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Research Article

POPULATION PHARMACOKINETICS AND CLINICAL RESPONSE OF METOPROLOL IN SOUTH INDIAN HYPERTERNSIVE PATIENTS

MAHENDER VATTIPALLY, ARUN KUMAR MAHESH, DEVENDER KODATI, NARSIMHA REDDY YELLU*

Department of Pharmacology and Clinical Pharmacy, University College of Pharmaceutical Sciences, Kakatiya University, Warangal – 506 009, Andhra Pradesh, INDIA. Email: ynrkuc@gmail.com

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ABSTRACT

Population pharmacokinetics (PPK) is the study of the variability, its source and magnitude in populations. This information is used to design dosage regimens that account for individual patient characteristics.

Objective: The objective of this study was to perform a Non linear mixed-effects analysis of the pharmacokinetics of metoprolol, indicated for treating hypertension and to study the effect of covariates like age, body surface area [BSA] and creatinine clearance [CRCL] on the population pharmacokinetics of metoprolol in South Indian hypertensive patients.

Methods: A simple, rapid and sensitive isocratic HPLC-UV method for detection and quantification of metoprolol in plasma had been developed. Intra-and inter-assay variations were <1and <2% respectively. Recovery of metoprolol was 98-99%. Total 258 blood samples for metoprolol plasma concentration measurements following a single 100 mg and 300 mg /day dose of metoprolol were obtained from 86 subjects having age in between 18-75 years. The population PK model was built using NONMEM 7.2.0. The FO and FOCE method was used to estimate base and covariate models for metoprolol.

Results: One-compartment model with first-order absorption and elimination (ADVAN 2 TRANS 2) was best fit to the plasma concentration-time data of metoprolol. A combined error model was best described the pattern of residual and between subject variability .The final model estimates of CL and V estimated by FOCE method were 93.4 L/h and 83.1 L.

Discussion: There were no past reports on PopPK of metoprolol. With covariate models, significant decrease was observed in OFV, between and within subject variability when compared to base model. The model found to best describe the data following the FOCE method was: Clearance (CL) = θ1*(CLCR/0.75) *EXP (η1) and Volume (V) = θ2*(AGE/50) *EXP (η2). These parameters are utilized for individualizing the loading and maintenance doses in hypertensive patients. CRCL for CL; AGE for V were found as an informative covariates of metoprolol.

Conclusion: In order to minimize the variability associated with drug exposure in Indian hypertensive patients, the results of the population PK analysis support AGE and CRCL adjusted dosing of metoprolol.

Keywords: NONMEM, Creatinine clearance, Covariate, Residual variability, Metoprolol.

INTRODUCTION

Metoprolol is the cardio selective (β1) blocker. Metoprolol is well absorbed after oral administration and are widely distributed in body tissues. Peak serum level of the metoprolol is obtained within 1-3 hours of oral administration of the drug [1]. Bioavailability of the metoprolol is between 40 to 50% [2]. The mean terminal plasma elimination half-life of metoprolol ranges from approximately 3 to 4 hours following single or multiple doses of metoprolol given orally or intravenously [3]. Population pharmacokinetics (PPK) is the study of this variability, its source and magnitude in populations [4]. This information is used to design dosage regimens that account for individual patient characteristics [5]. Population pharmacokinetics therefore seeks to identify and measure factors, and define the extent of their influence on the dose concentration interaction. [6]

Dosage regimens have traditionally been determined based on detailed pharmacokinetic studies of a few, typically healthy, individuals. This dosage may therefore not be appropriate in the clinical use of a drug. Diseased humans frequently have disturbed metabolic systems, which may alter drug absorption and disposition when compared to healthy individuals [5]. Flexible dosing may prove to be more appropriate [7]. Determining appropriate drug doses requires estimating the pharmacokinetic parameters (such as clearance and volume of distribution) as they relate to covariates or variables, including the precision of these estimates [5,8].

Therapeutic response to antihypertensive drugs can show large intra and inter individual variability therefore it is necessary for serum/plasma concentrations to be monitored during the drug administration, if target serum concentrations are to be achieved. The hypothesis tested in this study was that the population pharmacokinetic modeling approach can be used to evaluate and describe the concentration time data collected in the metoprolol clinical trials. Using this approach, precise estimates of the pharmacokinetic parameters and their variability has to be quantifiable and significant covariates would be identified.

