Pharmacokinetics of Ofloxacin in Drug-Resistant Tuberculosis

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Abstract

The pharmacokinetics of ofloxacin were investigated in 11 drug-resistant pulmonary tuberculosis (TB) patients with a mean age (SD) of 38.09 (11.97) years. All patients received ofloxacin 10 mg/kg once daily combined with other active anti-TB drugs. Following an 8-h overnight fast, serum samples were drawn prior to and from 0.25 up to 24 hours after dosing. Serum ofloxacin concentrations were determined by high performance liquid chromatography (HPLC) assay.

Pharmacokinetics of ofloxacin were well described by a linear, 2-compartment open model with first-order absorption and first-order elimination. Mean ± SD of C_{max} was 9.61 ± 2.17 μg/ml occurred at 1.68 ± 1.21 hours. Means ± SD of AUC_{0-24} and $AUC_{0-\infty}$ were 70.57 ± 26.40 and 82.45 ± 43.64 μg x h/ml, respectively. Ofloxacin distributed widely with a mean ± SD of V_{ss}/F of 1.37 ± 0.24 L/kg. Mean ± SD of CL/F was 8.19 ± 2.53 L/h, whereas mean ± SD of $T_{1/2\beta}$ and mean residence time were 8.03 ± 3.37 and 10.77 ± 4.55 hours, respectively. The free C_{max}/MIC of *Mycobacterium tuberculosis* of 7.7-15.4 : 1 was estimated. These suggested that ofloxacin 10 mg/kg once daily combined with other active anti-TB drugs provides sufficient C_{max}/MIC ratio and long $T_{1/2\beta}$ which supported its use in drug-resistant TB.

Key word : Ofloxacin, Pharmacokinetics, Drug-Resistant Tuberculosis

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Ofloxacin is one of the most prominent fluoroquinolones which demonstrates *in vitro* and *in vivo* activity against *Mycobacterium tuberculosis*[1-4]. Its *in vitro* MIC_{90} value for this pathogen has been reported to be 0.5-1 μg/ml[5-8]. At achievable concentrations, the drug has a pivotal role in drug-resistant tuberculosis (TB)[6,9-11]. Moreover, ofloxacin has favorable pharmacokinetic properties including rapid and complete oral absorption and good tissue penetration, in particular, to alveolar macrophages[3, 7,12-14]. Accordingly, ofloxacin is commonly used with other effective anti-TB drugs for the treatment and prophylaxis of drug-resistant TB[4,15-17]. However, other pharmacokinetic data of this drug in this particular group of patients are still rather scarce. The aim of the present study was, therefore, to evaluate the pharmacokinetics of ofloxacin at a dose of 10 mg/kg/day used concomitantly with other anti-TB drugs in drug-resistant TB patients. The results would ensure the effectiveness of the recommended dosage regimens of ofloxacin in these patients.

PATIENTS AND METHOD

Patients

Twelve patients with drug-resistant pulmonary TB requiring ofloxacin in their treatment regimen were enrolled in the study. All received ofloxacin (Daiichi Pharmaceuticals, Japan) at a daily dose of 10 mg/kg concomitant with other anti-TB drugs, mainly ethambutol (EMB), pyrazinamide (PZA) and para-aminosalicylic acid (PAS). A few patients also received isoniazid (INH) and/or rifampicin (RFP) because their isolates were susceptible to these drugs. All were compliant with the treatment protocol and were determined to be in acceptable health without co-morbid conditions, except for diabetes mellitus. None had a history of hypersensitivity to fluoroquinolones. Patients with a history of congestive heart failure, uncontrolled hypertension and ischemic heart disease or had serum urea nitrogen higher than 20 mg/dL, serum creatinine higher than 1.5 mg/dL or those who were pregnant or lactating were excluded from the study. Any medication containing Al^{3+}, Fe^{2+} and Zn^{2+} which could interfere with ofloxacin absorption was prohibited for at least two weeks prior to the study. Those who developed adverse reaction to ofloxacin during the study were also excluded. The protocol was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol University. All participants gave the written informed consent after the aims and procedures for the study were clearly explained.

Study design and procedures

Ofloxacin was administered after breakfast to each patient concomitantly with other anti-TB drugs which were taken at bedtime for at least two weeks before commencement of blood sample collection. On the study day, after an 8-hour overnight fast, ofloxacin was given to each patient with 200 ml of water at 6 a.m. All patients were allowed to have lunch at 12 a.m. and have dinner at 6 p.m.

