Review

ISSN 1975-7425(Print) / ISSN: 2288-016X(Online)
http://dx.doi.org/10.14777/kjutii.2015.10.1.1
Korean J Urogenit Tract Infect Inflamm 2015;10(1):1-6

항생제 Fluoroquinolones의 약동학 및 약력학에 관한 최신 정보

고영휘, 송필현

영남대학교 의과대학 비뇨기과학교실

Current Updates in Pharmacokinetics and Pharmacodynamics of Fluoroquinolones

Young Hwii Ko and Phil Hyun Song

Department of Urology, Yeungnam University College of Medicine, Daegu, Korea

The ultimate goal of antimicrobial treatment is to decrease the morbidity and mortality related to infection. Maximizing these outcomes requires an understanding of the complex interactions between the drug administered, the host, and the infecting pathogen. Pharmacokinetics, which deals with the disposition of a drug in the body, focuses on such parameters as absorption, distribution, and elimination. Pharmacodynamics more specifically focuses on the interaction between the drug concentration at the site of action over time and the resulting antimicrobial effect. Use of quinolones has increased in vitro activity against several important pathogenic organisms as well as augmented pharmacokinetic parameters. These properties result in enhanced pharmacodynamic characteristics and should improve therapeutic outcomes against selected pathogens. In this article the pharmacokinetics and pharmacodynamic potential of these quinolones, particularly fluoroquinolones, is reviewed.

Keywords: Fluoroquinolones; Pharmacokinetics; Pharmacology

Received: 27 March, 2014
Revised: 13 April, 2014
Accepted: 13 April, 2014

Correspondence to: Phil Hyun Song
http://orcid.org/0000-0002-3801-258X
Department of Urology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 705-703, Korea
Tel: +82-53-620-3693, Fax: +82-53-627-5535
E-mail: sph04@hanmail.net

INTRODUCTION

Most decisions with regard to the selection of appropriate antimicrobial therapy were based on whether a drug would safely attain the necessary concentration in serum in order to inhibit or kill the infecting organism, and the following factors were usually considered: activity against the likely pathogen, resistance patterns, adverse effects and allergies, ease of dosing, cost, pharmacokinetics and pharmacodynamics.[1,2]

This static parameter, referred to as the "minimum inhibitory concentration (MIC)" was the final arbiter of potential treatment success or failure.[1] However, this in vitro measurement cannot provide information on either the rate of eradication of the organism or whether alterations in dosage or delivery of the drug would result in improved eradication, decreased emergence of resistance, or, ultimately, increased survival.[2]

This review will summarize the pharmacokinetics and pharmacodynamic principles of antimicrobial therapy and apply these principles to the currently available fluoroquinolone class of antimicrobials.

FLUOROQUINOLONES

Quinolones are unusual among antimicrobials in that they were not isolated from living organisms, but rather synthesized by chemists. The first quinolone, nalidixic acid, was derived from the antimalarial drug chloroquine.[3] Subsequent agents were derived through side chain and nuclear manipulation.[4] The development of the fluoroquinolone class may be described in generational terms, with each generation sharing similar features or antimicrobial spectra.[3-5] First-generation agents possess activity against aerobic gram-negative bacteria, but little activity against aerobic gram-positive bacteria or anaerobes. Second-generation agents are the original fluoroquinolones, named for the addition of a fluorine atom at position C-6 (Fig. 1). These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage. Third-generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, in combination with good activity against anaerobes. Fourth-generation fluoroquinolones have superior coverage against pneumococci and anaerobes.[5]

1. Structure-Activity Relationships

Decades of fluoroquinolone development provide considerable insight into the effects of structural modification upon the antimicrobial activity and pharmacologic properties of these agents. Fig. 1 depicts the core quinolone nucleus. Position 1 affects drug potency, pharmacokinetics, and the potential for interaction with theophylline. Positions 2, 3, and 4 determine antibacterial activity by influencing the affinity for bacterial enzymes. Additionally, positions 3 and 4 are involved in metal chelation and the resulting interaction with di- and trivalent cations. The presence of a methoxy side chain at position 5 enhances gram-positive activity and phototoxicity. The addition of a fluorine atom to position 6 transforms a quinolone into a fluoroquinolone, enhancing drug penetration into the bacterial cell and activity against gram-negative bacteria. Position 7, like position 1, is instrumental in drug potency, pharmacokinetics, and the interaction with theophylline. This position is also implicated in the central nervous system toxicity of some fluoroquinolones owing to their proclivity to bind to gammaaminobutyric acid. The addition of a piperazine moiety at position 7 augments activity against *Pseudomonas aeruginosa*, whereas a pyrrolidine group improves gram-positive activity. The presence of any halogen at position 8 can increase a drug's half-life, absorption, and anti-anaerobic activity; however, the resulting phototoxicity of di-halogenated compounds renders them unacceptable for clinical use. In contrast, superior pneumococcal activity is achieved by the addition of a methoxy group at position 8 without attendant phototoxicity.[6,7]