Population PK analysis is helpful to identify factors that affect PK of drug or to explain variability in target population. To date, however there is no report on POP PK of metoprolol although this drug is widely used as anti hypertensive drug in India. In present study we developed a PPK model for metoprolol by analyzing the pooled data obtained from Indian hypertensive patients. Since metoprolol shows large individual variability in pharmacokinetics, it is useful to develop a PPK model by integrating the currently available information for this drug. The obtained PPK model explains several factors that can cause inter individual variability in pharmacokinetics, and the model is capable to describe and predict the plasma concentration-time profile for the patients with various backgrounds.

METHODS

Patients and Study design

The population data base consisted of 258 metoprolol concentrations obtained from 86 (36 female and 50 male) south Indian hypertension patients who were on long term treatment with oral metoprolol tablets. The study design followed was a sparse and

random sampling design. The patients group was selected from the patients who visited the cardiology ward of M.G.M. Hospital

(Warangal, India) and other private hospitals in Warangal and Hyderabad, India. Informed consent was taken from the patients who were willing to participate in the study. Institutional Ethical Committee approval was taken before starting the study. Demographic data of all the patients were collected which includes name, age, sex, weight, height, disease status, concomitant diseases (C.V.S, C.N.S., and Renal diseases), and concomitant medications taken along with metoprolol.

Selection of Patients

Inclusion Criteria

Patients of any cardiovascular disease, who are on treatment of the metoprolol.

Patients who are 18 years or older, either sex. [9]

Exclusion Criteria

Severe disability/ malnutrition Pregnancy & lactation Age less than 18 years, any other reasons as decided by clinician.

Assay of metoprolol concentrations

Plasma concentrations of metoprolol were determined by a validated reverse phase high-performance liquid chromatographic method using UV detection and liquid-liquid extraction technique [10]. All plasma samples collected were analyzed by the same procedure at the Department of Drug Metabolism and Pharmacokinetics, University College of Pharmaceutical Sciences, Kakatiya University, India. The chromatographic apparatus was a Shimadzu liquid chromatography system equipped with a LT 10AT VP pump, a SPD 10A VP variable wavelength UV visible Spectrophotometric detector and a Rheodyne 20 microliter loop injector system was used (Shimadzu, Kyoto, Japan). An INERTSIL ODS-3V C-18, 4.6x250mm [Merck Ltd, Mumbai, India] chromatography column was used for analysis.

Model development

The PPK modeling was performed using the NONMEM 7.20 (double precision, Version 7, Level 2.0 and the FORTRAN power station compiler) with its library subroutines ADVAN2 and TRANS2. A one-compartment linear model with first order absorption was used as a best structural model. The basic pharmacokinetic parameters were oral clearance (CL/F, L/hr), volume of distribution (V/F, L).The first-Order (FO) and First- order conditional estimation (FOCE) was used throughout the analysis. The population pharmacokinetic analysis consisted of several major steps like base pharmacokinetic model building, covariate model building, and model reduction to obtain the final model. In the process of model building, a constant coefficient of variation error model described the inter-individual variability best. The data set was analyzed using both FO and FOCE methods in ADVAN2 and TRANS2 and the results are displayed separately. Our results indicated that the one compartment model gave a better OFV (Objective function value) as compared to the two compartment model, hence it was used for describing the pharmacokinetics of metoprolol.

The inter-individual variability for basic pharmacokinetic parameters was modeled by the log normal distribution, as described in equation 1&2

$$CL/F_j = TVCL.exp(\eta_{jCL/F}) \quad \ldots\ldots\ldots\ldots (1)$$

$$V/F_j = TVV.exp(\eta_{jV/F}) \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Where $\eta_{jCL/F}$ is a random variable that represents the difference between individual clearance of the j-th individual (CL/F_j) and the population mean value (TVCL).The random variable $\eta_{jCL/F}$ is a normally distributed with an expectation of zero and a variance of $\omega^2_{CL/F}$.

Residual variability was similarly modeled by the log normal distribution as shown in equation 3.

$$C_{ij} = C_{pred,\,ij.exp}(\varepsilon_{ij}) \quad \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where C_{ij} is the i-th observed plasma concentration of metoprolol for the j-th individual, $C_{pred,ij}$ is the concentration predicted by the PPK model, and ε_{ij} is a randomly distributed variable with mean of zero and variance of σ^2.The minimum value of the NONMEM 7.2.0 OFV was used as a statistic to choose suitable models during the model-building process. Since the difference in OFV between one model and the other approximates a χ^2 distribution with freedom of the number of parameter difference, a difference in OFV of 3.84 for 1 degree of freedom ($P<0.05$) was considered statistically significant in the model-building process[11].