Ten milliliters of venous blood were collected from a catheter fixed on a forearm vein of each patient prior to dosing, 5 ml were tested for liver and renal function, another 5 ml were analysed for baseline ofloxacin level. Other 5-ml samples of venous blood were collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 12 and 24 hours after ofloxacin administration. These venous blood samples were centrifuged at 5,250 rpm for 5 minutes at 4°C. The serum was separated and kept at -80°C until analysis.

Quantitative drug analysis

Ofloxacin levels in serum were determined by high performance liquid chromatography (HPLC) modified from the method described by Chulavatnatol et al[18] using the HPLC model LC-10 AD (Shimadzu Co., Japan). A reversed-phase column, Shim-Pack CLC-ODS® C_{18}, 5 μm (4.6 mm x 25 cm) was used as an analytical column. A mixture of methanol, acetonitrile and 0.4 M citric acid in the ratio of 3 : 1 : 10, pH 4.0 was used as the mobile phase. Pipemidic acid 0.15 mg/ml was applied as an internal standard. Peak detection was performed by a fluorescence detector (Model RF-10A, Shimadzu Co., Japan) at an excitation wavelength of 290 nm and an emission wavelength of 500 nm. The ofloxacin standard was supplied by Daiichi Pharmaceuticals, Japan. The sample preparation procedures were as described in Chierakul et al[19]. In such an assay system, ofloxacin and pipemidic acid were well separated as sharp and symmetrical peaks. No interferences from endogenous substances and concomitant anti-TB drugs (INH, RFP, PZA, EMB and PAS) were demonstrated. Calibration plots were constructed by least-square linear regression of peak area ratio on ofloxacin concentrations. These were linear (r = 0.9999) for ofloxacin concentrations between 0.1 and 15 μg/ml. Between-day and

within-day imprecision were less than 6 per cent (CV) while inaccuracy was less than 5 per cent and recovery was higher than 98 per cent.

Pharmacokinetic analysis

Serum concentration-time profile of ofloxacin from each patient was plotted semi-logarithmically and the pharmacokinetic parameters were derived. Maximum serum concentration (C_{max}) and time to reach maximum serum concentration (T_{max}) were obtained from the raw data of the serum concentration-time profile. The values for elimination rate constant (β), elimination half-life ($T_{1/2\beta}$), distribution rate constant (α), distribution half-life ($T_{1/2\alpha}$), absorption rate constant (k_a) and absorption half-life ($T_{1/2ka}$) were obtained by the method of residuals [20]. Area under the serum concentration-time curve (AUC) from 0 to 24 hours (AUC_{0-24}), AUC from 0 to infinity ($AUC_{0-\infty}$), apparent volume of distribution at steady state (V_{ss}/F), apparent total body clearance (CL/F) and mean residence time (MRT) were calculated from the MK model program (version 4.84 Biosoft, Cambridge, UK), based on noncompartmental moment analysis method.

RESULTS

Patients' demographic data and history of anti-TB drugs used are presented in Table 1. Data from one subject was excluded because the patient missed 2-3 doses of ofloxacin prior to the blood sampling day. For the rest, none were withdrawn or developed adverse reactions to ofloxacin throughout the study. Patients' means ± SD of age, and weight were 38.09 ± 11.97 years and 59.34 ± 11.47 kg, respectively. The mean ± SD of ofloxacin daily dose was 590.9 ± 122.1 mg. Most of the patients suffered from multidrug-resistant TB (MDR-TB), mainly with INH and RFP. The serum concentration-time profiles of ofloxacin were described by 2-compartment model with first-order absorption and first-order elimination. The mean ± SD of serum concentration-time profile is demonstrated in Fig. 1. Ofloxacin was absorbed with a mean ± SD of T_{max} of 1.68 ± 1.21 hours while means ± SD of k_a and $T_{1/2ka}$ were 2.21 ± 1.54 h^{-1} and 0.36 ± 0.21 h, respectively. This produced a mean ± SD of C_{max} of 9.61 ± 2.17 μg/ml while means ± SD of AUC_{0-24} and $AUC_{0-\infty}$ were 70.57 ± 26.40 μg x h/ml and 82.45 ± 43.64 μg x h/ml, respectively. Mean ± SD of V_{ss}/F of 1.37 ± 0.24 L/kg with a mean ± SD of distribution rate constant (α) of 1.02 ± 1.50 h^{-1} were derived. This resulted in a mean ± SD of $T_{1/2\alpha}$ of 1.64 ± 1.19 hours. Ofloxacin was eliminated with a mean ± SD of CL/F of 8.19 ± 2.53 L/h and the means ± SD of elimination rate constant (β) and $T_{1/2\beta}$ were 0.10 ± 0.03 h^{-1} and 8.03 ± 3.37 hours, respectively, while a mean ± SD of MRT was 10.77 ± 4.55 hours.

