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Pharmacokinetic comparison of two levofloxacin 100-mg tablet formulations and determination of time point appropriately reflecting its area under the curve

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Levofloxacin is a broad-spectrum antibiotic with activity against gram-positive and -negative bacteria. This study compared the pharmacokinetics (PK) and evaluated the bioequivalence of two levofloxacin 100-mg tablet formulations. An open, randomized, two-way crossover study was conducted in 28 healthy volunteers. The reference (Cravit Tab 100-mg, Jeil) or test (Levobacter Tab, Seoul) formulation was administered and serial blood samples were collected over 24 h for PK analysis. Levofloxacin plasma concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The correlation of levofloxacin concentration at various time points with the area under the concentration time-curve over the time interval from 0 extrapolated to infinity (AUC_{inf}) was estimated to determine the best reflected time point. The average half-life, maximum plasma concentration (C_{max}), and AUC_{last} were comparable. The 90% confidence intervals (CIs) of the geometric mean ratio (GMR test/reference) of AUC_{last} and C_{max} were 0.8200–1.0633 and 0.9474–1.0643 respectively. Both formulations were tolerated with no clinically relevant safety issues. Plasma levofloxacin concentrations at various time points correlated well with the AUC_{inf}, and showed high correlation coefficients ($r > 0.7$, $P < 0.001$) for both drugs 8 and 12 h after administration. Both formulations showed similar PK profiles while levofloxacin plasma levels after administration indicated their bioequivalence. The C_{max} and AUC_{last} GMR 90% CIs were 0.80-1.25. Moreover, 12 h was the best time point to predict the AUC_{inf} and therefore suitable for therapeutic drug monitoring.

Introduction

Levofloxacin, a fluoroquinolone antibiotic, is the optical S-(-) isomer of the racemic drug ofloxacin.[1] It is valued for its broad-spectrum activity, excellent tissue penetration, and availability as both oral and intravenous formulations.[1] It has broad-spectrum activity against both gram-positive and negative bacteria, including most strains of pathogens responsible for respiratory and urinary tract infections, cellulitis, prostatitis, anthrax, endocarditis, meningitis, pelvic inflammatory disease, traveler's diarrhea, and tuberculosis, as well as gastrointestinal and abdominal infections.[2] Levofloxacin, similar to other fluoroquinolones, exerts its antibacterial effects by inhibiting the type 2 topoisomerase enzyme, topoisomerase IV and deoxyribonucleic acid (DNA) gyrase, which is responsible for supercoiling DNA.[3]

A previous study showed that an oral dose of levofloxacin was rapidly absorbed.[4] Peak plasma concentrations are attained within 1–2 h following oral administration of levofloxacin.[3]

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Levofloxacin pharmacokinetics (PK) obeys a two-compartment model with first-order elimination.[3] The mean terminal plasma elimination half-life ($t_{1/2\beta}$) is from approximately 6–8 h.[3,4] Levofloxacin is less metabolized than other fluoroquinolones, and approximately 80% is excreted as the unchanged form in the urine through glomerular filtration and tubular secretion within 48 h; minimal metabolism occurs with no metabolites possessing relevant pharmacological activity being formed.[3]

The primary aim of the present study was to compare the PK profiles of two formulations of levofloxacin 100-mg tablets and evaluate their bioequivalence. The reference and test formulations were Cravit (Jeil Pharmaceutical Co. Ltd., Seoul, South Korea) and Levobacter (Seoul Pharma Co., Ltd., Seoul, South Korea), respectively, which contained the same amount of active ingredient and excipients as the branded levofloxacin formulations do. The secondary aim was to identify a single time-point which appropriately reflects AUC for the plasma concentration of levofloxacin by correlation coefficients between the AUC and concentrations at each time-point.

Methods

The study was conducted at the Clinical Trials Center (CTC), Kyung Hee University Hospital (KHUH), Seoul, South Korea in compliance with the ethical principles of the Declaration of Helsinki, all International Conference on Harmonization Good Clinical Practice Guidelines, and local laws and regulations.[5] The protocol was approved by the Institutional Review Board (IRB) of KHUH. Subjects' written informed consent were obtained after a detailed explanation of the study and before the screening test for eligibility was performed. Furthermore, the study was conducted in accordance with the bioequivalence study guideline published by the US Food and Drug Administration (FDA) and the Korean Ministry of Food and Drug Safety (MFDS), South Korea.

