PHARMACOKINETIC STUDY OF CEPHRADINE IN PAKISTANI HEALTHY MALE VOLUNTEERS

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ABSTRACT

To observe and discuss the difference in the pharmacokinetics of Cephradine in Pakistani population with the reported data of other ethnic origins. A Single group pharmacokinetic study was conducted having six healthy male volunteers of 20-24 years of age. Blood samples were collected at appropriate times up to 7 hours. Plasma concentrations of Cephradine was determined by HPLC technique and pharmacokinetic parameters were determined by both compartmental and noncompartmental methods using Kinetica ver 4.4.1 and Winnonlin ver 5.01. Peak plasma concentration was 11.49±1.73 μg/ml achieved at 0.76±0.12 hr, after the administration of 250 mg Cephradine to fasting volunteers. Area under the serum concentration-time curve was found to be 16.4±1.71 μg.hr/ml. Absorption, distribution, disposition and elimination half lives were calculated as 0.183 ± 0.038hr, 0.248 ± 0.143 hr, 2.126 ± 0.341 hr and 0.441±0.193 hr respectively where as the volume of central compartment and total body clearance were found to be 9.65±3.78 L and 15.4±1.89 L/hr. The plasma concentration time curves showed the absorption rate constant was 3.968 ± 0.05 hr^{-1}, disposition rate constant was 0.333±0.05 hr^{-1}, distribution rate constant was 3.64±2.18 hr^{-1} and elimination rate constant was 1.738±0.468 hr^{-1}. The value of micro-constants i.e. K_{12} (central to peripheral compartment) and K_{21} (peripheral to central compartment) were found to be 1.529± 1.499 hr^{-1} and 0.704 ± 0.44 hr^{-1} respectively, where as MRT and AUMC were calculated as 2.04±0.09 hr and 35.92±1.86 hr^2×ug/mL. The findings showed that the results of Pakistani subjects are slightly different when compared with the reported data of other ethnic origin.

Keywords: Pharmacokinetics, Cephradine.

INTRODUCTION

Many studies illustrate that differences in manufacturing procedures as well as in the composition of dosage form can affect the bio-availability of the drug product, in addition it can also be influenced by the physiology of the patient and other factors such as content of the gastrointestinal tract, rate of gastrointestinal tract transit, local blood flow, condition of the gastrointestinal tract membrane, metabolism or degradation in gastrointestinal tract during the first pass effect, age, sex, race, body size, time or day and bed rest v/s ambulatory. Moreover most of the drugs can not be taken as pure chemicals but are formulated in to pharmaceutical dosage form, such drug products may be relatively a simple solution compressed in to a tablet form containing excipients, capsule form or suspension form etc. Because of the different dosage forms, few of the formulations and manufacturing variables could influence the bio-availability of the drug product, such as salt form, crystalline form, composition of the dosage form, tablet compression force, processing variables, particle size of drug or excipients, environmental conditions.

Interethnic differences are important factors accounting for interindividual variations in drug responsiveness. However, these differences in drug response have been a relatively neglected area of investigation, so that similar doses are prescribed to different ethnic populations without consideration of interethnic pharmacokinetic and pharmacodynamic variation. With the differences in drug disposition and responses calls into question the failure of drug licensing authorities to demand information on dosage, efficacy and toxicity in different ethnic groups, and to accept data from limited ethnic groups such as Caucasians (Wood and Zhou, 1991). With the increased recognition of genetically determined polymorphism in metabolising ability as an important factor in drug disposition, concern has developed for the importance of individualising drug dose to account for racial differences.

Cephradine was developed at the Squibb Institute for Medical Research (Dolfini *et al.*, 1971; Miroglia *et al.*, 1973). It is very similar to Cephalexin in its antimicrobial activity and in most other respects (Mollering and Swartz, 1976). Unlike Cephalexin for which a parenteral preparation is not generally available, Cephradine is marketed in some countries for both oral and parenteral use (Kucers *et al.*, 1997). Cephradine is broad spectrum Cephem, active *in vitro* against *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Staphylococcus aureus*,

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including β-lactamase producing but non methicillin resistant strain (Bill and Washington, 1977).