Table 1. Demographic data of patients who participated in the study.

Subject number	Age (yr)	Sex	Weight (kg)	Resistant anti-TB drug	Ofloxacin daily dose (mg)	Anti-TB drugs used concomitantly with ofloxacin (daily dose*)
1	44	M	59	INH, RFP	600	EMB (1,000), PAS (10)
2	50	M	59.2	NA	600	INH (300)
3	23	F	53	INH, RFP, EMB	500	PZA (1,500), PAS (9)
4	59	M	71	INH, RFP	700	PZA (1,750), EMB (1,200), PAS (12)
5	30	M	64	INH, RFP	600	PZA (1,200), EMB (1,000), PAS (12)
6	24	M	75	NA	800	INH (600), RFP (600)
7	35	M	68	INH, RFP	600	PZA (2,000) PAS (12)
8	27	F	37	INH	400	RFP (450), EMB (800)
9	38	F	44.5	INH	400	RFP (450), PZA (1,500)
10	37	M	67	INH, RFP	700	PZA (2,000), EMB (1,200), PAS (12)
11	52	M	55	INH, RFP	600	PZA (1,200), EMB (800), PAS (10)
Mean	38.09		59.34		590.9	
SD	11.97		11.47		122.1	

* all doses were in mg except for PAS was in g, F = female, M = male, EMB = ethambutol, INH = isoniazid, NA = not available, PAS = para-aminosalicylic acid, PZA = pyrazinamide, RFP = rifampicin

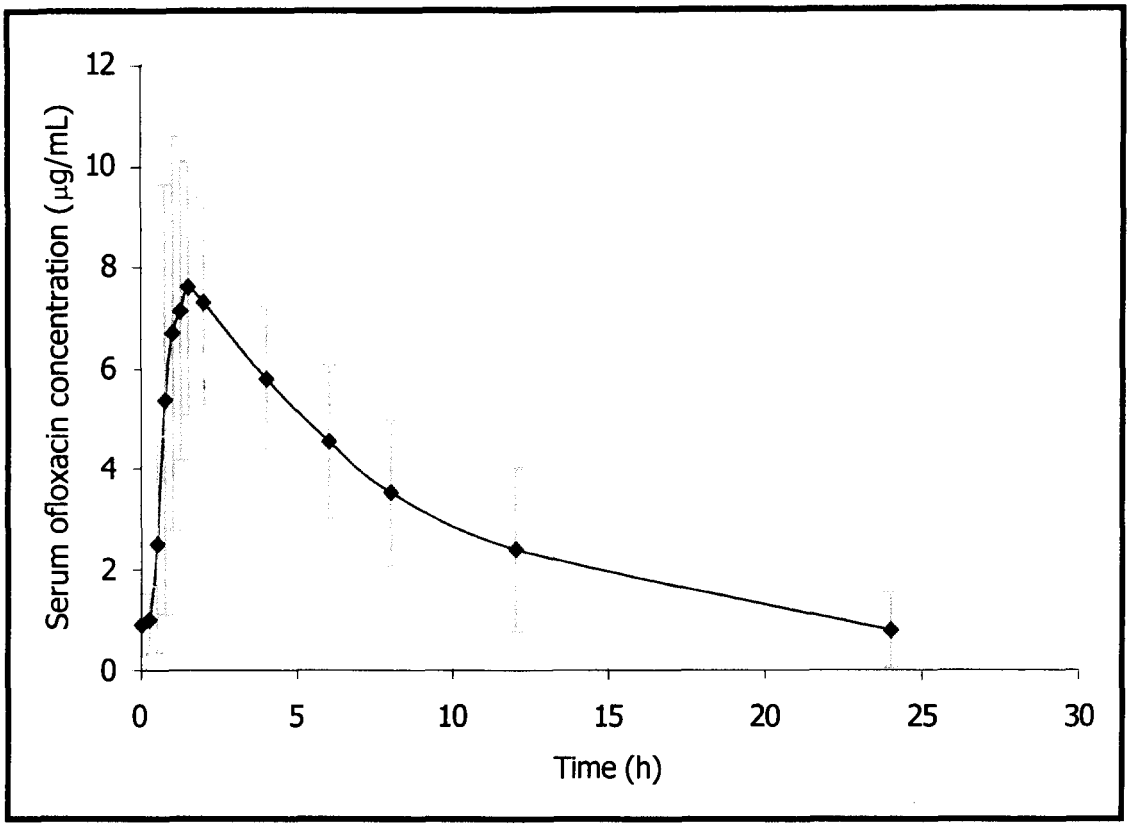

Fig. 1. Mean ± SD serum concentration-time profile of ofloxacin after the administration of ofloxacin 10 mg/kg/day orally to 11 drug-resistant tuberculosis patients.

