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Biodisposition Kinetics of Levofloxacin in Female Volunteers Following Oral Administration

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Abstract: Biodisposition kinetics of levofloxacin was determined in 9 female volunteers following oral administration of 500 mg tablets. The blood samples were collected at specific time intervals. Concentration of levofloxacin in plasma was determined by microbiological assay, that was found to be 2.39 µg/ml having 1.75 SD and 75% CV values. The pharmacokinetic parameters were determined according to single compartment open model. The average absorption rate constant was 2.00 L/h while absorption half life was 0.34 hours. Average C_{max} and T_{max} values were 2.43 mg/L and 1.60 hours while volume of distribution was 177 L. From T_{max} studies, it is concluded that absorption is delayed due to non-fasting. It is suggested that levofloxacin can be administered orally with regard to food. It was observed the elimination half life and total body clear values were 7.40 hours and 16.54 h respectively while total area under curve was found to be 30.2 h.mg/L. It is also suggested that elimination half life is not affected by the presence of absence of food.

Key words: Biodisposition kinetics, levofloxacin, oral, human females

Introduction

Levofloxacin is a fluoroquinolone antibiotic and is the L-isomer of ofloxacin (Katzung, 1998). It has broad spectrum of *in vitro* activity, Levofloxacin is significantly more active against bacterial pathogens than ofloxacin (Fish and Chow, 1997) and it is microbiologically more potent than other quinolones (Chien *et al*., 1997a). Levofloxacin is a pyridone carboxylic acid derivative, structurally related to nalidixic acid and it exerts its antibacterial effects through inhibition of DNA-gyrase type II topoisomerase. (Fish and Chow, 1997). The absolute bioavailability of an oral dose of levofloxacin 500 mg is approximately 99%. Administration of levofloxacin with food apparently has little effect on drug absorption (Fish and Chow, 1997).

Drug disposition is the term used to describe the absorption, distribution, metabolism and elimination of drug. Biodisposition kinetic parameters about accumulation of drug in blood and tissue. Geographical varieties are known to influence the disposition and fate of drug (Nawaz, 1994). Such environmental influences are due to geographical locations on the genetics of a population are manifested by biochemical and physiological parameters and were described by an original term "geonetics" (Nawaz and Shah, 1985; Nawaz *et al*., 1988). Biodisposition kinetics of levofloxacin was studied in local environment, because difference due to genetics and environmental influences described by "geonetics" which apprise of need for investigating disposition under circumstances in which drug is used.

Materials and Methods

Drug Administration and Sampling: Pharmacokinetics of levofloxacin was investigated following a single oral dose of 500 mg in 9 healthy, female volunteers, aged between 21-25 years having 55 kg of average body weight. Blood samples were drawn intravenously at 0, 0.5, 1, 1.5, 2.0, 2.5, 3, 4, 5, 6, 8 and 12 hours after the drug administration. Blood samples ere centrifuged at 4000 rpm for 15 min., then plasma was carefully separated from the sedimented cells.

Microbiological Assay: Levofloxacin concentration in plasma was determined following microbiological assay by agar diffusion technique using *Staphylococcus aureus* as test organism (Arret *et al*., 1971). Media containing bacteria was incubated for 24 hours then growth was washed with 50 ml normal saline. Now 2 gm nutrient agar/0.5 gm NaCl media was preferred and 100 µl spore supension was added in 100 ml media. It was poured on petridish and 100 ml of each standard dilution was added on to disc. Then these were incubated for 24 hours. Zone of inhibition due to activity of drug after 24 hours were obtained which were measured by zone reader.

Preparation of Standard curve and Analysis of plasma samples: 0.1% levofloxacin solution in dist. water was prepared and a standard curve was plotted between the log concentration (ug/ml) and zone of inhibition (mm). Plasma samples from levofloxacin were analyzed by following the same procedure.