The aim of the present study was to determine the pharmacokinetics of Cephradine in a Pakistani population, as there was no racial data available which explain the pharmacokinetics of this widely used drug in Pakistan.

MATERIAL AND METHODS

Study Design and volunteer selection

In this design six healthy volunteers were selected having age group ranges between 20-24 years. The volunteers were informed in detail about the study and a written consent was obtained. Selection of those volunteers was made according to FDA guide lines.

Volunteers were examined by a medical practitioner and tested for hepatic, renal and haemopoetic functions before being included in the study. Exclusion criteria include:

1. Subject whose height and weight ratio was not within ±10% of the acceptable range as described by the FDA.
2. History of cardiac, hepatic, renal, epileptic or haemopoetic factor.
3. Laboratory values outside the acceptable normal ranges.
4. Any kind of medications within four weeks prior to the start of the study.
5. History of drug or Alcohol abuse.
6. Hospitalization for any reason within eight weeks prior to the start of the study.
7. Donation or loss of 450 ml of blood within past three months.
8. Positive test for Hbs. Ag and HIV.
9. Excessive smoking habits (more than 15 cigarettes per day).

Drug administration

Volunteers were asked to come fasted on the morning of the test day. Each volunteer swallowed one capsule of 250mg of the test product manufactured by a multinational pharmaceutical company in Pakistan.

Sample Collection

Ten ml blood was drawn by vena puncture at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 7 hrs. Samples were collected in screw capped sterile Heparinized Centrifuge tubes. Plasma was separated from each sample by Centrifugation (Labofuge 200, Hereus, Oesterode, Germany) at 3000 rpm for 3min. Labeled plasma samples were stored in glass vial at -20ºC till the time of analysis.

Preparation of Samples

Protein was separated from plasma using 1ml of the sample and 1ml 6% Trichloroacetic acid, mixed and vortexed (whirl mixer, England) and then centrifuged at 4000 rpm for 10 min. Sample was filtered by 0.2µ Millipore filters using Swinney Filtration Assembly. Supernatant was injected from 50µL syringe (SGE Corp) in the Rheodyne Injector having 20µL loop.

Assay condition

Chromatographic procedure

Chromatographic separation was performed with a reverse phase column (Lichrospher 4.6 x 250 mm) on High performance liquid chromatograph (LC-5A, Shimadzu corporation, Tokyo, Japan) coupled with UV-detector (SPD-2A, Shimadzu corporation, Tokyo, Japan) having detection wavelength of 254 nm. Mobile Phase consisted of analytical grade of 1 volume of 5M Acetic acid, 17ml of 3.62% w/v solution of Sodium acetate, 200ml of Methanol and 782ml of distilled water (B.P. 2000). Mobile phase was filtered (Sartorious, Gottingen, Germany) using 0.2µ pore size Millipore Filters. Mobile Phase was degassed for 15min in Ultrasonic Bath (Clifton, Nickel Electro Ltd. Somerset, England).

Calibration of the assay procedure

A calibration plot was first constructed, based on samples (standards) that contained known concentrations (or weight) of the Cephradine (Reference standard) dissolved in plasma. After deproteination a fixed volume of each standard solution was then injected and processed as in the assay procedure. The calibration plot was proven to be linear between 1 and 12µg/ml. The intra- and interassay coefficients of variation, determined with calibration standards and quality control samples, ranged from 0.4 to 6.3% and from 1.3 to 2.3%, respectively. Limit of detection was 9-10 ng/ml and the limit of quantification was 60-70 ng/ml.

Pharmacokinetic analysis

The concentrations of drug were estimated by compartmental and non-compartmental analysis using Pharmacokinetic softwares, Winnonlin version 5.1 (Pharsight corporation, Mountain View California) and Kinetica 4.4.1 (Thermoelectron Corp).