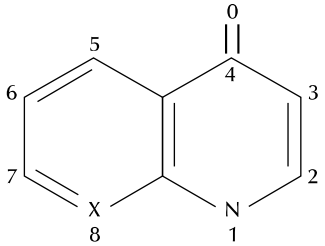

Fig. 1. The core quinolone nucleus.

PHARMACOKINETICS

Fluoroquinolones have favorable pharmacokinetic properties that have encouraged their widespread use. They are well absorbed and have good tissue penetration, which facilitates their use for many clinical syndromes.[6]

1. Absorption

Fluoroquinolone antimicrobials normally exhibit rapid dissolution in the gastrointestinal tract and are absorbed in the duodenum and jejunum. Peak serum concentrations are usually attained 1-2 hours after dosing in healthy persons.[7] The third-generation quinolones also exhibit maximal serum concentration (Cmax) in 1-2 hours, with the exception of sparfloxacin. Sparfloxacin is more slowly absorbed, and its Cmax is observed in 4-5 hours.[8] This finding is most likely the result of the lower solubility of sparfloxacin in aqueous solution. Coingestion with food usually increases the time to peak serum concentration by 1 hour for these fluoroquinolones, but other pharmacokinetic values are unaltered.[9-11]

The Cmax varies significantly among these compounds.

Following a 200-mg dose, peak levels in the range of 0.7 μg/ml (sparfloxacin) to 2.9 μg/ml (trovafloxacin) are attained. In dose-ranging studies it has been observed that an increase in dose will result in a linear increase in the Cmax for these fluoroquinolones.[8-10,12,13] The area under the serum concentration-time curve (AUC) for these agents also increases linearly in proportion to dose. In contrast to its low Cmax, sparfloxacin has a large AUC due to its long elimination half-life (Table 1).

2. Distribution

The distribution volumes of the third-generation fluoroquinolones are large and may exceed those of second-generation compounds. For instance, the distribution volumes of grepafloxacin and sparfloxacin have been estimated to be 3.5 L/kg and 4.5 L/kg, respectively.[14] These compounds, like their predecessors, exhibit low protein binding. Displacement of highly protein-bound drugs is unlikely with these fluoroquinolones, including trovafloxacin.[13] The penetration of third-generation quinolones into several different tissues and body fluids in humans has been demonstrated. Levofloxacin has been most extensively studied and has characteristics similar to those of ofloxacin.[9] Levofloxacin concentrations in most tissues or fluids are generally higher or similar to those observed in plasma.[15] Inflammatory fluid penetration of several of the newer fluoroquinolones has been studied.[14,16] In healthy volunteers, peak concentrations in chemically induced blisters ranged from 41-81% of those found in serum (Table 2).

High concentrations of these antimicrobials have also been observed in kidney parenchyma, gallbladder tissue and bile, and genital tract tissues.[9,17,18] In a study of six surgical patients, mean grepafloxacin concentrations of 0.9 μg/ml, 5.6 mg/kg, and 51 μg/ml were attained in serum, gallbladder tissue, and bile, respectively, at 2-5 hours after oral administration of 300 mg.[17]

3. Elimination

The fluoroquinolones are removed from the body by both renal and nonrenal routes of elimination.[7] High concentrations of unchanged drug can be found in the urine, bile, and feces. When analyzing the urinary excretion of the third-generation quinolones, one finds that these compounds fall into two distinct groups. Greater than 60% of unchanged drug can be recovered in urine following administration of levofloxacin and clinafloxacin.[9,12] In contrast, lower than 10% of unchanged drug is found in the urine after doses of grepafloxacin, sparfloxacin, and trovafloxacin.[8,13,14]

Table 1. Pharmacokinetic properties of fluoroquinolones

Fluoroquinolone	Oral dose (mg)	t_{max} (h)	Cmax (μg/ml)	t1/2β (h)	AUC ([mg·h]/L)
Sparfloxacin	200	4.0	0.7	21.0	19.0
Levofloxacin	200	1.5	2.0	6.0	20.0
Grepafloxacin	200	2.1	0.7	11.0	8.8
Trovafloxacin	200	0.7	2.9	7.8	24.0
Clinafloxacin	200	1.5	1.6	6.3	11.0

t_{max}: time after dosing for maximal concentration to be reached, Cmax: maximal serum concentration, t1/2β : elimination half-life, AUC: area under the serum concentration curve.

