Population Pharmacokinetics and Pharmacodynamics Modeling of Oral Levofloxacin

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Background: *Levofloxacin, a fluoroquinolone, is an isomer of ofloxacin with an extensive spectrum of antimicrobial efficacy. In common with other fluoroquinolones, the main pharmacokinetic/pharmacodynamic (PK/PD) index that correlates with its therapeutic efficacy is the area under the plasma time-concentration curve (AUC)/the minimum inhibitory concentration (MIC) ratios.*

Objective: *To evaluate the population PK and determine the efficacy of various dosage regimens in achieving the probability of target attainment (PTA) and the cumulative fraction of response (CFR) of oral levofloxacin when prescribed as the switching therapy after intravenous levofloxacin treatment.*

Material and Method: *The PK studies were conducted in 45 healthy volunteers who received one 500 mg tablet of levofloxacin and PTAs were determined by using a Monte Carlo simulation. The dosage regimens were predicted to achieve CFR greater than or equal to 90% by referral to the MIC distributions database of the European Committee on Antimicrobial Susceptibility Testing.*

Results: *The population PKs of levofloxacin were; the volume of distribution (V) = 101.71±1.41 L, total clearance (CL) = 8.51±1.43 L/hour and the area under the plasma time-concentration curve from 0 to 24 hours (AUC_{0-24}) = 66.19±1.30 mg*hour/L. The predicted CFRs for a target AUC_{0-24}/MIC ratio of 30 for S. aureus and S. pneumoniae were 83.12% and 92.63%, respectively for 500 mg levofloxacin, and 84.96% and 98.17%, respectively for 750 mg levofloxacin. The predicted CFRs for a target AUC_{0-24}/MIC ratio of 125 for E. coli and Klebsiella spp. were 84.25% and 88.81%, respectively for 500 mg levofloxacin and 86.00% and 91.34%, respectively for 750 mg levofloxacin.*

Conclusion: *The population PKs of levofloxacin in the present study were similar to the values obtained from the previous study. Both 500 mg qd and 750 mg qd of oral levofloxacin dosage regimens had a high probability of achieving optimal impact against S. pneumoniae, but only the 750 mg qd dosage regimen achieved optimal exposure against Klebsiella spp.*

Keywords: *Pharmacodynamics, Population pharmacokinetics, Levofloxacin, Monte Carlo simulation, Pharmacokinetic/pharmacodynamic index*

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Levofloxacin, a fluoroquinolone antibiotic, is the isomer of ofloxacin with a broad spectrum of antimicrobial activity. This agent is active against gram-positive aerobic bacteria, gram-negative aerobic bacteria, and some atypical pathogens. Moreover, levofloxacin provides good pharmacokinetic (PK) properties, including high bioavailability, high plasma concentrations, and extensive tissue distribution[1]. Therefore, it is approved for the treatment of several infections, such as upper and lower respiratory tract, genitourinary tract, skin and soft tissue, and obstetric and gynecological infections[1]. In common with other fluoroquinolones, this agent is characterized by concentration-dependent antimicrobial activity and the main pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with its therapeutic efficacy is the area under the plasma time-concentrations curve/minimum inhibitory concentration (AUC/MIC) ratios. Therefore, its antimicrobial activity increases with plasma drug exposure over a certain target[2]. However, there have been no pharmacodynamic modeling studies of levofloxacin, particularly oral form, in Thai population. To our knowledge, the current study is the first pharmacodynamic modeling study of this agent using a Monte Carlo simulation (MCS) in Thai healthy volunteers. The aims of the present study were to: (i) evaluate the population PK, and

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(ii) determine the efficacy of various dosage regimens in achieving the probability of target attainment (PTA) and the cumulative fraction of response (CFR) of oral levofloxacin when prescribed as the switching therapy after intravenous levofloxacin treatment.

Material and Method

Subjects

The present study was conducted in 45 nonsmoking, nonalcoholic, not obese healthy male volunteers from previous bioequivalence studies of levofloxacin, with a mean age of 27.13±1.26 years (range 20 to 42.90 years), a mean weight of 60.60±1.11 kg (range 52 to 76.48 kg), and a mean body mass index of 21.13±1.10 kg/m^2 (range 18.29 to 25.38 kg/m^2). The protocol for the present study was approved by the Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University (Ref Number: REC 57-356-14-1; 23 December 2014). Written informed consent was obtained from each subject prior to the study. All subjects underwent a pre study evaluation to ensure that they had no underlying illness and were not currently taking or had not recently taken any medications. All subjects had a creatinine clearance rate of greater than or equal to 80 mL/minute and no known history of intolerance to levofloxacin. All subjects had normal biochemical and hematological laboratory profiles.