Study Population

Korean male volunteers aged 19–55 years were screened for the study. Eligibility criteria was based on successful completion of a clinical evaluation, which consisted of the followings: collection of demographic data (age, weight, and height), physical examination, vital signs (blood pressure and pulse rate), and performance of clinical laboratory tests (hematology, clinical chemistry, and urinalysis) for each volunteer. Subjects were excluded if they showed evidence or history of clinically significant diseases such as hepatic, renal, pulmonary, cardiac, gastrointestinal, neurologic, or hematologic disorders.

Study Design

A randomized, single-dose, two-treatment, two-period, two-sequence crossover study was conducted in healthy subjects who were admitted to the Clinical Trial Center, Kyung Hee University Hospital from day -1 to 2 of each study period. The study periods were separated by a 10-day washout period. Subjects were randomly assigned to one of two sequences in a 1:1 ratio (Group A, reference formulation to test formulation and Group B, test formulation to reference formulation).

We calculated the number of subjects required to perform a bioequivalence study analysis at a 5% significance level with a power of 90%, assuming that the intra-subject coefficient of variation for the PK parameters was 22%, and the geometric mean ratio (GMR, test/reference) for both maximum plasma concentration (C_{max}) and last area under the curve (AUC_{last}) was 1. Considering for 15% withdrawal ratio, a total of 28 subjects were planned for the enrollment.[6]

The test formulation was Levobacter, levofloxacin 100-mg film-coated tablets provided by Seoul Pharma Co., Ltd., South Korea (batch number 10001) and the reference drug was Cravit, levofloxacin 100-mg tablets, manufactured by Jeil Pharm. Co., Ltd., South Korea (batch number CVJC01). The subjects received one tablet of either the reference or the test formulation with 240 mL of water after an overnight fast of at least 10 h on day 1 of each period. The subjects were not allowed to consume any drinks and food for 2 and 4 h after drug administration, respectively.

To determine the plasma levofloxacin concentration, blood samples were collected at the following time points: prior to administration (0 h) and 0.33, 0.67, 1, 1.5, 2, 2.5, 4, 6, 8, 12 and 24 h post-dosing. The collected blood samples were centrifuged immediately at 1,800×g for 10 min, the plasma was collected, and then stored at -70°C in a deep freezer until analyzed.

The safety and tolerability of the formulations were assessed based on the occurrence of adverse events (AEs), vital signs, clinical laboratory evaluations, and physical examination throughout the study period.

Quantification of levofloxacin plasma concentrations

The plasma concentrations of levofloxacin were analyzed by using a high-performance liquid chromatography (HPLC, Agilent 1200 series, Agilent Technologies, USA) coupled with a tandem mass spectrometry (LC-MS/MS, API 3200 system, Applied Biosystems/MDS SCIEX, Foster City, CA, USA). The plasma samples were prepared by deproteinization with acetonitrile followed by sample dilution with 0.2% (v/v) formic acid, and the schedule was run at a flow rate of 0.3 mL/min. The compounds were separated using a Luna 3u HILIC 200A column (100×2.0 mm, Phenomenex Inc., USA).

The lower limit of quantification (LLOQ) was 0.1 μg/mL and the calibration curve was linear over a concentration range of 0.1–10 μg/mL following administration of levofloxacin five times daily for 5 days. The coefficient of variance (% C.V) of the within and between day assay precisions were 3.62–9.87 and 4.93–19.36%, respectively, while the within and between day assay accuracy (%) were 89.44–103.57 and 97.54–99.84%, respectively, indicating that the bioanalytical method was accurate and precise.

PK analysis

The PK parameters were calculated and estimated using a noncompartmental analysis program by Phoenix® WinNonlin® (version 6.3., Pharsight, Mountain View, CA, USA). The C_{max} and the time to achieve C_{max} (T_{max}) were obtained directly from the observed values.[7] The terminal elimination rate constant (k_e) used for the extrapolation was determined by regression analysis of the log-linear part of the concentration-time curves.[7] The $t_{1/2}$ was calculated by dividing ln2 by the k_e. The area under the plasma concentration-time curve from time zero to the last observed time point (AUC_{last}) was calculated according to the noncompartmental method using the linear up, log down trapezoidal rule. The AUC from time zero to infinity (AUC_{inf}) was determined as the sum of the AUC_{last} and the extrapolated area beyond the last plasma concentration. The total apparent clearance (CL/F) was calculated using the following formula: $CL/F = dose/AUC_{inf}$.