Table 2. Inflammatory fluid penetration of fluoroquinolones

Parameter	Grepafloxacin (400 mg)	Levofloxacin (500 mg)	Sparfloxacin (400 mg)	Trovafloxacin (200 mg)
Serum				
t_{max} (h)	2.0	1.2	2.7	0.75
Cmax (μg/ml)	1.5	6.6	1.6	2.9
t1/2β (h)	5.2	8.0	18	7.8
AUC ([mg·h]/L)	12	53	32	24
Blister fluid				
t_{max} (h)	4.8	3.7	5.0	4.0
Cmax (μg/ml)	1.1	4.3	1.3	1.2
t1/2β (h)	13	8.0	20	7.1
AUC ([mg·h]/L)	22	54	37	15
Percentage penetration (blister fluid value/serum value)				
Cmax	73	65	81	41
AUC	180	100	117	63

t_{max}: time after dosing for maximal concentration to be reached, Cmax: maximal serum concentration, t1/2β : elimination half-life, AUC: area under the serum concentration curve.

Changes in renal function can have a significant impact on the elimination of these drugs, including those that have low urinary recovery. For instance, the serum elimination half-life of sparfloxacin in patients with moderate or severe renal impairment (glomerular filtration rates of 22 ml/min and 7.7 ml/min, respectively) was found to be approximately two times higher than observed in healthy volunteers.[19] The effect of renal impairment on the pharmacokinetics of levofloxacin has also been studied.[9] The mean elimination half-lives in patients with creatinine clearances of 40-70 ml/min, 20-40 ml/min, and <20 ml/min were 6.4, 11, and 28 hours, respectively. The serum elimination half-life of the third-generation quinolones ranges from 4.6 to 21 hours in healthy adults (Table 1).

DRUG INTERACTIONS

The absorption of quinolone antibiotics is significantly decreased by concomitant administration of compounds that contain multivalent metal cations such as aluminum, magnesium, zinc, iron, and calcium.[20] This effect appears to be due to the formation of insoluble drug-cationic chelate complexes in the gastrointestinal tract.[21] The bioavailability of third-generation quinolones has been shown to be decreased by 50% when they are administered with aluminum-magnesium antacids.[22] It has been recommended that fluoroquinolones be given at least 2 hours prior to administration of these compounds.[23]

The clearance of other drugs can be altered by the coadministration of certain fluoroquinolones.[20] For instance, ciprofloxacin and enoxacin have been shown to inhibit theophylline and caffeine metabolism, resulting in adverse effects such as nausea, vomiting, and central nerve system excitement. Pharmacokinetic studies of sparfloxacin, levofloxacin, and trovafloxacin have found that these fluoroquinolones do not significantly alter theophylline metabolism in healthy volunteers.[9,24] And additional investigations of potential drug interactions with third-generation quinolones are warranted, especially with regard to medications such as warfarin and cyclosporine.

PHARMACODYNAMICS

Almost 30 years ago, several investigators proposed that antibacterials can be divided into 2 major categories on the basis of their major mechanism of bacterial killing: time-dependent or concentration-dependent activity (Table 3).[25]

1. Time-Dependent Antibacterials

The first group of antibacterials includes agents whose effect depends on the length of time that the drug is in contact with the bacteria at concentrations exceeding the MIC. Maximum killing is achieved at concentrations approaching 4-5 times the MIC,[26] but any further increases in concentrations provide little to no additional benefits. Therefore, the length of time that the drug concentration is above the MIC (T>MIC) has been determined to be the most important parameter for determining clinical and microbiological success.[25]

For β-lactam antibacterials, when the T>MIC exceeds 40% to 50% of the dosing interval, clinical and bacteriological efficacy theoretically approaches >90% (Table 4). However, a few qualifying statements need to be made. Additionally, maximizing the T>MIC may improve outcomes for hospitalized patients infected with relatively

Table 3. Pharmacokinetic and pharmacodynamic parameters in antibiotic therapy

Parameters
Mechanism of bacterial killing
Concentration-independent
Concentration-dependent
Three parameters correlating with outcome
T>MIC
Cmax:MIC
AUC:MIC

MIC: minimum inhibitory concentration, T>MIC: time that the drug concentration is above the MIC. Cmax: maximal serum concentration, AUC: area under the serum concentration curve.