Compartmental parameters includes maximum plasma concentration (C_{max}), time to achieved Cmax (T_{max}), disposition rate constant (β), distribution rate constant (α), elimination rate constant (K_{el}), microconstants (K_{12}, K_{21}), volume of the central compartment (Vc), Area under plasma concentration time curve (AUC), half lives.

Non compartmental parameters include AUC_{0-t} by trapezoidal method and $AUC_{0-\infty}$, Mean residence time (MRT), Area under the first moment curve (AUMC), First

Plasma concentration of Cephradine 250mg capsule in six healthy volunteers

Time(hrs)	Concentration (µg/ml)						Mean	S.D
	1	2	3	4	5	6		
0.5	8.97	7.09	7.12	8.93	8.86	8.83	7.19	3.0672
1	9.9	8.44	8.97	9.91	10.3	9.34	8.27	3.2656
1.5	4.5	5.34	4.48	4.91	5.06	4.57	4.34	1.2914
2	2.22	3.5	2.88	2.19	2.21	2.23	2.46	0.5347
3	1.37	1.61	1.81	1.28	1.38	1.37	1.69	0.6063
4	0.84	1.11	1.29	1.03	0.89	0.84	1.43	1.1456
5	0.57	0.71	0.78	0.74	0.59	0.58	1.28	1.6419
6	0.44	0.42	0.41	0.41	0.37	0.47	1.22	2.1093
7	0.35	0.37	0.25	0.32	0.26	0.25	1.26	2.5328

order rate constant associated with the terminal log-linear portion of the curve (λz).

RESULTS

Volunteers

Six healthy male volunteers having mean age of 21.83 years (median, 22 years; range, 21-23 years), mean body weight was 64.33 kg (median, 64.5 kg; range, 55-76kg), mean body height was 174.4 cm (median, 175.3 cm; range, 170.1-180.3 cm) and mean body mass index was 22.57kg/m^2 (median, 22.46 kg/m^2; range 21.83-23.13 kg/m^2).

Safety evaluation of the volunteers

Cephradine was well tolerated by all volunteers. No serious adverse effect occurred during the study.

Drug concentration in plasma

The drug concentrations in plasma are given in table 1 and the mean plasma concentration is shown in fig. 1.

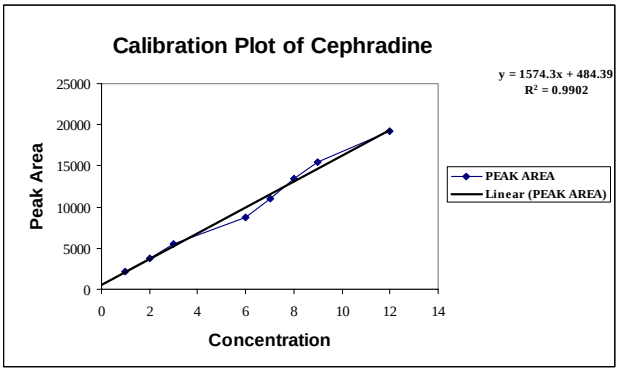

Fig. 1: Calibration Plot of Cephradine

Pharmacokinetic Parameters

The pharmacokinetic parameters includes both compartmental and noncompartmental analysis are given in tables 2 and 3 and their iterative analysis are given in figs. 2 and 3.

DISCUSSION

This study comprised of the pharmacokinetic properties of Cephradine in six healthy volunteers of local ethnic origin.