Pharmacokinetics of Levofloxacin: The pharmacokinetic parameters were determined by following single comportment open model (Baggot, 1977). Parameters such as Peak concentration (C_{max}), Time to peak (T_{max}), Absorption rate constant (K_a), Absorption half life ($T_{1/2\alpha}$), area under curve (AUC), volume of distribution (V_d), elimination half time ($T_{1/2\beta}$), total body clearance (C_l) were determined by using computer program Nw/PHARM version 3.02 (Rombout, 1987).

Statistical Analysis: Determination of regression line, standard deviation (SD) and coefficient of variation (CV) values were calculated by Steel and Torrie (1984).

Results and Discussion

The plasma concentration of levofloxacin was measured in 9 female volunteers and the results with SD and CV values are given in Table 1 and graphically in Fig. 1. The graph shows a gradual increase in plasma concentration and C_{max}, was reached after which a decline in curve which is in

Table 1: Plasma concentration of levofloxacin (μg/ml) in female volunteers following oral administration of 2 x 250 mg (500 mg) tablet to each volunteer

Volunteer No.	Plasma Concentration μg/ml or mg/L at time in hours										
	0.5	1	1.5	2	2.5	3	4	5	6	8	12
1	1.62	5.27	5.39	4.64	5.62	6.26	5.62	5.16	3.74	3.66	2.49
2	1.59	2.54	2.89	2.44	2.14	2.49	1.43	1.59	1.81	1.46	0.91
3	2.71	2.6	2.71	2.83	2.54	2.14	1.92	1.59	1.20	1.15	1.08
4	4.16	4.54	3.82	4.08	5.62	3.99	3.99	3.82	3.29	2.05	1.55
5	0.73	1.59	1.18	0.97	1.20	1.03	0.77	1.15	ND	ND	0.32
6	0.38	0.53	1.15	1.18	0.46	0.47	1.06	0.78	0.99	0.93	0.42
7	ND	ND	0.82	1.18	1.46	1.62	1.31	1.06	1.28	0.70	0.70
8	2.66	1.59	0.91	0.87	0.99	0.87	ND	ND	0.52	0.67	0.32
9	0.35	0.49	0.99	0.91	0.95	1.13	1.23	1.28	0.93	0.58	0.35
Avg.	1.78	2.39	2.21	2.12	2.33	2.22	2.17	2.13	1.72	1.4	0.91
SD	1.34	1.75	1.61	1.45	1.97	1.85	1.72	1.53	1.17	1.04	0.73
CV%	75.20	75.00	72.90	68.60	84.40	83.20	79.40	71.30	68.20	74.00	80.20

Table 2: Pharmacohinetic parameters of levofloxacin in female voluntreers after oraldose of 2 X 250 mg (500 mg) tablets. One comartmental open model was applied

Parameter	Unit	1	2	3	4	5	6	7	8	9	Average +/-
$t_{1/2}a$	h	0.31	0.11	0.89	0.26	0.03	0.74	0.56	0.00	2.41	0.34
Ka	t/h	2.23	6.30	7.77	2.62	21.50	0.93	1.20	74.40	0.28	2.00
t_{max}	h	1.89	1.10	0.61	1.26	0.70	3.11	3.17	0.37	3.54	1.60
C_{max}	mg/L	5.82	2.57	2.72	4.18	1.40	0.85	1.51	1.45	1.11	2.43
AUC	h.mg/L	77.30	28.60	28.30	50.80	11.40	16.70	17.20	10.80	10.50	30.20
AUC_{poly}	h.mg/L	48.80	19.20	19.90	37.00	8.77	8.80	12.10	8.60	10.20	20.30
AUC_{poly}	h.mg/L	48.30	19.60	19.20	36.10	10.10	9.15	11.70	8.98	9.03	19.90
$t_{1/2}\beta$	h	8.08	7.22	6.80	6.36	5.47	11.10	6.20	5.11	2.39	7.40
Vd	L	0.15	182.00	173.00	90.40	345.00	480.00	260.00	340.00	163.00	177.00
CL	L/h	0.01	17.40	17.60	9.84	43.70	29.80	29.10	46.20	47.30	16.50
K_1	h	0.08	0.09	0.10	0.10	0.12	0.06	0.11	0.13	0.29	0.09
$K_1 = K10$		0.08	0.09	0.10	0.10	0.12	0.06	0.11	0.13	0.28	0.09
Lag time	h	0.37	0.36	0.04	3.74	0.46	2.13	1.04	0.28	0.07	301 X 10^8
B		6.63	2.74	2.88	5.52	1.44	1.04	1.97	1.46	3.05	2.82
MRT	h	12.40	10.90	9.98	9.56	8.40	17.10	10.80	7.67	7.01	11.10