Covariate model

Initially, the model was developed without including patient-specific covariates (basic model). Starting from a simple one compartment model, a variety of covariates that could influence the pharmacokinetics of metoprolol were stepwise added to the basic model (addition method) Statistical significance for incorporation of each covariate was judged based upon change in OFV (ΔOFV). Initially, exponential error models were used to describe the inter-individual variability terms and were included on both pharmacokinetic parameters in the model, and the initial residual error model used consisted of two components: an additive and a proportional component. Once an appropriate base pharmacokinetic model had been developed, individual parameters were generated in NONMEM and their relationship with covariates graphically explored. Covariates that were evaluated included anthropometric variables, including body weight, height, body surface area (BSA), age, gender, CRCL, smoking history and alcohol consumption. Once a full model was developed which incorporated all possible covariates, each covariate was in turn examined removing one by one (deletion method) to confirm the statistical significance using criterion of ΔOFV with 6.84 ($P<0.01$).The continuous covariates showing correlation with the pharmacokinetic parameters were normalized to their corresponding medians and then introduced into the model as shown by equation 4.

$$P_k = \theta k1 \; X \; (Cov/Cov_{median})\; \theta k2 \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where P_k is the PK parameter, θk1 is the typical value of the pharmacokinetic parameter in the population, θk2 is the coefficient of the covariate, Cov is the value of the covariate, and Cov_{median} is the median of the covariate in the population under investigation. The least significant parameter (smallest change in objective function) was then removed from the model. This entire cycle was repeated in a stepwise fashion until only significant parameters remained in the "Final" NONMEM structural model [12].

RESULTS

Demographic background for the population participating in the present PPK analysis is summarized in the following table.

Table 1: Description of the population participating in the present study.

Parameter	Range	Mean (± SD)
Age (years)	18-75	48.87(±11.32)
Body weight (kg)	45– 85	60.17 (±8.49)
Dose (mg)	12.5 – 100	11.45 (±6.21)
Serum level (µg/ml)	0.1– 1.0	1.01 (±0.21)
Sampling time (h)	0-12	2.96 (±1.67)

All the patients in the study were confirmed to be compliant in taking medication. The physician fixed the dosage regimen. After the drug concentration levels reach the steady state, at least 3 - 7 blood samples (4-5ml) from each patient during the metoprolol treatment,

at 0.5, 1, 1.5, 2, 2.5, 3,3.5,4,4.5,5.5,6,6.5,7,7.5,8,8.5,9,10,10.5,11,11.5 and 12h before the next dose. These sampling schedules were randomly allocated. Sampling intervals are not fixed for all patients. Blood samples were collected in EDTA coated tubes and immediately centrifuged at 3000×g for 8 min at room temperature. The collected samples were stored at −80°C until further analysis was carried out.

Metoprolol Estimation

The mobile phase consisted of Sodiumdihydrogen phosphate (50mM; pH 3.0±0.5), Acetonitrile with the ratio of 80:20 respectively. The flow rate was 1ml/minute and the eluent was monitored spectrophotometrically at 227nm at room temperature. Amlodipine (20µg/ml) was used as internal standard. Sensitivity of the assay was <50ng/ml. Intra-and inter-assay variations were <1and <2% respectively. Recovery of metoprolol was 98-99%. Using 500µl of plasma sample, standard curves were linear from 0. 05 to 0.5 µg/ml (r^2 =0. 9926).

Model development

A one-compartment open model with first order absorption was used as a basic structural model, and random variables for inter-individual variability and covariates were added stepwise to develop the PPK model for metoprolol.

In the preliminary screening phase covariates like Creatinine clearance, Age reduces the objective function. In the forward stepwise model-building the cumulative inclusion of age, creatinine clearance reduced the objective function by 28.68(P<0.01). Finally in the backwards elimination phase only weight exceeded the objective function by more than 1.13(P>0.05) when it was omitted individually from the model. No covariate significantly varied the Clearance and volume of distribution. But the inclusion of creatinine clearance in clearance and inclusion of age in the volume of distribution has reduced the minimum objective function significantly.

Table 2: Mean pharmacokinetic parameters and inter-individual variability for metoprolol.

Model	OFV	Population estimate (%SE)	Between subject variability (% SE)
Base model/ Final model	753.881		
CL=θ1*(CLCR/0.75)*EXP (η1)			
V = θ2 *(AGE/50) *EXP (η2)			
CL (L/hr)		1.6 (24.2)	80 % (16)
V (L)		10(29.2)	10%(20)
Residual variability			
Additive error	0.4µg/mL (51.3)		

The final structural model was:

FO Method:

CL= θ1*(CLCR/0.75) *EXP (η1)

V = θ3*(AGE/50) *EXP (η2)

FOCE Method:

CL= θ1*(CLCR/0.75) *EXP (η1)

V = θ2*(AGE/50) *EXP (η2)

The population pharmacokinetic model parameter estimates obtained by using the final model are given below.