The correlation of levofloxacin concentration at various single time points with the AUC_{inf} was estimated to determine the best reflected time point.

Statistical analysis

All statistical analyses were performed using the SAS system (version 9.4; SAS Institute Inc., Cary, NC, USA). The demographic characteristic comparisons between the sequence groups were performed using an unpaired t-test. All the PK parameters were summarized using descriptive statistics. The individual log-transformed C_{max}, AUC_{last} and AUC_{inf} were compared between the test and reference formulations using a mixed effect model; the period, sequence and formulation as the fixed effects and subjects in nested sequences as the random effect. The least square mean differences with 90% confidence interval (CI) of C_{max}, AUC_{last}, and AUC_{inf} were transformed to the original scale to obtain GMR with 90% CI. According to the bioequivalence study guidelines published by the US FDA and the Korean MFDS, the two tablet formulations would be considered bioequivalent if the 90% CIs for GMR were within the range of 0.80–1.25.[7,8]

The correlations between the plasma levofloxacin concentration at various time-points and the AUC_{inf} of the reference and test drugs were tested using Pearson's correlation coefficient test. A $p \leq 0.05$ and correlation coefficient (r) > 0.7 was regarded as significant.[7] Also, the linear regression model was applied to determine the relationship between AUC_{inf} and levofloxacin concentration at each time points.[9]

Results

Subjects

A total of 28 healthy male volunteers were enrolled, and four were dropped (two each from groups A and B), due to personal reasons leading to non-compliance and 24 subjects eventually completed the study. The mean age, height, and weight were 24.6±3.2 years, 174.3±6.2 cm, and 68.1±9.3 kg, respectively. There were no clinically relevant differences between groups A and B in any of the demographics (Table 1).

Table 1. Demographic data of study population of healthy Korean volunteers

	Sequence		Total (N=24)	*P-value*
	Group A (N=12)	Group B (N=12)		
Age (yr)	24.0±3.3	25.2±3.0	24.6±3.2	0.38
Height (cm)	175.6±5.8	173.0±6.6	174.3±6.2	0.32
Weight (kg)	70.4±9.3	65.8±9.2	68.1±9.3	0.24

Notes: N=24; values are mean±standard deviation (SD). *Group A versus B. Group A subjects first received reference formulation (Cravit) then test formulation (Levobacter); group B subjects first received test formulation (Levobacter) then reference formulation (Cravit).

PK analysis

The mean plasma concentration-time curves of the two levofloxacin 100-mg tablet (test and reference) formulations are shown in Figure 1 while their mean PK parameters are illustrated in Table 2.

The mean plasma concentration-time profiles of the two tablet formulations after a single oral administration were similar. Both formulations were absorbed rapidly and they were eliminated mono-exponentially. The median T_{max} of the test and reference drugs were similar (1.00 h each, range 0.33–2.50 and 0.67–4.00 h, respectively), and the average $t_{1/2}$ of levofloxacin was similar for both the test and reference drugs after administration (6.03±1.66 and 6.15±1.52 h, respectively). The mean AUC_{last} was 7.54±1.68 and 7.53±1.79 h·μg/mL after administration of the test and reference drugs, respectively. The mean AUC_{inf} was 9.03±1.71 and 9.07±1.80 h·μg/mL, and the mean C_{max} was 1.61±0.75 and 1.66±0.47 μg/mL for the test and reference drugs, respectively (Table 2). The GMR (test/reference) 90% CIs for the C_{max}, AUC_{last}, and AUC_{inf} were 0.9338 (0.8200–1.0633), 1.0041 (0.9474–1.0643), and 0.9974 (0.9594–1.0370), respectively. Therefore, based on the US FDA and Korean MFDS guidelines, the 90% CIs for the relevant PK parameters such as C_{max} and AUC_{last} fell within an acceptable range of 0.80–1.25, indicating PK bioequivalence between both tablet formulations of levofloxacin (Table 2).

