies of ciprofloxacin 750 mg twice daily in nonelderly patients would be helpful. The impact of dosage for other drugs reported to affect warfarin is reflected in case reports.[56,57] Specifically, ranitidine 300 mg daily and isoniazid 300 mg daily do not affect warfarin, but doubling the dose to 600 mg daily for both agents has been reported to increase the PT dramatically.[56,57] It is reasonable to suspect that higher doses of

quinolones in some patients increase the likelihood of an effect on warfarin.

Studies of concurrent use of quinolones and warfarin clearly demonstrate that the interaction is unpredictable and frequently is not clinically significant. However, existing case reports of increased hypoprothrombinemia with bleeding due to this interaction warrant careful monitoring of PT, preferably with the international normalized ratio (INR), when using these agents concurrently.

Interactions Resulting in Decreased Oral Absorption of Quinolones

Gastrointestinal absorption of quinolones is dramatically reduced with concomitant administration of antacids or sucralfate. Proper management of these interactions is essential to assure adequate serum concentrations of these antimicrobials.

Antacids

Antacids containing magnesium, aluminum, or calcium impair the gastrointestinal absorption of oral quinolones, resulting in decreased serum and urine concentrations.[58–61] For example, serum ciprofloxacin concentrations are decreased by up to 85% if antacids are administered at roughly the same time as ciprofloxacin.[58] Such dramatic decreases in bioavailability obviously could result in therapeutic failure in some patients.

The mechanism of this interaction appears to be the result of a complex formed between functional groups on the quinolone and the antacid cation. The resulting complex has no antibacterial activity. Formation of quinolone-antacid complexes appears to vary depending on the type of metal ion. Aluminum-magnesium–containing antacids bind with quinolones to a greater extent than calcium products. Also, the effects of antacids seem to vary at least somewhat among the quinolones. While each quinolone studied to date may be significantly affected by the concurrent administration of antacids, the strongest interaction is seen with norfloxacin, followed by ciprofloxacin and enoxacin. Ofloxacin appears to show the weakest interaction.

Nix et al[58] studied the effects of aluminum and magnesium antacids on the absorption of ciprofloxacin. With a 7-day washout period between each ciprofloxacin dose, healthy subjects received ciprofloxacin 750 mg either alone or following a 30-mL dose of antacid at the following times: 5 to 10 minutes, 2 hours, 4 hours, or 6 hours. Ciprofloxacin was also given 2 hours *before* the antacid. When the antacid was given 5 to 10 minutes before ciprofloxacin, bioavailability of the antimicrobial was reduced 85% (Figure 1). Similarly, marked reductions in serum concentrations were seen when antacids were administered 2 hours (77% decrease) and 4 hours (30% decrease) before ciprofloxacin. When ciprofloxacin was administered *2 hours before the antacid*, the interaction was completely avoided. Giving ciprofloxacin 6 hours after the antacid also circumvented the interaction. To ensure that this interaction is not based on increased gastric pH, Nix et al[58] also gave ranitidine with ciprofloxacin and found no effect on the bioavailability of the antibacterial agent.

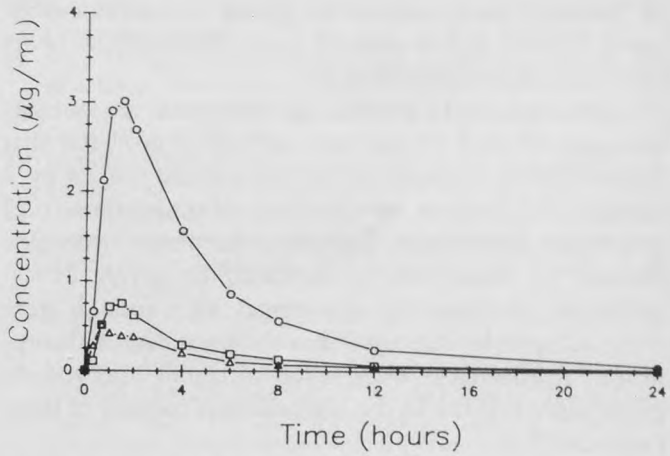

Figure 1. Ciprofloxacin concentration vs time profiles for ciprofloxacin 750 mg adminstered alone (circles), 5 to 10 minutes after 30 mL antacid (triangles), and 2 hours after 30 mL antacid (squares). Reprinted from Nix DE, Watson WA, Lener ME, et al. Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. Clin Pharmacol Ther 1989; 46: 700–5. Reproduced with permission of Mosby-Year Book Inc.

Magnesium-aluminum hydroxide "hidden" in didanosine chewable tablets was also found to dramatically reduce peak serum concentrations of ciprofloxacin.[59] Magnesium-aluminum hydroxide is found in didanosine chewable tablets because the drug is very acid labile and requires a buffering agent to minimize hydrolysis in the stomach by acid.