The compartmental analysis showed that the drug fits into open two compartment model with elimination from the central compartment. Nightingale *et al.*, in 1975 observed biexponential decay of Cephradine serum concentration against time, therefore he used two compartment open model system for Pharmacokinetics assessment (Nighingale *et al.*, 1975). Mean C_{max} was 11.49±1.73 µg/ml which was higher and mean T_{max} was 0.76hr which was slightly lower than the published studies; Rattie *et al.*, in 1976 reported C*max* of 250mg of Cephradine capsule was 9 µg/ml having T*max* of 1 hr. Neiss in 1973, Zaki *et al.*, in 1974 and Klastersky *et al.*, in 1973 reported that the peak plasma concentration in the serum ranging from 6 – 7 µg/ml with the T*max* of 1hr after administering a 250mg Cephradine capsule. Mean Area under the curve through compartmental analysis was 16.4±1.71, while AUC_{0-t} and $AUC_{0-\infty}$ through non compartmental analysis was 16.90±0.28 and 17.58±0.31. These values were higher than the published study (Rattie *et al.*, 1976). Mean Rate constant and intercept such as K_a, K_{el}, α , β, A and B was found to be 3.968±0.995, 1.738±0.468, 3.64±2.18, 0.33±0.06, 25.39±7.248 and 2.79±0.81, these values were not in a close agreement with the reported studies (Ratttie *et al.*, 1976; Neiss, 1973; Simon *et al.*, 1973). Difference was also observed with the previous studies in micro constants, Rattie *et al.*, reported 1.731/hr and 1.796/hr, Neiss in 1973 reported 2.167/hr and 1.720/hr, Simon *et al.*, in 1973 reported 2.349/hr and 3.893/hr values for K_{12} and K_{21} as compared to that of 1.529±1.499 and 0.70±0.44 in this study. Nightingale *et al.* in 1975 reported volume of distribution of Cephradine was 22L.

Weliky and Zoki in 1973 identified *Vd* of 17±3.9Litres/ 1.73m2. Neiss in 1973 reported *Vdβ* of Cephradine, 24.651L. Simon *et al.* in 1973 study finds Vd_β 19.993L and V_c, 10.562Litres. Ritschel in 1992 reported *Vd* 32Litres. Rattie *et al.*, in 1973 reported 22.53L. Variations was also observed with the previous work as the values are 9.653±3.787 and 33.8239±3.32482L for volume of central compartment and volume of distribution at β phase (Vz_F). Mean Clearance calculated by both compartmental and noncompartmental analysis was 15.4±1.89 and 14.1946± 0.29287 L/hr, these values were in closed concurrence with the published work of Rattie *et al.* (1973). Elimination half life of Cephradine in was 0.4414±0.1931 hr while the terminal half life according to the noncompartmental analysis was 1.65248±0.16843 hr, these results were slightly different to the previous ones. Adam *et al.*, in 1976 reported plasma half life of 0.7-0.8 hr after oral administration, 0.85 hr by Rattie *et al.*, in 1973 for intravenous preparation, 0.8 and 1hr for suspension in fasted and fed state by Ginsburg and McCracken in 1979.

Other important noncompartmental parameters such as MRT_{0-t}, $MRT_{0-\infty}$, $AUMC_{0-t}$ and $AUMC_{0-\infty}$ have values of

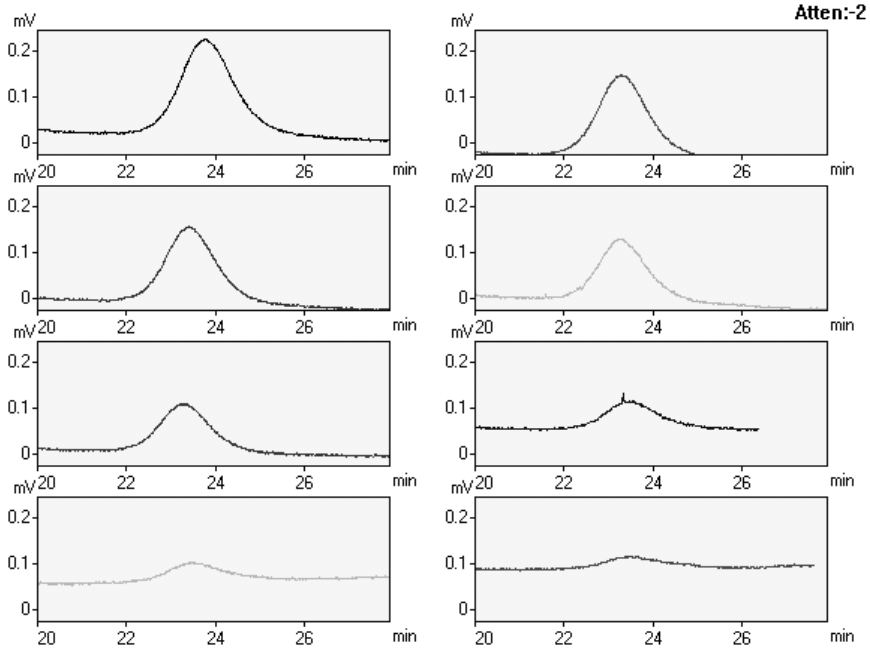

Fig. 2: Chromatograms for different drug concentrations in calibration curve.