The plasma levofloxacin concentration at various time points correlated well with the AUC_{inf}. The plasma concentrations at 6, 8, 12 h and 8, 12 h (reference and test drugs respectively) after administration showed high r values (> 0.7 and $P < 0.001$). Therefore, the plasma concentrations 8 and 12 h after drug administration (C8 and C12, respectively) showed high r values for the reference and test formulations. Moreover, the concentration at the 12 h time point (C12) revealed that this was the best time point for predicting the AUC_{inf}. The r values of 0.923

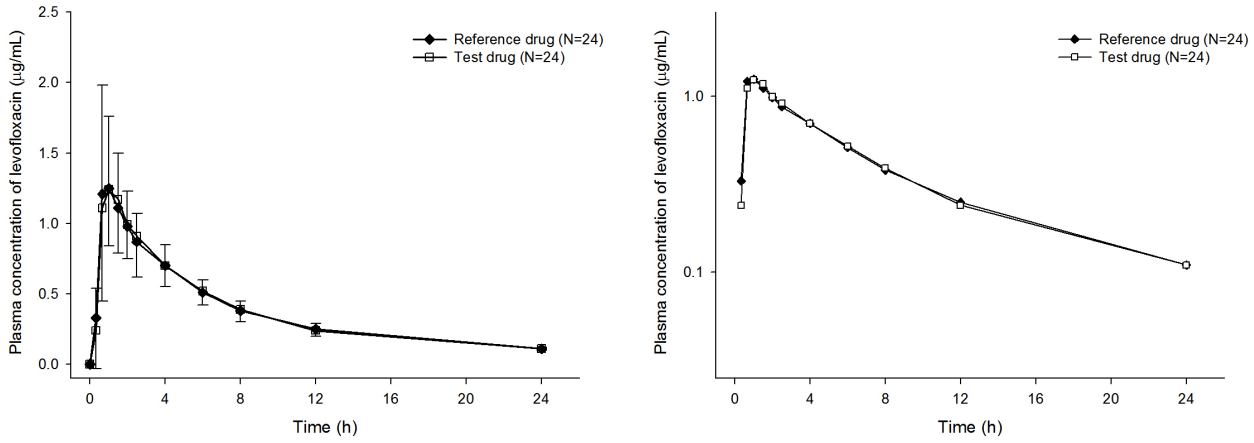

Figure 1. Mean plasma concentration–time curve for test and reference formulations of 100-mg levofloxacin after a single oral dose N = 24, error bars represent standard deviation (SD); Left and right linear and log scale, respectively.

Table 2. Pharmacokinetic parameters following single oral administration of two 100-mg formulations of levofloxacin (test and reference drugs) in healthy Korean volunteers

Parameters	Test drug (N=24)		Reference drug (N=24)		Geometric mean ratio (90% CI)[b]
	Mean (SD)	CV (%)	Mean (SD)	CV (%)	
T_{max} (h)[a]	1.00 (0.33–2.50)		1.00 (0.67–4.00)		–
C_{max} (μg/mL)	1.61 (0.75)	46.46	1.66 (0.47)	28.47	0.9338 (0.8200–1.0633)
AUC_{last} (h·μg/mL)	7.54 (1.68)	22.33	7.53 (1.79)	23.75	1.0041 (0.9474–1.0643)
AUC_{inf} (h·μg/mL)	9.03 (1.71)	19.89	9.07 (1.80)	18.96	0.9974 (0.9594–1.0370)
Half-life (h)	6.03 (1.66)	27.59	6.15 (1.52)	24.64	–
CL/F (L/h)	11.47 (2.21)	19.31	11.46 (2.30)	20.08	–

Values are presented as mean ± standard deviation (SD) and coefficient of variation (%C.V). T_{max}, time to peak concentration; C_{max}, peak plasma concentration; AUC_{last}, area under the plasma concentration-time curve from 0 to the last measurable time; AUC_{inf}, area under the plasma drug concentration-time curve over the time interval from 0 extrapolated to infinity; CL/F, apparent clearance; [a]median value [min–max], [b]geometric mean ratio of test/reference, exponentiation of least square mean difference (90% CI) of logarithmic transformed C_{max} and AUC values.

and 0.965 at 12 h were calculated for the reference and test formulations, respectively (Table 3). For the linear regression model, C12 values were the best predictors for AUC (R^2 = 0.9286 for the reference and 0.8446 for the test) and the corresponding models were as follows;

Reference formulation: AUC = 1.16 + 32.22 x C12 (1)

Test formulation: AUC = 1.14 + 32.47 x C12 (2)

Safety evaluation

No serious adverse events occurred in this study and unexpected adverse events that could have influenced the outcome of the study were not reported as well. The vital signs including blood pressure, pulse rate, body temperature, and the physical examination results for the study subjects showed no clinically significant changes.