Table 3: Estimation of Pharmacokinetic Parameters by FO Model.

Parameter	Meaning	Estimation
θ1	Coefficient (CL)	2.93E+00
θ2	Coefficient (V)	1.00E+01
θ3	Coefficient (KA)	1.94E+00
ω1	Inter-patient Variability (CL)	5.26E+00
ω2	Inter-patient Variability (V)	5.00E-05
€1	Residual Error	5.35E-01

Table 4: Estimation of Pharmacokinetic Parameters by final FOCE Model

Parameter	Meaning	Estimation
1θ	Coefficient (CL)	1.68E+00
2θ	Coefficient (V)	1.00E+01
3θ	Coefficient (KA)	3.94E+00
1ω	Inter-patient Variability (CL)	6.45E-01
2ω	Inter-patient Variability (V)	1.20E-02
1	Residual Error	1.75E-01

DISCUSSION

To date, there are no published population pharmacokinetic models for metoprolol in hypertension patient population. Our study population is the representative of the Indian hypertension patient population. Metoprolol, it appears that a standard dose produces a large variability in their plasma concentrations. It has been shown that the patients with low volume of distribution and high clearance of these drugs suffering with low efficacy and required more dosage, while the patients with high concentrations are more likely to suffer from adverse events. The principal objective of this study was to account for the inherent individual variability in the population in terms of readily identifiable factors that influence pharmacokinetics of metoprolol in an Indian hypertension patient population. A better understanding of the intra- and inter-individual variabilities associated with the pharmacokinetic and pharmacodynamic behaviour of the therapeutic agents can lead to a safer and more efficacious use of drugs. These include physiological, pathological, and treatment characteristics (age, wt, renal, hepatic function, etc.).This information can be used for individualization of dosage regimen. Apart from this it is also possible to estimate the variability in concentrations achieved, which for any dosage regimen should permit calculation of proportion of patients at risk of attaining toxic or ineffective concentrations. Estimation of pharmacokinetic parameters in target population is more highly desirable than in healthy volunteers [13].

The PPK model of metoprolol has been developed based upon the pooled pharmacokinetic data obtained from the hypertension patients in India. The CL/F was found to be associated with CRCL but not related to other covariates like age, BSA, gender, smoking and alcohol consumption and the V/F was related to Age. Our study populations were hypertension in and out patients who were treated oral metoprolol. Population values of CL and V for metoprolol were calculated and final structural models using FO and FOCE method was given. From these methods it was observed that the CL/F was found to be associated with CLCR but not related to other covariates like age, BSA, gender, smoking and alcohol consumption and the V/F was related to Age. As the metoprolol is renally eliminated drug, it is reasonable that CL/F was affected by renal function. This finding was also consistent with the result of a separate clinical study where the 2 fold increase in CL/F was observed in patients with moderate renal failure [14]. On the other hand, it will be useful and important to examine the hepatic functional covariates have any effect or not on CL/F of the metoprolol. One past study reported that the lower starting doses

are recommended for the patients with a history of hepatic impairment [15], since the number of patients with hepatic impairment was very less in the present data set and this number thought insufficient for the analysis, the effect of hepatic impairment could not be examined in this analysis.

In the clinical setting, one compartment model has been usually employed, although several studies reported that the pharmacokinetics of metoprolol is better characterized by a two-compartment model [16]. In the present study we found that the one-compartment model better describes the pharmacokinetics of metoprolol by comparing the OFV values obtained after analyzing the data using ADVAN2 TRANS2 which resulted in a OFV value of 5.87 using FO method and 6.42 using FOCE method. In our study it was observed that the mean population estimates of clearance as 1.6 L/h and volume of distribution (V) as 10.2L.These values were seems to be very low when comparing with the CL and V found in health volunteers [11]. No reports were found in the literature regarding the PPK of metoprolol in any of the other patient population.

The range of metoprolol concentrations obtained in different patients was 0.17-11.96 (µg/mL), and these values are higher than the values previously reported study conducted in healthy volunteers. The values of the CL/F and V/F are much less when compared with previous literature values obtained from a clinical study conducted in healthy volunteers. This may be due to the differences in the protein binding and differences in the CYP metabolic enzymes of our population with that of other healthy subjects.

CONCLUSION

A POPPK model for metoprolol has been developed based upon the data obtained in the Indian hypertension patient population. Covariates such as age and CRCL have been found to be factors that affect the individual variability in pharmacokinetics of metoprolol. The present PPK model well described the individual exposure to metoprolol and can have a positive impact on management of metoprolol therapy in the study population.

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