In a similar study, Nix and associates[60] found highly significant reductions in serum concentrations of norfloxacin when aluminum-magnesium hydroxide was given 5 minutes before the antimicrobial agent: only 9% of norfloxacin was absorbed. In the same study using a calcium carbonate antacid, less than 40% of norfloxacin was bioavailable. On the other hand, when norfloxacin was administered *2 hours before* the antacid, bioavailability was greater than 80%. Similar results have been reported for concomitant administration of enoxacin and magnesium-aluminum antacids.[61] Dramatic reductions in absorption

of enoxacin were avoided by giving the antimicrobial agent 2 hours before antacid or, in this study, 8 hours after antacid administration.[61]

Ofloxacin and ciprofloxacin absorption are not significantly affected by calcium carbonate, provided that doses of these quinolones and antacid are spaced by 2 hours.[62,63] However, if ofloxacin administration is 2 hours after ingestion of magnesium-aluminum hydroxide antacid, its absorption is decreased by about 22%.[62] Although administering quinolones with food is generally acceptable, one study has shown reduced absorption of ciprofloxacin when taken with milk and yogurt, presumably because of the high calcium content of these products.[64]

Based on clinical trials to date, concomitant administration of quinolones and antacids should be avoided if possible. However, if both agents are required, it is recommended to give the quinolone *2 hours before* or *at least 6 hours after* the antacid.

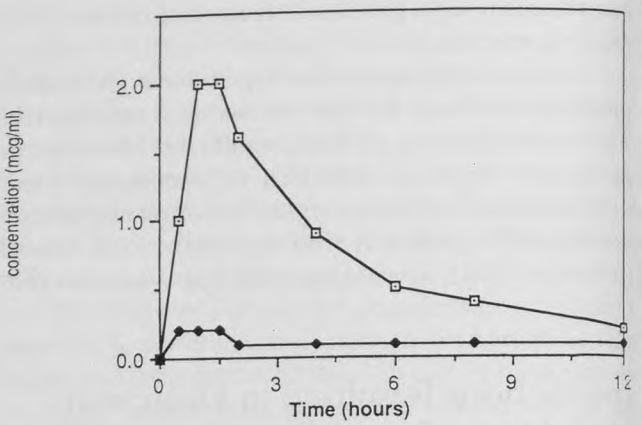

Figure 2. Plot of mean serum concentrations of ciprofloxacin vs time for subjects receiving ciprofloxacin alone (open squares) and with sucralfate (closed diamonds). Reproduced with permission from Garrelts JC, Godley PJ, Peterie JD, et al. Sucralfate significantly reduces ciprofloxacin concentrations in serum. Antimicrob Agents Chemother 1990; 34:931–3. Reproduced with permission of the American Society for Microbiology.

Sucralfate

Each 1-g dose of sucralfate contains 207 mg of aluminum. Sucralfate releases aluminum ions upon dissolution, which may form a complex with quinolones. Consequently, as with antacids, there are clinically significant reductions in absorption of quinolones when given with sucralfate.

Garrelts et al[65] reported a highly significant reduction in ciprofloxacin bioavailability when sucralfate was given concurrently. Peak serum concentrations after a 500-mg dose of ciprofloxacin alone were 2.0 μg/mL, but were only 0.2 μg/mL when sucralfate was administered with ciprofloxacin (Figure 2). Other authors have also found significant decreases in absorption of ciprofloxacin and norfloxacin when sucralfate is given, even when doses are spaced.[66,67] Until further clinical research is conducted to determine adequate dose spacing strategies, use of sucralfate with quinolones should be avoided. If concurrent use is absolutely necessary, administration of quinolones several hours before sucralfate is preferable.

Iron Products, Zinc-Containing Multivitamin Products, and Enteral Feeding Products

Ferrous sulfate and other iron preparations as well as multivitamin products containing zinc may interfere with oral absorption of quinolones, resulting in decreased serum and urine concentrations of these antibacterial agents. The mechanism for these interactions appears to be the same as for the effect of antacids and sucralfate on quinolone absorption.

Polk et al[68] found a 60% mean reduction in ciprofloxacin absorption in subjects given ferrous sulfate 325 mg three times daily for 1 week, with a 500-mg single dose of ciprofloxacin given with the last dose of iron. The peak concentrations of ciprofloxacin were below the minimal inhibitory concentration for 90% of strains of many bacteria usually considered susceptible. In the same study, a 25% decrease in ciprofloxacin absorption was detected in subjects who took a multivitamin with zinc for 1 week and a 500-mg single dose of ciprofloxacin with the last dose of multivitamin.[68]

Kara et al[69] further established the importance of the effect of iron products on reducing ciprofloxacin serum concentrations. Ferrous sulfate 300 mg and ferrous gluconate 600 mg reduced peak ciprofloxacin concentrations after a 500-mg single dose of the quinolone from 3.0 μg/mL to 2.0 μg/mL, and from 3.0 μg/mL to 1.3 μg/mL, respectively.

Mueller et al[70] recently reported that enteral feeding with Ensure significantly reduced oral bioavailability of ciprofloxacin, and to a lesser extent, ofloxacin. Presumably, the divalent cations in this enteral feeding product and others may result in reduced absorption of quinolones.

Summary

Quinolones are effective antimicrobial agents for several infectious diseases. Because indiscriminate use of quinolones has resulted in increased patterns of resistance, it is important to give careful thought to the site of infection

and potential pathogens in each patient. These agents have excellent oral absorption. When prescribing quinolones for any of their numerous indications, attention to dosing based on estimated creatinine clearance is clinically important. Quinolones are associated with several clinically significant drug interactions. Some of these agents are well-documented inhibitors of hepatic metabolism of theophylline, caffeine, and warfarin. It is well documented in the literature that divalent and trivalent cations in several products significantly reduce the absorption of quinolones. Avoidance or proper management of these interactions is required to ensure optimal safety and efficacy.

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