Table 4. Pharmacodynamic parameters predictive of the outcome associated with various classes of antimicrobials

Parameter	Class of antimicrobial
T>MIC	Penicillin
	Cephalosporins
	Carbapenems
	Macrolides
Cmax:MIC	Aminoglycosides
	Fluoroquinolones
AUC_{24}:MIC	Fluoroquinolones
	Azalides
	Ketolides

MIC: minimum inhibitory concentration, T>MIC: time above the MIC, Cmax: maximal serum concentration, AUC_{24}: 24-h area under serum concentration curve.

resistant pathogens. Increasing the dosing frequency, total dose, or duration of infusion may maximize the T>MIC in select circumstances, thereby improving the outcome.[26,27] Further studies will be necessary before standard recommendations can be made.

2. Concentration-Dependent Antibacterials

The second group of antibacterials includes agents whose effects depend on increasing concentrations of the antibacterial (Table 4). The parameters that most closely correlate with the success of these agents include the ratio of Cmax to the MIC (Cmax:MIC) and the ratio of the 24-h area under the plasma concentration curve (AUC_{24}) to the MIC (AUC_{24}:MIC).[2] Most authors agree that only the concentration of free drug is important in making these calculations or for allowing accurate comparisons between drugs of the same class with different degrees of protein binding.[28] Throughout the remaining discussion, "AUC:MIC" refers to free AUC:MIC, unless otherwise noted. Fluoroquinolones, aminoglycosides, and ketolides have been classified primarily as concentration-dependent antibiotics (Table 4). Many recently published studies in this field have focused on dissecting these parameters with regard to the fluoroquinolones. Overall, the AUC:MIC has had the greatest correlation with outcome in either in vitro or animal models of infection,[28] but the greatest debate has focused on the magnitude of the AUC:MIC that is necessary to maximize outcome or prevent emergence of resistance.

The correlation of drug concentration and pharmacodynamics of an antibiotic class is based on the integration of microbiological activity and pharmacokinetics.[29] The fluoroquinolones exert concentration-dependent killing, and both the AUC/MIC and Cmax/MIC ratios have been shown to be pharmacodynamic correlates of efficacy.[30] In vitro models suggest that Cmax/MIC ratios of >8 and AUC_{24}/MIC ratios of >125 are necessary for rapid bacterial eradication and prevention of regrowth with resistant subpopulations of certain bacteria.[29,30]

Animal and patient studies have confinned these findings. In a neutropenic rat model of *Pseudomonas aeruginosa* sepsis, the serum peak/MIC ratio was linked to survivorship, particularly when high ratios (20:1) were obtained.[31] In a study of acutely ill patients treated with ciprofloxacin, an AUC_{24}/MIC ratio of >125 was highly predictive of a microbiological and clinical cure.[30] These findings suggest that the clinical utility of this fluoroquinolone will depend on whether it can attain high Cmax/MIC (10:1) or AUC_{24}/MIC (125:1) ratios against clinically important pathogens.

CONCLUSIONS

Fluoroquinolones have gained widespread use owing to their favorable pharmacokinetics, pharmacodynamics, and broad antimicrobial spectra. These quinolones are concentration-dependent killers, however, a new high dose and short course approach, while keeping pharmacodynamic principles in mind, may work faster, encourage better patient compliance, have similar toxicity, decrease cost, and prevent resistance development.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-10.
2. Mueller M, de la Peña A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. Antimicrob Agents Chemother 2004;48:369-77.
3. Andriole VT. The quinolones: past, present, and future. Clin Infect Dis 2005;41(Suppl 2):S113-9.
4. Ball P. Adverse drug reactions: implications for the development of fluoroquinolones. J Antimicrob Chemother 2003;51(Suppl 1):21-7.
5. Jacoby GA. Mechanisms of resistance to quinolones. Clin Infect Dis 2005;41(Suppl 2):S120-6.
6. O'Donnell JA, Gelone SP. The newer fluoroquinolones. Infect Dis Clin North Am 2004;18:691-716.
7. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. Ann Pharmacother 2007;41:1859-66.
8. Montay G, Bruno R, Vergniol JC, Ebmeier M, Le Roux Y, Guimart C, et al. Pharmacokinetics of sparfloxacin in humans after single oral administration at doses of 200, 400, 600, and 800 mg. J Clin Pharmacol 1994;34:1071-6.
9. Davis R, Bryson HM. Levofloxacin. A review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994;47:677-700.
10. Nakashima M, Uematsu T, Kosuge K, Umemura K, Hakusui H,