Discussion

To ensure the therapeutic equivalence of generic products, bioequivalence studies need to be performed. Therefore, the present study was conducted to compare the PK profiles of a generic and a branded levofloxacin formulation and evaluate their bioequivalence in healthy volunteers. In this study, the 100-mg

Table 3. Correlation between plasma levofloxacin concentration at various time-points and area under the concentration time-curve over the time interval from 0 extrapolated to infinity (AUC_{inf}) of reference and test drugs

Sampling time (h)	Test drug (N = 24)		Reference drug (N = 24)	
	r	*p*	*r*	*p*
0.33	0.262	0.217	-0.243	0.253
0.67	0.290	0.170	0.131	0.542
1	0.463	0.023	0.158	0.462
1.5	0.618	0.001	0.231	0.277
2	0.491	0.015	0.612	0.002
2.5	0.511	0.011	0.597	0.002
4	0.294	0.163	0.629	0.001
6	0.597	0.002	0.818	<0.001
8	0.846	<0.001	0.889	<0.001
12	0.923	<0.001	0.965	<0.001
24	0.801	0.017	0.781	0.022

r, Correlation coefficient.

levofloxacin Levobacter and Cravit tablets showed similar PK characteristics. Specifically, the 90% CIs for the GMRs of the C_{MAX} and AUC_{last} was shown to be within the acceptable range of 0.80–1.25, which indicates bioequivalence and is used by the US FDA and Korean MFDS as the regulatory standard for approving generic formulations.[9,10]

With regards to the extrapolated AUC (AUC_{extra}), the mean (range) of AUC_{last}/AUC_{inf} (%) were 82.54 (75.9–90.01) for the reference and 83.08 (73.87–90.70) for the test formulation. If AUC_{all}, which is defined as AUC from zero to the last sampling time-point (LLOQ is assumed to be zero), was used instead of AUC_{last}, the mean (range) of AUC_{all}/AUC_{inf} (%) were 93.30 (85.45–99.73) for the reference and 93.85 (85.61–100.64) for the test formulation. These findings suggested that the measurements (n=32) of LLOQ at 24 hours provided a cause for the AUC_{last}/AUC_{inf} (%) < 80%. However, considering the 90% CI (0.9594–1.0370) for the GMR of AUC_{inf}, AUC_{last}/AUC_{inf} (%) < 80% did not cause bias to the bioequivalent results between the test and reference formulations in the present study.

The blood sampling times were designed to determine the relevant PK parameters for levofloxacin including the C_{max} and AUC. The mean C_{max} and AUC_{last} values of 1.66 and 7.53, respectively, in the present study were obtained after a single-dose administration of levofloxacin, and these systemic exposures were similar to those after single-dose administration in the previous study.[3] Also, the $t_{1/2}$ of levofloxacin in the present study was similar with 6–8 h reported in a previous study.[3] Meanwhile, the washout period of 10 days, which is more than five times the $t_{1/2}$ was sufficient and appropriate to ensure complete elimination of the first drug before the administration of the alternate drug in the crossover period.

A previous study showed that levofloxacin was well tolerated and the most commonly encountered adverse effects included mild to moderated nausea, diarrhea, and headache (1.2–6.6, 1.2–5.4, and 1.2–5.4%, respectively).[11]

Levofloxacin, a fluoroquinolone antibiotic, acts concentration-dependently. PK parameters can be used to quantify the time course of serum level of an antibiotic.[12] The three critical PK parameters for evaluating antibacterial drug efficacy are the C_{max}, trough level (C_{trough}) and AUC.[13] The AUC/minimum inhibitory concentrations (MICs) ratio is used to predict the antibacterial efficacy of quinolones.[14] The data from *in vitro* suggested that AUC_{24h}/MIC correlated best with their antibacterial activity and clinical efficacy.[9] Therefore, it is clinically important to predict a target AUC_{24h} of levofloxacin using a limited number of plasma concentrations from patients in therapeutic drug monitoring (TDM).[7]

The results of the present study showed high *r* values between the plasma levofloxacin C8 and C12 after drug administration and the AUC_{inf}. The use of the C8 or C12 following the initial administration of antibiotic drug treatments to patients might be useful for determining the necessary dose modification required to adequately and rapidly predict the AUC_{inf} and the appropriate dose for clinical treatment.