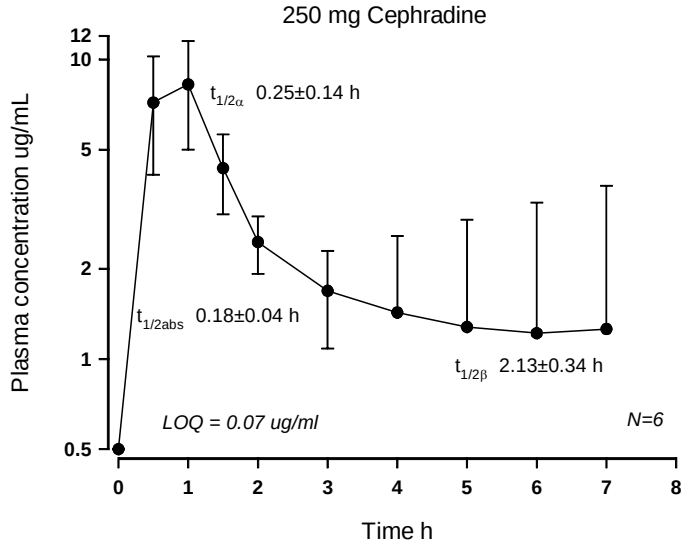

Fig. 3: Plasma Concentration Time Profile of cephradine 250mg capsule in six healthy volunteers

Table 1: Compartmental pharmacokinetic analysis of cephradine

S. No	A	a	B	b	AUC	C_{max}	T_{max}	K_a	K_{el}	K_{12}	K_{21}	$T_{1/2\,Ka}$	$T_{1/2\,a}$	T_{abs}	$T_{1/2b}$	$T_{1/2\,Kel}$	T_{lag}	V_c	Cl
	mg/ ml	hr^{-1}	mg/ ml	hr^{-1}	hr*ug/ mL	mg/ ml	hr	hr^{-1}	hr^{-1}	hr^{-1}	hr^{-1}	hr	hr	hr	hr	hr	hr	L	L/hr
1	31.99	3.576	2.617	0.334	16.7942	13.05	0.696	3.402	2.061	1.27	0.579	0.204	0.194	1.019	2.078	0.336	0.39	7.224	14.89
2	11.74	1.333	2.722	0.319	17.3405	9.688	0.725	5.643	0.834	0.308	0.51	0.123	0.52	0.614	2.174	0.831	0.365	17.29	14.42
3	23.39	7.803	4.373	0.435	13.044	8.987	0.999	4.754	2.128	4.514	1.596	0.146	0.089	0.729	1.592	0.326	0.8	9.005	19.17
4	28.44	2.934	2.084	0.261	17.6907	12.41	0.708	3.308	1.726	1.026	0.443	0.21	0.236	1.048	2.66	0.402	0.369	8.19	14.13
5	29.21	2.992	2.362	0.318	17.1895	12.88	0.714	3.374	1.837	0.955	0.518	0.205	0.232	1.027	2.18	0.377	0.38	7.919	14.54
6	27.58	3.188	2.578	0.334	16.363	11.94	0.696	3.323	1.843	1.101	0.578	0.209	0.217	1.043	2.074	0.376	0.366	8.289	15.28
Mean	25.39	3.638	2.789	0.333	16.4037	11.49	0.756	3.968	1.738	1.529	0.704	0.183	0.248	0.913	2.126	0.441	0.445	9.653	15.4
S.D	7.248	2.181	0.808	0.057	1.7084	1.728	0.119	0.995	0.468	1.499	0.44	0.038	0.144	0.191	0.341	0.193	0.174	3.787	1.885