Drugs and chemicals

Levofloxacin (Cravit®) was purchased from Daiichi Pharmaceutical (Bangkok, Thailand). Levofloxacin standard powder and pipemidic acid (internal standard) were purchased from Sigma-Aldrich® (St. Louis, MO, USA). All solvents were of high-performance liquid chromatography (HPLC) grade.

Study design

Each subject received a single 500 mg tablet of levofloxacin with 100 mL distilled water after fasting. A population PK and a MCS were performed to assess the efficacy of various dosage regimens of levofloxacin.

Blood sampling

Levofloxacin PK studies were carried out after the administration of levofloxacin. Blood samples (5 mL) were obtained through a peripheral venous catheter at the following times: shortly before (time 0) and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 6, 8, 10, and 24 hours after the start of administration of levofloxacin. All blood samples were added to a heparinized tube and centrifuged at 5,000 rpm for five minutes. All plasma samples were stored at -80°C until analysis within one week.

Levofloxacin assay

Concentrations of levofloxacin were determined by reverse-phase HPLC by the modified method of Chulavatnatol et al[3]. Pipemidic acid (60 mg/L) was used as the internal standard. A 0.150 mL of plasma sample, 0.05 mL of pipemidic acid, and 0.6 mL of methanol were mixed by vortex for 30 seconds, and then the mixture sample was centrifuged at 13,000 rpm for 20 minutes. A 0.02 mL aliquot of the sample was injected using an automated injection system (Waters 717 plus Autosampler; Waters Associates, Milford, MA) onto a Micro-Bondapak C18 column (Waters Associates; 3.9x300 mm). The mobile phase was 0.4 M citric acid-methanol-acetonitrile (20:6:1, v/v/v), pH 3.0, at a flow rate of 1 mL/minute. The column effluent was monitored by a Fluorescence Detector Model 470 (Waters Associates) at an excitation wavelength of 250 nm and an emission wavelength of 288 nm. The lower limit of quantitation of levofloxacin was 0.03125 mg/L and the specificity was confirmed by the absence of peak at the retention time of levofloxacin and internal standard. The standard curve was linear within the 0.03125 to 10 mg/L, with an average r^2 value of 0.9997. The intra-assay precision values characterized by coefficients of variation (CVs) were 2.72%, 2.23%, and 1.55% for samples containing 0.1, 2, and 8 mg/L, respectively. The inter-assay precision, calculated by CVs, were 5.74%, 2.66%, and 6.70% for samples containing 0.1, 2, and 8 mg/L, respectively. The recoveries of levofloxacin concentrations from plasma were within range of 93.47 to 99.02%.

Pharmacokinetics analysis

Model building

The log concentration-time plot showed distinct distribution and elimination phases. We found that a two-compartment model was sufficient to describe the actual data. The data were analyzed by nonlinear regression analysis of differential equations describing the two-compartment model. Differential equations were solved numerically with the Taylor series method until convergence was achieved[4]. The objective function to be minimized was the sum of square errors of the concentrations. The minimization

of the objective function was performed using the Solver package in Microsoft Excel (Microsoft Corp.) to reach local minima for each random initial condition, together with a random heuristic optimization algorithm[5] repeatedly until the global minima was ascertained. We found that in some cases regression analysis failed to converge and could not describe the distribution phase because the contribution of the objective function from the distribution region was too small, but after using the area under the plasma time-concentration curve from 0 to 24 hours (AUC_{0-24}) as an additional data point, a best-fit line could be converged easily and could describe all portions of the concentration-time profile without bias. Therefore, we used AUC_{0-24} as an additional data point in all cases.

Covariate exploration

From patient information (age, body weight, height, and creatinine clearance (CrCL)), we found that CrCL and body surface area (BSA) had a weak correlation with $\ln(k_e)$ ($r = 0.37$ and 0.43 respectively). Since both parameters were within a narrow range (BSA 1.47-1.99 m^2, CrCL 3.30-7.98 L/hour), we did not use them for further simulation studies.

Covariate model diagnostics

From the correlation coefficient matrix, a Choleski decomposition was performed and multiplied with simulated standardized z-score before conversion to simulate PK parameters in a log-normal scale[6]. These simulated parameters retained the statistical behavior (i.e., mean, standard deviation, correlation matrix) of the original parameters.