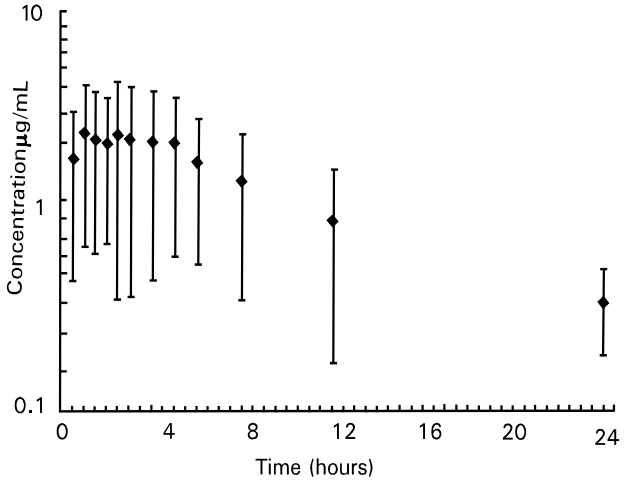

Fig. 1: Representative plot for plasma concentration varsus time for all volunteers

accordance with earlier observation in healthy volunteers (Fish and Chow, 1997).

The pharmacokinetic parameters were determined following one compartment open model and the results are arranged in Table 2. Absorption half life is the time in which half of the drug is absorbed. In present studies its average value was 0.346 hours. The absorption of levofloxacin was slightly delayed by food, although the overall bio-availability of levofloxacin following a high fat meal was not altered (Lee *et al.*, 1997). The changes in levofloxacin absorption were not likely to be clinically significant. So, it could not administered orally without regard to food (Fish and Chow, 1997). The average absorption rate constant was found 2/hour, which average is known to be rate constant for absorption of drug.

In present research studies, average value of time to peak was 1.60 hours. It was found to be 1.80 hours in 5 healthy non-fastening volunteers by Fish and Chow (1997) and it was 1.0 and 2.0 hours for non-fasting and fed conditions respectively as reported by Lee *et al*. (1997). Chien *et al*. (1997b) found these values as 1.3 hours in 10 healthy male volunteers. T_{max} values from our studies are in accordance with others findings, only the difference is due to non-fasting conditions. So it is concluded that absorption is delayed due to non-fasting.

Peak concentration is defined as the maximum concentration given by drug and it is found to be 2.43 mg/L average value in our study. According to Fish and Chow (1997), C_{max} was 2.6 and 5.2 mg/L with in 1 to 2 hours after oral administration of levofloxacin 250 and 500 g tablets respectively. Following the single oral doses of levofloxacin 50 to 1000 mg to healthy volunteers, C_{max} ranged from 0.6 to 9.4 mg/L (Fish and Chow, 1997). Lower values of C_{max} in our studies are due to non-fasting and application of microbiological assay while in all the studies HPLC was used.

Area under curve is the total area under plasma concentration curve and average value was 30.2 h mg/L. In 16 healthy volunteers by administration of 750 mg

levofloxacin AUC value was 7.13 h.µg/ml and 90.7 h.µg/ml when 1 gm dose was given (Chien *et al*., 1997b). Single oral doses of levofloxacin 50-100 mg produce AUC ranging from 4.7-108 h.mg/L as increasing linearly in a dose proportional fashion (Fish and Chow, 1997).