A = Intercept of the distribution phase
B = Intercept of the disposition phase
b = Disposition rate constant
a = Distribution rate constant
AUC = Area under plasma concentration time curve
C_{max} = maximum plasma concentration
T_{max} = Time to attain maximum plasma concentration
K_a = Absorption rate constant
K_{el} = Elimination rate constant
K_{12} = Rate constant from central to peripheral compartment
K_{21} = Rate constant from peripheral to central compartment
$T_{1/2Ka}$= Absorption Half Life
$T_{1/2a}$ = Distribution Half Life
$t_{1/2b}$ = Dispositiuon Half Life
$T_{1/2Kel}$ = Elimination Half Life
T_{lag} = Lag time
Vc = Volume of the Central Compartment
Cl = Clearance

Table 2: Non compartmental analysis

Parameters	*Volunteers*						Mean	S.D
	1	2	3	4	5	6		
Lambda_z (λ_z) (hr^{-1})	0.37	0.45	0.49	0.38	0.43	0.41	0.42	0.04
AUClast (AUC_{0-t}) hr*ug/mL	1.86	1.54	1.41	1.82	1.61	1.67	1.65	0.17
AUCINF_obs ($AUC_{0-\infty\_obs}$) hr*ug/mL	16.75	17.10	16.86	17.14	17.13	16.43	16.90	0.28
AUCINF_D_obs hr*ug/mL	17.69	17.92	17.37	17.98	17.73	17.03	17.62	0.36
AUC_%Extrap_obs	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.00
Vz_F_obs (L)	5.32	4.60	2.93	4.66	3.41	3.54	4.08	0.92
Cl_F_obs (L/hr)	37.97	31.08	29.33	36.43	32.77	35.38	33.82	3.32
AUCINF_pred($AUC_{0-\infty\_pred}$)	14.14	13.95	14.39	13.91	14.10	14.68	14.19	0.29
AUCINF_D_pred	17.57	17.78	17.40	17.95	17.71	17.07	17.58	0.31
AUC_%Extrap_pred	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.00
Vz_F_pred (L)	4.70	3.83	3.10	4.54	3.28	3.74	3.87	0.65
Cl_F_pred (L/hr)	38.21	31.33	29.28	36.47	32.81	35.31	33.90	3.36
AUMClast (hr*hr*ug/mL)	14.23	14.06	14.37	13.93	14.12	14.65	14.23	0.26
AUMCINF_obs (hr*hr*ug/mL)	28.08	31.88	31.77	29.40	28.26	27.72	29.52	1.88
AUMC_%Extrap_obs	37.19	39.49	36.37	37.46	33.89	33.39	36.30	2.31
AUMCINF_pred	24.48	19.26	12.66	21.52	16.62	16.98	18.59	4.13
AUMC_%Extrap_pred	36.08	38.17	36.64	37.24	33.67	33.73	35.92	1.86
MRTlast (hr)	22.16	16.48	13.29	21.07	16.07	17.82	17.81	3.31
MRTINF_obs (hr)	1.68	1.87	1.88	1.72	1.65	1.69	1.75	0.10
MRTINF_pred (hr)	2.10	2.20	2.09	2.08	1.91	1.96	2.06	0.11

Lambda_z = First order rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of time vs. log conc.
AUCINF_obs = AUC from Dosing_time extrapolated to infinity, based on the last observed concentration (obs). $AUCINF\_obs = AUClast + Clast_{obs}/\lambda z$
AUCINF_D_obs = AUCINF_obs divided by dose.

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1.75±0.10hr, 2.04±0.090 hr, 29.517±1.875 (hr*hr*µg/ml).