Pharmacodynamic assessment using Monte Carlo simulation

The concentration-time profiles were simulated (N at least 100,000) by solving numerically for the differential equation describing the 2-compartment model with a Runge-Kutta-4 algorithm[4]. From the covariate model, it was used as a generator in MCS. The MCS was performed by generating individual PK parameters and solved the involved differential equation to create a concentration-time profile. The characteristics of the curve such as AUC or maximum concentration (C_{max}) could be determined numerically. By repeating this process for different PK parameters, the confidence interval or the % attainment could be computed. The simulation size in the present study is 130,000 for determining the PTA for levofloxacin regimens achieving target AUC_{0-24}/MIC ratio of 30 and 125. PTA is defined as the probability that at least a specific value of a pharmacodynamic index is achieved at a certain (minimum inhibitory) concentration. This simulation size should provide the uncertainty of the % attainment to be below 0.3%.

Cumulative fraction of response and minimum inhibitory concentration distribution

MIC distributions were derived from levofloxacin MIC_{50} and MIC_{90} (MICs for 50% and 90% of the organisms, respectively) and MIC range obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST, updated 26 January 2015) for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Klebsiella* spp. isolates. MIC distributions were estimated from 27,556 strains of *S. aureus*, 85,564 strains of *S. pneumoniae*, 9,144 strains of *E. coli*, and 1,423 strains of *Klebsiella* spp. The CFRs were determined for each regimen against each population of *S. aureus*, *S. pneumoniae*, *E. coli*, and *Klebsiella* spp. CFR is defined as the expected population probability of target attainment for a specific drug dose and a specific population of microorganisms. The optimal CFR was defined as ≥90%.

Results

The population PK parameters of levofloxacin were shown in Table 1. The PTAs for the three levofloxacin regimens achieving targets of an AUC_{0-24}/MIC ratio of 30 and an AUC_{0-24}/MIC ratio of 125 at specific MICs were shown in Table 2 and Fig. 1. Assessments of CFR for subjects who achieved the target AUC_{0-24}/MIC ratio of 30 for the three levofloxacin regimens against *S. aureus* and *S. pneumoniae* and the target AUC_{0-24}/MIC ratio of 125 for the three levofloxacin regimens against *E. coli* and *Klebsiella* spp. were shown in Table 3. For pathogens with a MIC of 0.5 mg/L, the PTAs of achieving the target AUC_{0-24}/MIC ratio of 30 following administration of 250 mg qd, 500 mg qd and 750 mg qd of levofloxacin were 94.22%, 99.96% and 100%, respectively. For pathogens with a MIC of 1 mg/L the PTAs of achieving the target AUC_{0-24}/MIC ratio of 30 following administration of 250 mg qd, 500 mg qd, and 750 mg qd of levofloxacin were 40.23%, 94.23%, and 99.95%, respectively. For pathogens with a MIC of 0.25 mg/L, the PTAs of achieving the target AUC_{0-24}/MIC ratio of 125 following administration of 250 mg qd, 500 mg qd, and 750 mg qd of levofloxacin were 36.20%,

Table 1. Population pharmacokinetic parameters of a single 500 mg levofloxacin tablet

Parameter	Geometric mean	Geometric SD	Median	95% CI
k_d (/hour)	2.947	2.037	2.686	0.777-8.288
k_a (/hour)	2.737	1.962	2.637	0.759-7.572
k_{12} (/hour)	1.510	2.300	1.309	0.339-10.268
k_{21} (/hour)	0.650	1.929	0.603	0.270-2.467
k_e (/hour)	0.307	1.603	0.284	0.159-1.176
V (L)	101.710	1.419	101.897	59.333-199.716
CL (L/hour)	8.510	1.433	7.392	4.878-19.377
AUC_{0-24} (mg* hour/L)	66.198	1.305	71.057	32.852-97.866

SD = standard deviation; CI = confidence interval; k_d = dissociation rate constant; k_a = absorption rate constant; k_{12} = intercompartmental transfer rate constant from compartment X_1 to X_2; k_{21} = intercompartmental transfer rate constant from compartment X_2 to X_1; k_e = elimination rate constant from X_1; CL = total clearance; V = volume of distribution at steady state of central compartment; AUC_{0-24} = the area under the plasma time-concentrations curve 0-24 hours

Table 2. Probability of target attainment (PTA) for levofloxacin regimens achieving target AUC_{0-24}/MIC ratios of 30 and 125 in 45 normal volunteers