In the present research work, the elimination half life was 7.40 hours average value. This was found 6-8 hours in individual with normal renal function (Fish and Chow, 1997) and our resultant values fall in this range. The mean $T_{1/2\beta}$ is not affected by presence or absence of food when levofloxacin 500 mg tablet was administered (Lee *et al*., 1997). The average value of volume of distribution was 177 L. According to Chien *et al*. (1998) there is not much variation from single to multiple dosages mean steady state value of V_d following 750 mg dose was 105 l in 16 volunteers. The variation in results is due to average body wt which was 55 kg in our studies.

Total clearance of drug obtained was 16.57 L/hour from 9 volunteers. It was reported as 13.40 L/hour in 5 non-fasting volunteers after 100 mg levofloxacin dose (Fish and Chow, 1997). This is not a big differences so it is concluded that our results obtained from pharmacokinetic parameters are appropriate if any difference in results, it is due to analytical and environmental conditions.

References

Arret, D., D. Johnson and K. Amiel, 1971. Outline of detail for microbiological assr of antibiotics. J. Pharm. Sci., 60: 373-378.

Baggot, J.D., 1977. Principles of Drug Disposition in Domestic Animals. W.B. Saunders Co., Philadelphia.

Chien, S.C., A.T. Chow, J. Natarajan, R.R. Williams, F.A. Wong, M.C. Rogge and R.K. Nayak, 1997a. Absence of age and gender effects on the pharmacokinetics of a single 500-milligram oral dose of levofloxacin in healthy subjects. Antimicrob. Agents Chemother., 41: 1562-1565.

Chien, S.C., M.C. Rogge, L.G. Gisclon, C. Curtin and F. Wong *et al*., 1997b. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. Antimicrob. Agents Chemother., 41: 2256-2260.

Chien, S.C., F.A. Wong, C.L. Fowler, S.V. Callery-D'Amico, R.R. Williams, R. Nayak and A.T. Chow, 1998. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750-milligram and 1-gram doses of levofloxacin in healthy volunteers. Antimicrob. Agents Chemother., 42: 885-888.

Fish, D.N. and A.T. Chow, 1997. The clinical pharmacokinetics of levofloxacin. Clin. Pharmacokinetics, 32: 101-119.

Katzung, B.G., 1998. Basic and Clinical Pharmacology. 7th Edn., Lange Medical Book, USA.

Lee, L.J., B. Hafkin, I.D. Lee, J. Hoh and R. Dix, 1997. Effects of food and sucralfate on a single oral dose of 500 milligrams of levofloxacin in healthy subjects. Antimicrob. Agents Chemother., 41: 2196-2200.

Nawaz, M. and B.H. Shah, 1985. Geonetical consideration in quality assurance of pharmaceutical. Proceedings of the International on Policies Management and Quality Assurance of Pharmaceutical, April 21-25, 1985, WHO and Ministry of Health, Government of Pakistan.

Nawaz, M., 1994. Geonetical factors affecting biodisposition of drugs. Can. J. Physiol. Pharmacol., 72: 24-29.

Nawaz, M., T. Iqbal and R. Nawaz, 1988. Geonetical consideration in disposition kinetic evaluation of chemotherapeutic agents. Veterinary pharmacology toxicology and therapy in food producing animals. Proc. 4th Cong. Eur. Assoc. Vet. Pharm. Therap. Budapest,2 2: 260-260.

Rombout, F., 1987. In cooperation with University Centre for pharmacy. Deptt. of Pharmacology and Therapeutics, Univ. of Gronigen and MEDI/ware, Copyright 1987-1991.

Steel, R.G.D. and J.H. Torrie, 1984. Principles and Procedures of Statistics. McGraw Hill Book Co. Inc., New York, USA.