Tanaka M. Pharmacokinetics and tolerance of DU-6859a, a new fluoroquinolone, after single and multiple oral doses in healthy volunteers. Antimicrob Agents Chemother 1995;39: 170-4.
11. Cohen KA, Lautenbach E, Weiner MG, Synnestvedt M, Gasink LB. Coadministration of oral levofloxacin with agents that impair absorption: impact on antibiotic resistance. Infect Control Hosp Epidemiol 2008;29:975-7.
12. Barton TD, Fishman NO, Weiner MG, LaRosa LA, Lautenbach E. High rate of coadministration of di- or tri-valent cation-containing compounds with oral fluoroquinolones: risk factors and potential implications. Infect Control Hosp Epidemiol 2005;26:93-9.
13. Teng R, Harris SC, Nix DE, Schentag JJ, Foulds G, Liston TE. Pharmacokinetics and safety of trovafloxacin (CP-99,219), a new quinolone antibiotic, following administration of single oral doses to healthy male volunteers. J Antimicrob Chemother 1995;36:385-94.
14. Child J, Andrews JM, Wise R. Pharmacokinetics and tissue penetration of the new fluoroquinolone grepafloxacin. Antimicrob Agents Chemother 1995;39:513-5.
15. Johnson JH, Cooper MA, Andrews JM, Wise R. Pharmacokinetics and inflammatory fluid penetration of sparfloxacin. Antimicrob Agents Chemother 1992;36:2444-6.
16. Child J, Mortiboy D, Andrews JM, Chow AT, Wise R. Open-label crossover study to determine pharmacokinetics and penetration of two dose regimens of levofloxacin into inflammatory fluid. Antimicrob Agents Chemother 1995;39:2749-51.
17. Tanimura H, Uchiyama K, Kashiwagi H. Gallbladder tissue concentrations, biliary excretion and pharmacokinetics of OPC-17116. Drugs 1995;49(Suppl 2):341-3.
18. Matsuda S. Clinical experience with OPC-17116 in the treatment of gynaecological infections and its penetration into gynaecological tissues. Japanese Collaborative Study Group of OPC-17116 in Gynaecology. Drugs 1995;49(Suppl 2):395-8.
19. Borner K, Borner E, Lode H. A metabolite of sparfloxacin in urine. Drugs 1993;45(Suppl 3):S303-4.
20. Radandt JM, Marchbanks CR, Dudley MN. Interactions of fluoroquinolones with other drugs: mechanisms, variability, clinical significance, and management. Clin Infect Dis 1992;14: 272-84.
21. Tanaka M, Kurata T, Fujisawa C, Ohshima Y, Aoki H, Okazaki O, et al. Mechanistic study of inhibition of levofloxacin absorption by aluminum hydroxide. Antimicrob Agents Chemother 1993; 37:2173-8.
22. Shiba K, Sakamoto M, Nakazawa Y, Sakai O. Effects of antacid on absorption and excretion of new quinolones. Drugs 1995; 49(Suppl 2):360-1.
23. Flor S, Guay DR, Opsahl JA, Tack K, Matzke GR. Effects of magnesium-aluminum hydroxide and calcium carbonate antacids on bioavailability of ofloxacin. Antimicrob Agents Chemother 1990;34:2436-8.
24. Johnson RD, Wilson J, Dorr MB, Jensen BK, Talbot GH, Heald DL. The effect of sparfioxacin on the pharmacokinetics of theophylline at steady-state conditions. J Clin Pharmacol 1995;35:936.
25. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. Clin Infect Dis 2005;41(Suppl 2):S127-35.
26. Grant EM, Kuti JL, Nicolau DP, Nightingale C, Quintiliani R. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. Pharmacotherapy 2002;22:471-83.
27. Dandekar PK, Maglio D, Sutherland CA, Nightingale CH, Nicolau DP. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. Pharmacotherapy 2003;23:988-91.
28. Ambrose PG, Bhavnani SM, Owens RC Jr. Clinical pharmacodynamics of quinolones. Infect Dis Clin North Am 2003;17:529-43.
29. Quintiliani R. Using pharmacodynamic and pharmacokinetic concepts to optimize treatment of infectious diseases. Infect Med 2004;21:219-32.
30. Stein GE. Pharmacokinetics and pharmacodynamics of newer fluoroquinolones. Clin Infect Dis 1996;23(Suppl 1):S19-24.
31. MacGowan AP, Rogers CA, Holt HA, Wootton M, Bowker KE. Pharmacodynamics of gemifloxacin against Streptococcus pneumoniae in an in vitro pharmacokinetic model of infection. Antimicrob Agents Chemother 2001;45:2916-21.