Absorption and disposition kinetics of levofloxacin tablets in human volunteers

Cinéticas de absorción y disposicón de tabletas de levofloxacina en voluntarios humanos

KHALID, R. Y NAWAZ, M.[1]

Drugs Division, Ministry of Health, Government of Pakistan and [1]Departament of Physiology & Pharmacology, University of Agriculture, Faisalabad 38040, Pakistan. E-mail: nawazn@paknet4.ptc.pk

RESUMEN

Levofloxacina es un agente antibacteriano del grupo de las fluoroquinolonas. Se ha investigado las cinéticas de absorción y disposición de levofloxacina tras la administración de tabletas de 500 mg por vía oral a 26 voluntarios jóvenes y sanos. Se obtuvieron los valores medios ± la desviación estándar (SD) del tiempo necesario para alcanzar la concentración plasmática máxima (Tmax) 2,08 ± 0,84 h.; la concentración plasmática máxima (Cmax) 4,79 ± 1,40 µg/mL, el aclaramiento total (CL) 10,8±4,60 L.h^{-1} y el volumen aoarente de distribución (Vd) 109±64 L. Estos resultados indican una amplia distribución del fármaco en los tejidos. El tiempo medio de eliminación del fármaco en plasma fue de 6,86±2,12 h. Una vez estimados los parámetros farmacocinéticos en sujetos normales, una aplicación óptima de esta fluoroquinolona requeriría una evaluación de la posología recomendada por los fabricantes en condiciones clínicas y con monitorización de los niveles séricos.

PALABRAS CLAVE: Biodisponibilidad, Farmacocinéticas, Levofloxacina, Humanos sanos.

ABSTRACT

Levofloxacin is an antibacterial agent of the fluoroquinolones group. The absorption and disposition kinetics of levofloxacin were investigated following single oral dose 500-mg tablet in 26 healthy young male volunteers. The study revealed mean ± SD value of Tmax 2.08 ± 0.84 h, Cmax 4.79 ± 1.40 µg/mL, total body clearance 10.8 ± 4.60 L.h^{-1} and apparent volume of distribution (Vd) 109 ± 64 L indicating extensive tissue distribution. Elimination half-life of the drug in plasma was 6.86 ± 2.12 h. Following verification of pharmacokinetics parameters in normal subjects, an appraisal of manufacturer's recommended dosage regimen in clinical conditions and therapeutic monitoring is appropriate for optimal application of this fluoroquinolone.

KEY WORDS: Bioavailability, Pharmacokinetics, Levofloxacin, healthy humans.

INTRODUCTION

The fluoroquinolones inhibit the DNA bacterial gyrase preventing the curling of the bacterial nucleic acid inside the nucleus (Hilliard et al., 1995). Levofloxacin is a fluoroquinolone antibacterial and is the optical S-(-) isomer of the racemic drug substance ofloxacin. It has a broad spectrum of in vitro activity against Gram-positive and Gram-negative bacteria, as well as certain other pathogens such as Mycoplasma, Chlamydia, Legionella and Mycobacteria spp. Levofloxacin is significantly more active against bacterial pathogens than R-(+)-ofloxacin. Levo-

[1] This work is part of Ph.D. thesis project of Rauf Khalid.

floxacin hemihydrate, the commercially formulated product, is 97.6% levofloxacin by weight. Levofloxacin pharmacokinetics are not appreciably affected by age, gender or race when differences in renal function, and body mass and composition are taken into account (Fish and Chow, 1997) Ofloxacin has been recently registered in Pakistan. Earlier studies have demonstrated that under geographical and genetic (geonetical) influences, the disposition kinetics of a drug is best described in the population and environment in which the drug is to be employed clinically (Nawaz, 1994). Therefore, this study describes the absorption and disposition kinetics of levofloxacin in healthy volunteers under indigenous conditions.