Some mean pharmacokinetic parameters in comparison to the data from other studies are presented in Table 2.

DISCUSSION

The serum concentration-time profiles of ofloxacin in the present study were best described by 2-compartment model with first-order absorption and first-order elimination, which agreed with the studies by Wolfson and Hooper[21] and Lode et al[13] and was consistent with the distribution property of the drug, which revealed a high V_{ss}/F of approximately 1.4 L/kg which was also agreed with the study by Flor [22]. In the presented patients, ofloxacin was absorbed with the T_{max} in between those reported in healthy volunteers[22] and patients with MDR-TB [23] (Table 2). However, the T_{max} was slightly slower than that reported by Lockley et al[24] who studied pharmacokinetics of a single dose ofloxacin in healthy volunteers. The delayed T_{max} in the present study was correlated with the slower k_a observed in the study ($2.21 \pm 1.54\ h^{-1}$) compared to the absorption rate constant reported by Lockley et al ($2.9 \pm 1.7\ h^{-1}$)[24]. In terms of C_{max} at steady state after the mean total daily dose of 590.9 mg, this could not be directly compared with other studies presented in Table 2 because different doses were studied. However, since the absorbed amount of ofloxacin increases linearly over the dose range of 100-600 mg[7,22], a comparison in a dose-proportional manner was thus demonstrated. As a result, the mean ± SD of C_{max} at steady state was higher than that reported by Flor[22] in healthy volunteers or in patients with MDR-TB as reported by Yew et al[23] but close to that reported by Lockley et al after a single dose study[24]. This might be the result of differences in rate of absorption as illustrated by T_{max} and the rate of elimination as demonstrated by $T_{1/2\beta}$ of the drug in these

Table 2. Some pharmacokinetic parameter values (mean ± SD) of ofloxacin obtained in the present study compared to the previously reported values.

Study conditions (reference)	Mean dose (mg/day)	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} (μg x h/ml)	$AUC_{0-\infty}$ (μg x h/ml)	V_{ss}/F (L/kg)	$T_{1/2\beta}$ (h)
Drug-resistant TB patients; MD (Present study)	590.9	9.61 ± 2.17	1.68 ± 1.21	70.57 ± 26.40	82.45 ± 43.64	1.37 ± 0.24	8.03 ± 3.37
Healthy volunteers; SD (Lockley et al [24])	600	10.7 ± 6.4	1.2 ± 0.9	NA	57.5 ± 11.3	NA	7.0 ± 1.1
	590.9*	10.5**			56.6**		
Healthy volunteers; MD (Flor [22])	400	5.0 ± 1.0	1.7 ± 0.6	NA	61.0 ± 21.5	1.2 ± 0.3	5.2
	590.9*	7.4**			90.1**		
MDR-TB patients; MD (Yew et al [23])	600	4.92 ± 1.43	1-2	NA	NA	NA	7.8
	590.9*	4.8**					

* adjusted dose by dose-proportional manner, ** adjusted mean value by dose-proportional manner, MDR-TB = multidrug-resistant tuberculosis, MD = multiple, oral dose study, NA = not available; SD = single, oral dose study; TB = tuberculosis