MIC (mg/L)	AUC_{0-24}/MIC ratio of 30			AUC_{0-24}/MIC ratio of 125		
	250 mg qd	500 mg qd	750 mg qd	250 mg qd	500 mg qd	750 mg qd
0.125	100.00	100.00	100.00	92.83	99.94	100.00
0.25	99.96	100.00	100.00	36.20	92.85	99.40
0.5	94.22	99.96	100.00	1.40	35.85	75.90
1	40.23	94.23	99.95	0.00	1.44	13.12
2	1.84	39.97	79.17	0.00	0.00	0.16

MIC = minimum inhibitory concentration; AUC_{0-24} = area under the plasma time-concentrations curve 0-24 hours

92.85%, and 99.40%, respectively. The predicted CFRs for PTAs achieving the target AUC_{0-24}/MIC ratio of 30 for *S. pneumoniae* following administration of 250 mg qd, 500 mg qd, and 750 mg qd of levofloxacin were 49.50%, 92.63%, and 98.17%, respectively. The predicted CFRs for PTAs achieving the target AUC_{0-24}/MIC ratio of 125 for *Klebsiella* spp. following administration of 250 mg qd, 500 mg qd, and 750 mg qd of levofloxacin were 83.73%, 88.81%, and 91.34%, respectively.

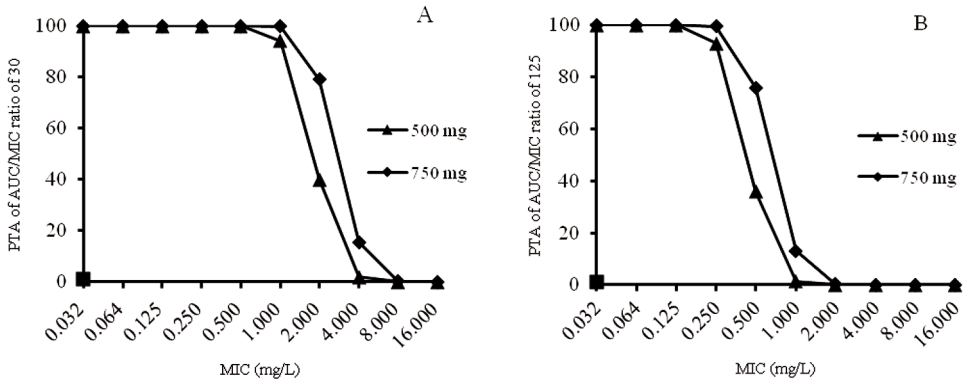

Fig. 1 Probability of target attainment (PTA) for levofloxacin regimens achieving a target (A) AUC_{0-24}/MIC ratio of 30, and (B) AUC_{0-24}/MIC ratio of 125 at specific minimum inhibitory concentrations (MICs) in 45 normal volunteers after administration of 500 mg qd of levofloxacin (closed triangles) and 750 mg qd of levofloxacin (closed diamonds).

Table 3. Cumulative fraction of response (CFR) for 250, 500, and 750 mg qd of levofloxacin against *S. aureus*, *S. pneumoniae*, *E. coli*, and *Klebsiella* spp. at PTAs achieving a target AUC_{0-24}/MIC ratios of 30 and 125 in 45 normal volunteers

		% susceptibility[a]	CFR (%) for EUCAST[b]		
			250 mg qd	500 mg qd	750 mg qd
AUC_{0-24}/MIC ratio of 30	*S. aureus*	82.49	81.51	83.12	84.96
	S. pneumoniae	98.81	49.50	92.63	98.17
AUC_{0-24}/MIC ratio of 125	*E. coli*	83.08	81.47	84.25	86.00
	Klebsiella spp.	87.56	83.73	88.81	91.34

[a] Susceptibility determined using 2015 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint of levofloxacin