MATERIALS AND METHODS

Absorption and disposition kinetics of levofloxacin was investigated in healthy male volunteers. The detailed experimental protocol is presented below:

Volunteers

A total of 26 volunteers with normal physical examination, hematology, hematochemistry, liver and kidney function tests were registered for this study. The volunteers were adult males with mean ± SD values for the age of 24 ± 3 years, body weight 65 ± 7 Kg, height 67 ± 2 inches. The volunteers registered for this study were apprised of the study protocol and possible drug effects, following which a written Consent Form was signed by each of them. The volunteers were not taking any medication and were asked to not take any solid food 12 hours before medication. The experiments were started early in the morning. The study was approved by the Institutional Ethics Committee.

Sampling

Before drug administration, a blank venous blood sample was collected from each volunteer through Branula (Branüle®, B. Braun, Melsungen AG) aseptically inserted in the vein of left arm. Following oral drug administration, blood samples were drawn at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12 and 24 hours through branula. The blood samples collected in heparinized centrifuge tubes were centrifuged at 3000 rpm for 7-10 min and plasma was separated and stored at -20 °C until used next day for analysis.

Drug Administration

With 250 ml of drinking water, each volunteer was given orally Cravit® (levofloxacin) 500 mg film-coated Tablets, Batch No. C 250–3, manufacturing date March 1998, expiry date March 2001, manufactured by Hilton Pharma (Pvt., Karachi, Pakistan) Ltd. under license of Daiichi Pharmaceuticals Co., Japan.

Drug Assay

For assay of levofloxacin in plasma, the Disc Agar Diffusion Method was standardized and validated for accuracy and precision by using *Streptococcus faecalis* as test organism by the method of Arret et al. 1971. The concentration of levofloxacin in plasma was determined. The zones of inhibition were measured with Zone Reader and the concentration of levofloxacin in plasma samples was calculated by comparison of the sample zones with those of the standards.

Calculations

Absorption and disposition kinetics (two-compartment model) were calculated with the computer program MWPHARM version 3.02 a Mediware product Holland. This program calculates the regression coefficient of best fit to depict the compartmental analysis for pharmacokinetics parameters. The results are presented as average ± SD.

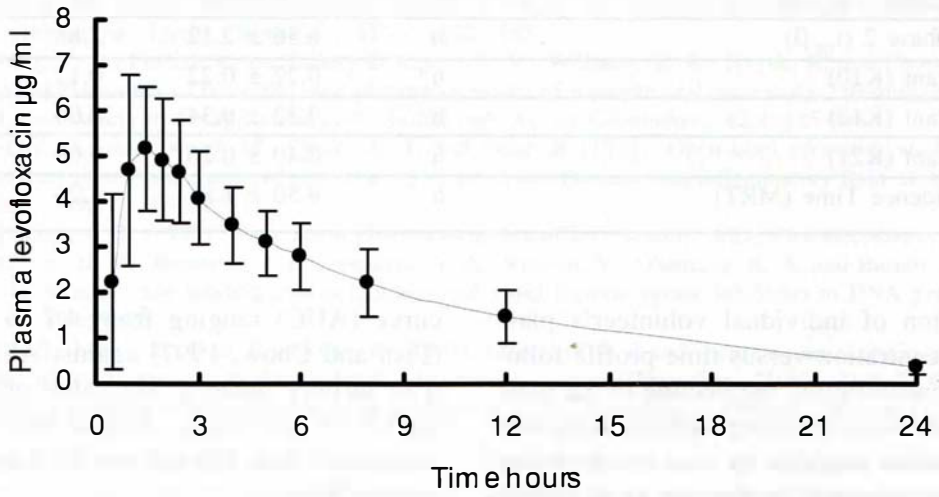
RESULTS AND DISCUSSION

Following oral administration of levofloxacin 500 mg tablet to each of the 26 healthy male volunteers, the mean ± SD and minimum and maximum values for the plasma concentration at various time intervals after oral administration of the drug are given in Table 1. The mean ± SD values for the plasma concentration of the drug versus time after administration have been plotted in Fig1.