studies. In those MDR-TB patients [23], the absorption rate was relatively slow compared to the presented patients while the rate of elimination was relatively comparable (Table 2). Therefore, the mean C_{max} was rather low compared with the presented patients. In contrast with healthy volunteers[22], the rate of absorption was relatively comparable with the presented patients but the rate of drug elimination was rather higher than the presented patients, thus the mean C_{max} was relatively lower. Moreover, it was proposed that C_{max} and AUC of some fluoroquinolones were higher in sick patients than in healthy volunteers[25]. This may partly describe the difference of pharmacokinetics revealed in the present study. However, this suggestion may not describe the relatively comparable AUC in healthy Western volunteers[22] and Oriental patients after multiple doses. The difference in ethnicity of the studied subjects might be the reason. The study by Lockley et al[24] showed comparable C_{max} with the presented patients even though the higher absorption rate in their subjects was demonstrated in comparison with the presented patients, but the elimination rate was rather comparable. Nevertheless, their AUC was rather smaller which might be the results of drug accumulation up to steady state after multiple doses in the present study. In addition to ethnic differences and the subjects' conditions either in sick or healthy status, subject sample size and the analytical method used in the study should also be concerned in the consideration of the different pharmacokinetics obtained. In the study by Yew et al[23], Oriental MDR-TB patients were studied as in the present study but the data from only four patients who used ofloxacin in their regimen were analysed for ofloxacin pharmacokinetic parameters. Such a few subjects and different analytical method might have caused the different results from the present study.

The apparent volume of distribution at steady state (V_{ss}/F) after an oral dose of 10 mg/kg/day ofloxacin in the present study was similar to previously reported values, ranging from 1.1 to 1.7 L/kg [7,12,22]. This high V_{ss}/F indicated good tissue distribution of ofloxacin while the prolonged $T_{1/2\alpha}$ also indicated that ofloxacin was slowly distributed into various body tissues, fluids and elimination organs. As a consequence, prolonged $T_{1/2\beta}$ and long MRT were revealed. The mean ± SD of elimination half-life ($T_{1/2\beta}$) of ofloxacin in the present study which was 8.03 ± 3.37 hours was relatively longer compared to the reported $T_{1/2\beta}$ in Western volunteers which

ranged from 5 to 8 hours[5,7,12,13,21,22,24]. This reflected in the lower CL/F of ofloxacin in the present study of 8.19 ± 2.53 L/h compared to the previously reported value of 11-16 L/h[5,7,13,21]. This also emphasized that ofloxacin was eliminated more slowly in the presented patients than in Western volunteers. The lower CL/F as well as the large V_{ss}/F should contribute to the prolonged $T_{1/2\beta}$ of the drug and support the prolonged MRT. Overall, these should contribute to the successful use of ofloxacin as once daily dosing regimen.

As ofloxacin exhibits concentration-dependent killing activity, its C_{max}/MIC and AUC_{24}/MIC ratios may be potential predictors of its outcome for TB. Many investigators have suggested that the rapid killing activity and the property to prevent the selection of resistant mutant of various fluoroquinolones correlate best with the free C_{max}/MIC ratio of ≥ 8-10 : 1 or free AUC_{24}/MIC ratio of ≥ 125 : 1 for Gram-negative bacteria, especially *Pseudomonas aeruginosa* [1,25]. In addition, the mechanism of action of the fluoroquinolones against TB is the same as that against aerobic Gram-negative bacilli, it is reasonable to expect the same potential outcome predictors, particularly C_{max}/MIC ratio[26]. However, study of the optimal C_{max}/MIC and AUC_{24}/MIC ratios of ofloxacin for *M. tuberculosis* is limited. In the present study, the MIC_{90} value of *M. tuberculosis* was not determined, thus, the actual ratios of these outcome predictors could not be specified. When the estimated free C_{max}/MIC and free AUC_{24}/MIC ratios based on the MIC_{90} of *M. tuberculosis* of 0.5-1 μg/ml and the per cent protein binding of ofloxacin of 20 per cent; as specified in the literature were derived, the free C_{max}/MIC ratio of 7.7-15.4 and the free AUC_{24}/MIC ratio of 56.5-112.9 were obtained. These were, however, higher than those reported by Yew et al[23]; C_{max}/MIC of 5-10 and by Crofton et al [27]; C_{max}/MIC of 2.5-5 (the specified MIC_{90} of *M. tuberculosis* was also 0.5-1 μg/ml). However, recent studies of *in vitro* susceptibility testing[28,29] presented that the MIC_{90} of ofloxacin against TB and MDR-TB was 1 to 2 μg/ml. Accordingly, the effective C_{max}/MIC ratio for these pathogens may be less than the previously specified values. Furthermore, it has been stated that when treating patients with TB, and in particular MDR-TB, the C_{max}/MIC ratios are much smaller[1]. In terms of the appropriate free AUC_{24}/MIC ratio, no previously suggested values are available for this pathogen. In the study by Yew et al[23], the sampling time was up to only 8 hours after dose. The authors' estimated free AUC_{24}/MIC ratio might, therefore, suggest the appropriate value for such pathogen. Nonetheless, further studies to characterize such effective pharmacokinetic/pharmacodynamic outcome predictors for ofloxacin against *M. tuberculosis* are necessary. In addition to those outcome predictors, tissue penetration is another factor that might need to be considered for the efficacy of the drug. The previous study demonstrated that ofloxacin could penetrate well into the intra-alveolar fluid which reflected the infection sites of *M. tuberculosis* with the epithelial lining fluid (ELF) to serum concentration ratio of 2.85[19]. This might also contribute to the effective therapeutic outcome of the drug as the clinical signs and symptoms of the presented patients were in good control. Therefore, ofloxacin, 10 mg/kg/day, in combination with other anti-TB drugs should be effective for the treatment of drug-resistant TB patients. Furthermore, such a dosage regimen would also improve patient compliance and be cost-effective.