[b] CFR determined using MIC distribution of 2015 EUCAST

Discussion

Fluoroquinolone antibiotics, including levofloxacin, are one of the most frequently used drugs for the treatment of severe infections in critically ill patients. These agents are lipophilic antimicrobial drugs that are characterized by their wide distribution into target tissues[1]. Plasma drug concentrations are most commonly used as surrogate measure for determining the PK/PD indices, and AUC/MIC is the best parameter that correlates with the antimicrobial activity of fluoroquinolones. Therefore, the high AUC should be PK parameters that would determine therapeutic outcomes. For Gram positive bacteria, the AUC/MIC ratio required for achieving effective bactericidal activity is greater than 30 and for Gram negative bacteria, the AUC/MIC ratio required for achieving effective bactericidal activity is greater than 125[2]. Previous studies, the guideline for pneumonia and acute bacterial rhinosinusitis of the Infectious Diseases Society of America and the guideline for pneumonia of the American Thoracic Society indicate that oral levofloxacin 750 mg once daily is recommended for the treatment of community-acquired and hospital-acquired pneumonia, complicated skin, and soft tissue infections. Oral levofloxacin 500 mg once daily is recommended for the treatment of acute bacterial sinusitis and acutely exacerbated chronic bronchitis and oral levofloxacin 250 mg once daily is recommended for the treatment of urinary tract infections[7-10]. In the current study, the population PK parameters of levofloxacin estimates in normal volunteers were similar to estimates in Chinese healthy volunteers in a previous study[11]. Comparison of the PK parameters between the present study and the previous study yielded: V, 101.71 vs. 107.3 L; CL, 8.51 vs. 8.17 L/ hour; and AUC_{0-24}, 66.19 vs. 73.3 mg*hour/L. The PD analyses indicated that the 750 mg of levofloxacin once daily provided good coverage against main pathogens of community-acquired pneumonia[11]. We performed a Monte Carlo dosing simulation to determine the probability of attaining a specific PD target using various regimens, including 250 mg qd, 500 mg qd, and 750 mg qd of levofloxacin when oral levofloxacin was prescribed as the switching therapy after intravenous levofloxacin treatment. The high PTA (greater than or equal to 90%) for achieving the target AUC_{0-24}/MIC ratio of 30 with an MIC of 0.5 mg/L was observed when levofloxacin was administered at a dosage of 250 mg qd. For pathogens with an MIC of 1 mg/L, the high PTA was achieved when the dosages of levofloxacin were increased to 500 mg qd and 750 mg qd. A high PTA for achieving the target AUC_{0-24}/MIC ratio of 125 with an MIC of 0.125 mg/L was observed when levofloxacin was administered at a dosage of 250 mg qd. For pathogens with an MIC of 0.25 mg/L, the high PTA was achieved when the dosages of levofloxacin were increased to 500 mg qd and 750 mg qd. Therefore, the results from the current study show that both 500 mg qd and 750 mg qd of levofloxacin dosage regimens can provide good coverage for pathogens with the same MIC levels. In addition, the 500 mg qd and 750 mg qd of levofloxacin dosage regimens had high probabilities of achieving optimal exposure against *S. pneumoniae* while only the 750 mg qd dosage regimen had a high probability of achieving optimal exposure against *Klebsiella* spp.

However, the present study had some limitations that must be mentioned. First, the study was conducted in healthy volunteers, therefore, it may be problematic to extrapolate the results from the present study to patients with sepsis due to PK changes in this patient population when compared with healthy volunteers. Second, the total levofloxacin concentrations in plasma were measured in the present study, whereas only unbound fraction of this agent correlates with the antimicrobial activity.

In conclusion, the population PK of levofloxacin in the present study were similar to the values obtained from a previous study. The high PTAs (greater than or equal to 90%) for target AUC_{0-24}/MIC ratios of 30 for a MIC of 1 mg/L and 125 for a MIC of 0.25 mg/L were observed when levofloxacin was administered by either 500 mg qd or 750 mg qd dosage regimens. Both the 500 mg qd and 750 mg qd of levofloxacin dosage regimens had a high probability of achieving optimal impact against *S. pneumoniae*, but only the 750 mg qd dosage regimen achieved optimal exposure against *Klebsiella* spp.

What is already known on this topic?

The current manufacturer's instructions and several guidelines indicate that levofloxacin is recommended for the treatment of upper and lower respiratory tract infections, skin and soft tissue infections, and urinary tract infections. Previous PD analyses study revealed that the 750 mg of levofloxacin once daily can achieve the PK/PD profile against the main pathogens of community-acquired pneumonia.

What this study adds?

The efficacy of various dosage regimens of oral levofloxacin in achieving the PTA and the CFR were demonstrated when this agent was prescribed as the switching therapy after intravenous treatment for gram positive and gram negative aerobic bacterias.

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Potential conflicts of interest

None.