TABLE 1. Plasma concentration of levofloxacin in 26 healthy male volunteers following oral administration of 500 mg tablet.

Time in Hours	Plasma concentration µg/ml		
	Mean ± SD	Minimum	Maximum
0.5	2.22 ± 1.93	0.00	7.80
1.0	4.68 ± 2.12	0.41	9.30
1.5	5.15 ± 1.38	2.20	8.20
2.0	4.91 ± 1.35	2.90	8.20
2.5	4.65 ± 1.14	2.80	7.16
3.0	4.08 ± 1.04	2.50	6.86
4.0	3.46 ± 0.85	2.10	5.52
5.0	3.08 ± 0.73	1.90	5.00
6.0	2.78 ± 0.76	1.40	4.56
8.0	2.21 ± 0.72	1.20	4.18
12.0	1.48 ± 0.56	0.60	3.28
24.0	0.34 ± 0.15	0.00	0.70

FIG 1.- Mean ± SD plasma concentration of levofloxacin in 26 healthy male volunteers against time following oral dose of 500-mg tablet.



The pharmacokinetics parameters that describe absorption, distribution and elimination of levofloxacin following an oral dose of 500 mg in healthy male volunteers have been presented in Table 2. From the Table it is seen that mean ± SD value for the time to peak concentration (Tmax) was 2.08 ± 0.84 hours little longer than 1.5 hour (Chien et al., 1997) when the peak

concentration (Cmax) was 4.79 ± 1.40 µg/mL. A Cmax of approximately 2.8 and 5.2 mg/L within 1 to 2 hours after oral administration of levofloxacin 250 and 500 mg tablets, respectively was recorded by Fish and Chow (1997) and 5.9 ± 1.3 µg/mL with 500 mg dose was observed by Lee et al (1997). Repeated oral levofloxacin 500 mg every 12 hours five doses and every 24 hours three doses produced a mean peak concentration in plasma of 9.3 and 6.6 µg/mL attained at 1.1 and 1.2 hour after the 12- and 24-hour regimen (Child et al., 1995).

TABLE 2. Pharmacokinetic parameters of levofloxacin in 26 healthy male volunteers following oral dose of 500 mg tablet.

Parameter	Units	Mean ± SD	Minimum	Maximum
Absorption kinetics				
Absorption rate constant (ka)	h^{-1}	0.98 ± 1.04	0.19	5.17
Absorption half life ($t_{1/2}$ abs.)	h	1.25 ± 0.84	0.13	3.66
Time to peak (Tmax)	h	2.08 ± 0.84	0.52	3.71
Peak concentration (Cmax)	µg/mL	4.79 ± 1.40	2.31	8.96
Disposition kinetics				
Zero time Pc of distribution phase (A)	µg/mL	8.81 ± 10.9	0.32	54.1
Distribution rate constant (α)	h^{-1}	0.85 ± 0.65	0.17	2.76
Zero time Pc of elimination phase (B)	µg/mL	4.14 ± 2.22	0.61	11.5
Elimination rate constant (β)	h^{-1}	0.16 ± 0.20	0.06	1.11
Area under Curve (AUC)	h.mg/L	45.1 ± 13.8	0.29	68.5
AUC polyexponential (AUC)	h.mg/L	43.0 ± 10.7	24.6	68.4
AUC trapezoidal rule (AUC)	h.mg/L	44.6 ± 12.4	24.3	77.9
Total Body Clearance (Cl)	L/h	10.8 ± 4.60	4.96	27.5
Volume of distribution compartment 1 (Vc)	L	47.7 ± 20.6	8.51	88.7
Vol. distribution steady state (Vdss)	L	81.8 ± 36.1	22.6	170.0
Apparent Volume of distribution (Vd)	L	109 ± 64	30.3	277.8
Half life phase 1 ($t_{1/2}$ α)	h	1.25 ± 0.81	0.25	3.60
Half life phase 2 ($t_{1/2}$ β)	h	6.86 ± 2.12	2.88	10.9
Rate constant (K10)	h^{-1}	0.27 ± 0.22	0.12	1.24
Rate constant (K12)	h^{-1}	0.32 ± 0.34	0.00	1.56
Rate constant (K21)	h^{-1}	0.40 ± 0.26	0.09	0.99
Mean Residence Time (MRT)	h	9.50 ± 1.81	7.26	13.6