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เภสัชจลนศาสตร์ของยาโอฟล็อกซาซิน ในผู้ป่วยวัณโรคที่ดื้อยา

สุวัฒนา จุฬาวัฒนทล, ปรด, บุษบา จินดาวิจักษณ์, ปรด*,*
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ทำการศึกษาเภสัชจลนศาสตร์ของยาโอฟล็อกซาซิน ในผู้ป่วยวัณโรคปอดที่ดื้อยาจำนวน 11 คน อายุเฉลี่ย (SD) 38.09 (11.97) ปี ผู้ป่วยได้รับยาโอฟล็อกซาซิน ขนาด 10 มิลลิกรัม/กิโลกรัม วันละครั้งร่วมกับยารักษาวัณโรคชนิดอื่น ภายหลังอดอาหารเป็นเวลาอย่างน้อย 8 ชั่วโมง ทำการเจาะเลือดก่อนรับประทานยา และตั้งแต่เวลา 0.25 ถึง 24 ชั่วโมง หลังรับประทานยาวิเคราะห์ความเข้มข้นของยาโอฟล็อกซาซิน ในซีรัมด้วยวิธี HPLC

เภสัชจลนศาสตร์ของยาโอฟล็อกซาซิน อธิบายได้ดีด้วย linear, 2-compartment open model ที่มีการดูดซึมและการกำจัดยาแบบ first-order ค่าเฉลี่ย ± SD ของระดับยาสูงสุดในซีรัม มีค่า 9.61 ± 2.17 ไมโครกรัม/มิลลิลิตร ซึ่งพบที่เวลา 1.68 ± 1.21 ชั่วโมง ค่าเฉลี่ย ± SD ของพื้นที่ใต้เส้นกราฟระหว่างระดับยาในซีรัมกับเวลาที่ 24 ชั่วโมง และที่เวลา infinity มีค่า 70.57 ± 26.40 และ 82.45 ± 43.64 ไมโครกรัม x ชั่วโมง/มิลลิลิตรตามลำดับ ยากระจายตัวได้กว้าง ปริมาตรการกระจายตัวที่ steady state มีค่าเฉลี่ย ± SD เท่ากับ 1.37 ± 0.24 ลิตร/กิโลกรัมน้ำหนักตัว อัตรากำจัดยามีค่าเฉลี่ย ± SD เท่ากับ 8.19 ± 2.53 ลิตร/ชั่วโมง ขณะที่ค่าเฉลี่ย ± SD ของค่าครึ่งชีวิตของยา และเวลาที่ยาจะอยู่ในร่างกายมีค่า 8.03 ± 3.37 และ 10.77 ± 4.55 ชั่วโมงตามลำดับ อัตราส่วนของระดับยาอิสระสูงสุดในเลือดต่อความเข้มข้นต่ำสุดของยาที่ยับยั้งเชื้อ *Mycobacterium tuberculosis* ร้อยละ 90 มีค่าประมาณ 7.7-15.4 : 1 ผลการศึกษาแสดงว่ายาโอฟล็อกซาซิน ขนาด 10 มิลลิกรัม/กิโลกรัม วันละครั้งร่วมกับยารักษาวัณโรคชนิดอื่น สามารถให้ค่าอัตราส่วนของระดับยาอิสระสูงสุดในเลือดต่อความเข้มข้นต่ำสุดของยาที่ยับยั้งเชื้อที่เพียงพอ และมีค่าครึ่งชีวิตที่ยาวจึงสนับสนุนการใช้ยานี้ในวัณโรคที่ดื้อยา

คำสำคัญ : โอฟล็อกซาซิน, เภสัชจลนศาสตร์, เชื้อวัณโรคที่ดื้อยา

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