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เภสัชจลนศาสตร์ในประชากรและการวิเคราะห์เภสัชพลศาสตร์เพื่อหาขนาดยา levofloxacin ชนิดกินที่มีประสิทธิภาพสูงสุด

สุเทพ จารุรัตนศิริกุล, อาชัญ เจษฎ์พัฒนานนท์, วิบุล วงศ์ภูวรักษ์, มนชนา นวกิจรังสรรค์, สุริยัน เต็งใหญ่, มาซีเต๊ะ สาแม็ง

ภูมิหลัง: *Levofloxacin เป็นยาปฏิชีวนะในกลุ่ม fluoroquinolones ที่เป็นไอโซเมอร์ของ ofloxacin เป็นยาที่ออกฤทธิ์ได้อย่างกว้างขวาง ยานี้เหมือนกับยาอื่นในกลุ่ม fluoroquinolones ที่ดัชนีเภสัชจลนศาสตร์/เภสัชพลศาสตร์หลักที่สัมพันธ์กับประสิทธิภาพในการรักษาคือค่าสัดส่วนระหว่าง area under the plasma time-concentration curve (AUC) กับค่า minimum inhibitory concentration (MIC)*

วัตถุประสงค์: *เพื่อประเมินค่าเภสัชจลนศาสตร์ในประชากรและศึกษาถึงประสิทธิภาพของยา levofloxacin ขนาดต่าง ๆ ที่จะใช้เปลี่ยนทดแทนยาฉีด โดยการศึกษาถึง probability of target attainment (PTA) และ cumulative fraction of response (CFR)*

วัสดุและวิธีการ: *การศึกษาเภสัชจลนศาสตร์ถูกดำเนินการในอาสาสมัครที่มีสุขภาพแข็งแรง 45 ราย ที่ได้รับยากิน levofloxacin ในขนาด 500 มิลลิกรัม จำนวน 1 เม็ด การศึกษา PTA โดยใช้วิธีการ Monte Carlo simulation และทำนายค่า CFR ที่ร้อยละ 90 โดยใช้ข้อมูลการกระจายของค่า MIC ของ The European Committee on Antimicrobial Susceptibility Testing*

ผลการศึกษา: *การศึกษาเภสัชจลนศาสตร์ในประชากรของ levofloxacin พบว่า ปริมาตรการกระจายเท่ากับ 101.71±1.41 ลิตร ค่าการกำจัดยาเท่ากับ 8.57±1.43 ลิตร/ชั่วโมง และค่าพื้นที่ภายใต้กราฟความเข้มข้นของยาเท่ากับ 66.19±1.30 มิลลิกรัม-ชั่วโมง/ลิตร จากการศึกษาสามารถทำนายได้ว่า สำหรับยาขนาด 500 มิลลิกรัม ค่า CFR สำหรับเป้าหมายค่า area under the plasma time-concentration curve ที่ 0 ถึง 24 ชั่วโมง (AUC_{0-24})/MIC เท่ากับ 30 ต่อเชื้อ S. aureus และ S. pneumoniae มีค่าเท่ากับร้อยละ 83.12 และ 92.63 ตามลำดับ สำหรับขนาดยา 750 มิลลิกรัม ค่า CFR สำหรับเป้าหมาย AUC_{0-24}/MIC เท่ากับ 30 ต่อเชื้อ S. aureus และ S. pneumoniae มีค่าเท่ากับร้อยละ 84.96 และ 98.17 ตามลำดับ สำหรับยาขนาด 500 มิลลิกรัม ค่า CFR สำหรับเป้าหมาย AUC_{0-24}/MIC เท่ากับ 125 ต่อเชื้อ E. coli และ Klebsiella spp. มีค่าเท่ากับร้อยละ 84.25 และ 88.81 ตามลำดับ สำหรับขนาดยา 750 มิลลิกรัม ค่า CFR สำหรับเป้าหมาย AUC_{0-24}/MIC เท่ากับ 125 ต่อเชื้อ E. coli และ Klebsiella spp. มีค่าเท่ากับร้อยละ 86.00 และ 91.34 ตามลำดับ*

สรุป: *ค่าเภสัชจลนศาสตร์ในประชากรจากการศึกษานี้เหมือนกับค่าที่ได้จากการศึกษาก่อนหน้านี้ ยากิน levofloxacin ทั้งขนาด 500 มิลลิกรัม และ 750 มิลลิกรัม วันละครั้งสามารถครอบคลุมเชื้อ S. pneumoniae ได้ดี แต่มีเพียงยาในขนาด 750 มิลลิกรัม วันละครั้งเท่านั้นที่สามารถครอบคลุมเชื้อ Klebsiella spp. ได้*