All these results indicate the difference in the pharmacokinetic data was may be due to interethnic variability. This variability varies substantially among drugs and depends on a variety of factors. It was reported in several papers that potential factors for the variability in drug pharmacokinetics and pharmacodynamics include food, drug interactions, body weight, gender, age, genetics, disease states of patients, and lifestyle variables (smoking and alcohol consumption), which may correlate with one another. Among these, various environmental factors (diet, nutrition, climate, lifestyle, and health) and cultural differences in attitudes toward the disorder are considered to be very substantial (Dollery *et al.*, 1979; Fraser *et al.*, 1979; Desai *et al.*, 1980; Kalow and Bertilsson, 1994; Thomas 1995; Smith and Mendoza, 1996; Tschanz and Stargel, 1996; Frackiewicz *et al.*, 1997; Fleisher *et al.*, 1999; Kalow, 2001; Burroughs *et al.*, 2002).

Both genetic and environmental factors can lead to ethnic differences in drug metabolism to a varying extent, depending on the ethnic groups and substrates. These ethnic differences in the drug's safety, efficacy, dosage, and dosage regimen have given rise to a reluctance to rely on foreign clinical data for drug approval. Therefore, requirements for the extensive duplication of a clinical evaluation for every drug can waste much time and expense during the new drug approval process in other regions. Recently, regulatory authorities and industry associations have made efforts to promote international harmonization of regulatory requirements. The International Conference on Harmonization (ICH) published the "Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data" in 1998

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AUC_%Extrap_obs = Percentage of AUCINF_obs due to extrapolation from Tlast to infinity = $\frac{AUCINF\_obs - AUClast}{AUCINF\_obs} \times 100$

Vz_F_obs = Volume of distribution based on the terminal phase = $\frac{Dose}{\lambda z \cdot AUCINF\_obs}$

Cl_F_obs = $\frac{Dose}{AUCINF\_obs}$

AUCINF_pred = AUC from Dosing_time extrapolated to infinity, based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression performed to estimate Lambda Z.

= $AUClast + Clast_{pred} / \lambda z$

AUCINF_D_pred = AUCINF_pred divided by dose.

AUC_%Extrap_pred = Percentage of AUCINF_pred due to extrapolation from Tlast to infinity = $\frac{AUCINF\_pred - AUClast}{AUCINF\_pred} \times 100$

Vz_F_pred = $\frac{Dose}{\lambda z \cdot AUCINF\_pred}$

Cl_pred, Cl_F_pred = $\frac{Dose}{AUCINF\_pred}$

AUMCINF_obs Area under the first moment curve (AUMC) extrapolated to infinity, based on the last observed conc. = $AUMClast + \frac{Tlast * Clast_{obs}}{\lambda z} + \frac{Clast_{obs}}{\lambda^2 z}$

AUMC_%Extrap_obs = Percent of AUMCINF_obs that is extrapolated. = $\frac{AUMCINF\_obs - AUMClast}{AUMCINF\_obs} \times 100$

AUMCINF_pred Area under the first moment curve (AUMC) extrapolated to infinity, based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression for Lambda Z. = $AUMClast + \frac{Tlast * Clast_{pred}}{\lambda z} + \frac{Clast_{pred}}{\lambda^2 z}$

AUMC_%Extrap_
Pred = Percent of AUMCINF_pred that is extrapolated. = $\frac{AUMCINF\_pred - AUMClast}{AUMCINF\_pred} \times 100$

MRTINF_obs Mean residence time (MRT) extrapolated to infinity.= AUMCINF_obs / AUCINF_obs.

MRTINF_pred Mean residence time (MRT) extrapolated to infinity.= AUMCINF_pred / AUCINF_pred.

(Committee ICoHS.Guidance). The purpose of this guidance is to facilitate the registration of drugs among ICH regions (European Union, Japan, the United States) by recommending a framework for evaluating the impact of ethnic factors on a drug's effect (i.e., its efficacy and safety at a particular dosage and dosage regimen). This guidance is intended to. recommend regulatory strategies for accepting foreign clinical data as full or partial support for approval of an application in a new region and also the use of bridging studies, when necessary, to allow extrapolation of foreign clinical data to a new region. One of the most important determinants in extrapolating clinical data from one region to another involves ethnic differences in the pharmacokinetics of the drug (Kim *et al.*, 2004).

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