Based on the World Health Organization (WHO) guideline for the management of drug-resistant tuberculosis, a later-generation fluoroquinolones (i.e. levofloxacin, moxifloxacin, gatifloxacin and sparfloxacin) should be used for longer duration than drug-susceptible tuberculosis.[15,16] Thus, this long-term use can have a risk of adverse events, although high concentrations of levofloxacin did not occur adverse drug reactions in patient studies.[17–19] Meanwhile, dosing should be adjusted for patients with renal impairment, because levofloxacin is mainly eliminated via kidney.[3] Therefore, TDM of levofloxacin using limited blood samples can be beneficial in the treatment of patients with comorbid conditions such as tuberculosis and renal impairment.[3]

In conclusion, the PK parameters of the two levofloxacin 100-mg tablet formulations, (Levobacter and Cravit) were confirmed to meet the regulatory criteria for bioequivalence. Furthermore, both tablet formulations were well tolerated despite the single dose of 100-mg levofloxacin doses. Finally, the present study demonstrated that the AUC of levofloxacin could be predicted and estimated using a limited sampling time point of 12 h.

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Conflict of interest

The authors have no conflicts of interest to disclose.

References

1. Galan-Herrera JF, Poo JL, Rosales-Sanchez O, Fuentes-Fuentes E, Cariño L, Burke-Fraga V, et al. Bioavailability of two oral formulations of a single dose of levofloxacin 500 mg: An open-label, randomized, two-period crossover comparison in healthy Mexican volunteers. Clin Ther 2009; 31:1796-1803. doi: 10.1016/j.clinthera.2009.08.004.
2. Shi SJ, Han ZM, Chen HT, Zeng FD. Pharmacokinetics and bioequivalence of levofloxacin in healthy Chinese subject. Asian Journal of Pharmacodynamics and Pharmacokinetics 2009;9:313-318.
3. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997;32:101-119.
4. Tsaganos T, Kouki P, Digenis P, Giamarellou H, Giamarellos-Bourboulis EJ, Kanellakopoulou K. Pharmacokinetics of levofloxacin after single and multiple oral doses in patients undergoing intermittent haemodialysis. Int J Antimicrob Agents 2008;32:46-49. doi: 10.1016/j.ijantimicag.2008.02.011.
5. Domján A, Kakuk P, Sándor J. The Helsinki Declaration at 50 years: comments on the 2013 modifications. Lege Artis Med 2014;24:152-158.
6. Chow SC, Wang H. On sample size calculation in bioequivalence trials. J Pharmacokinet Pharmacodyn 2001;28:155-169.
7. Niioka T, Uno T, Yasui-Furukori N, Shimizu M, Sugawara K, Tateishi T. Identification of the time-point which gives a plasma rabeprazole concentration that adequately reflects the area under the concentration-time curve. Eur J Clin Pharmacol 2006;62:855-861.
8. Guidance for Industry. Bioavailability and Bioequivalence studies for orally administered drug products – General considerations. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf/ Accessed Oct 15 2015
9. Slavik RS, Jewesson PJ. Selecting antibacterials for outpatient parenteral antimicrobial therapy. Clin Pharmacokinet 2003;42:793-817.
10. Minimum Requirements for Bioequivalence Test. http://www.mfds.go.kr/index.do?mid=1013&seq=8562&cmd=v Accessed Oct 15 2015
11. Wimer SM, Schoonover L, Garrison MW. Levofloxacin: A therapeutic review. Clin Ther 1998;20:1049-1070.
12. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. Clin Infect Dis 2005;41:S127-S135.
13. Millan X, Muggia V, Ostrowsky B. Antimicrobial agents, drug adverse reactions and interactions, and cancer. Cancer Treat Res 2014;161:413-462. doi: 10.1007/978-3-319-04220-6_14.
14. Macgowan AP, Wootton M, Holt HA. The antibacterial efficacy of levofloxacin and ciprofloxacin against Pseudomonas aeruginosa assessed by combining antibiotic exposure and bacterial susceptibility. J Antimicrob Chemother 1999;43:345-349.
15. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:153-161. doi: 10.1016/S1473-3099(09)70041-6.
16. WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2011 update. http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf. Accessed Feb 26 2016
17. Peloquin CA, Hadad DJ, Molino LP, Palaci M, Boom WH, Dietze R, et al. Population pharmacokinetics of levofloxacin, gatifloxacin and moxifloxacin in adults with pulmonary tuberculosis. Antimicrob Agents Chemother 2008;52:852-857.
18. Stambaugh JJ, Berning SE, Bulpitt AE, Hollender ES, Narita M, Ashkin D, et al. Ofloxacin population pharmacokinetics in patients with tuberculosis. Int J Tuberc Lung Dis 2002;6:503-509.
19. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs 2002;62:2169-2183.