Examination of individual volunteer's plasma drug concentration versus time profile following peak concentration, the decline in the plasma concentration profile being biphasic suggested pharmacokinetics analysis by two-compartment model as also adopted by Preston et al (1998) for the population pharmacokinetic analysis of levofloxacin. Area under plasma concentration versus time curves calculated by different methods of calculation was similar (Table 2). With varying single oral dose of levofloxacin 50 to 1000 mg produced area under concentration-time curve (AUC) ranging from 4.7 to 108 mg.h/L (Fish and Chow, 1997) against AUC from time 0 to infinity mean ± SD value of 45.1 ± 13.8 mg.h/L in this study. AUC(0-24h) following a single oral dose 750 mg was 71.3 mg.h/L (Chien et al., 1998).

Total body clearance (CL) of levofloxacin following 500 mg oral dose to male volunteers was 10.8 ± 4.6 $L.h^{-1}$ or 0.167 $L.h^{-1}.kg^{-1}$ comparable to the reported values 9.27 $L.h^{-1}$ (Preston et al., 1998) and 0.178 $L.h^{-1}.kg^{-1}$ (Tanigawara et al., 1995), respectively.

Volume of distribution of compartment 1 or central compartment (Vc) was 47.8 ± 20.6 L or 0.74 $L.kg^{-1}$ comparable to the value of 0.836 L.kg-1 (Preston et al., 1998). Levofloxacin is widely distributed in the body and penetrates well in most body tissues and fluids. The mean ± SD value for the apparent volume of distribution (Vd) was 109 ± 64 L or 1.68 $L.kg^{-1}$ was higher while steady state volume of distribution Vdss 1.25 $L.kg^{-1}$ was comparable with the reported values of 1.1 $L.kg^{-1}$ (Fish and Chow (1997) and 1.46 $L.kg^{-1}$ (Tanigawara et al., 1998). However, both the values Vd and Vdss indicate extensive tissue localization of the drug to combat infections.

Half-life in two-compartment model is associated with distribution and elimination phases of the plasma-concentration versus time curves and is inversely related with the rate constants for distribution (α) and elimination (β). The Distribution half-life ($t_{1/2}$ β) of levofloxacin was 1.25 ± 0.81 hour, which was equal to and governed by the absorption half-life. The mean terminal half-life for plasma (t1/2β) was 6.86 ± 2.12 hours in healthy male volunteers. The $t^{1/2}\beta$ was comparable with the reported levofloxacin half-life range from 6 to 8 hours in individuals with normal renal function (Fish and Chow, 1997), 7.9 hours in healthy male volunteers (Child et al., 1995) and 8.8 hours in healthy subjects (Chien et al., 1998).

The mean ± SD values for the intercompartmental rate constants, the rate constant from the central to the peripheral compartment (K_{12}) and the rate constant from the peripheral to the central compartment (K_{21}), were 0.32 ± 0.34 h^{-1} and 0.40 ± 0.26 h^{-1}, respectively. The values of transfer rate constants are slightly lower than the reported values of 0.487 h^{-1} and 0.647 h^{-1} for K_{12} (Kcp) and K_{21} (Kpc), respectively (Preston et al., 1998).

The results of this study indicate that the pharmacokinetic parameters of levofloxacin determined in healthy young male volunteers are within a comparable range with the similar studies conducted elsewhere. An adjustment of levofloxacin dosage regimen under geonetical influences (Nawaz, 1994) in the local population warrants clinical appraisal of the manufacturer's recommended dosage regimen and therapeutic monitoring is warranted for optimal application of this fluoroquinolone.

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