ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Issue 4, 2014

ISSN - 0974-2441

Research Article

POPULATION PHARMACOKINETICS OF PIOGLITAZONE IN SOUTH INDIAN TYPE-II DIABETIC PATIENTS

MAHENDER VATTIPALLI, 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

Received: 21 June 2014, Revised and Accepted: 04 July 2014

ABSTRACT

Introduction: Population pharmacokinetics (PPK) is the study of this 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 pioglitazone, indicated for treating diabetes and to study the effect of covariates such as age, body surface area and creatinine clearance on the PPK of pioglitazone in South Indian diabetic patients.

Materials and Methods: A simple, rapid, and sensitive isocratic high-performance liquid chromatography-ultra violet method for detection and quantification of pioglitazone in plasma had been developed. Intra- and inter-assay variations were <1 and <2% respectively. Recovery of pioglitazone was 98-99%. A total of 137 blood samples for pioglitazone plasma concentration measurements following a single 15 mg dose of pioglitazone were obtained from 43 subjects having age in between 18 and 75 years. The PPK model was built using NONMEM 7.2.0. The first-order (FO) and first-order conditional estimation (FOCE) method was used to estimate base and covariate models for pioglitazone.

Results: One-compartment model with FO absorption and elimination (ADVAN 2 TRANS 2) was best-fit to the plasma concentration-time data of pioglitazone. A combined error model was best-described the pattern of residual and between subject variability. The final model estimates of clearance (CL) and volume (V) estimated by FOCE method were 3.4 lt/hr and 43 L.

Discussion: There were no past reports on PPK of pioglitazone. With covariate models, a significant decrease was observed in object function value, between and within subject variability when compared with base model. The model found to best describe the data following the FOCE method was: CL=CL=θ1*EXP ([η1] and V=θ2*EXP [η2]). These parameters are utilized for individualizing the loading and maintenance doses in diabetic patients. No factor was found as informative covariate of pioglitazone.

Conclusion: In order to minimize the variability associated with drug exposure in Indian diabetic patients, the population parameter estimates were given without influence of covariates.

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

INTRODUCTION

Pioglitazone is a potent and highly selective agonist for peroxisome proliferator activated receptor-gamma. Pioglitazone is well-absorbed after oral administration and are widely distributed in body tissues. Peak serum level of the pioglitazone is obtained within 2 hrs of oral administration of the drug [1]. Bioavailability of the pioglitazone is between 8 and 85%. The mean terminal plasma elimination half-life of pioglitazone ranges from approximately 3 to 7 hrs following single or multiple doses of pioglitazone given orally or intravenously [2]. Population pharmacokinetics (PPK) is the study of this variability, its source and magnitude in populations [3]. This information is used to design dosage regimens that account for individual patient characteristics [4]. PPKs therefore seeks to identify and measure factors, and define the extent of their influence on the dose concentration interaction [5].

Dosage regimens have traditionally been determined based on detailed pharmacokinetic (PK) studies of a few, typically healthy, individuals. This dosage may therefore not be appropriate in the clinical use of the drug. Diseased humans frequently have disturbed metabolic systems, which may alter drug absorption and disposition when compared to healthy individuals. Flexible dosing may prove to be more appropriate [6]. Determining appropriate drug doses requires estimating the PK parameters (such as clearance [CL] and volume of the distribution [VD]) as they relate to covariates or variables, including the precision of these estimates [7]. Therapeutic response to ant diabetic 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 PPK modeling approach can be used to evaluate and describe the concentration time data collected in the pioglitazone clinical trials. Using this approach, precise estimates of the PK parameters and their variability has to be quantifiable and significant covariates would be identified.

PPK analysis is helpful to identify factors that affect PK of the drug or to explain variability in target population. Until date, however there is no report on PPK of pioglitazone although this drug is widely used as anti-diabetic drug in India. In the present study, we developed a PPK model for pioglitazone by analyzing the pooled data obtained from Indian diabetic patients. Since pioglitazone shows large individual variability in PKs, 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 PKs, and the model is capable of describe and predict the plasma concentration-time profile for the patients with various backgrounds.

METHODS

Patients and study design

The population database consisted of 137 pioglitazone concentrations obtained from 43 (18 female and 25 male) south Indian diabetic patients who were on long-term treatment with oral pioglitazone tablets. The study design followed was a sparse and random sampling design. The patients group was selected from the patients who visited the diabetic 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 the name, age, sex, weight, height, disease status, concomitant diseases (C.V.S, C.N.S., and renal diseases), and concomitant medications taken along with pioglitazone.

Selection of patients

Inclusion criteria

- Patients of diabetes, who are on treatment of the pioglitazone.
- Patients who are 18 years or older, either sex [8].

Exclusion criteria

- Severe disability/malnutrition.
- Pregnancy and lactation.
- Age <18 years.
- Any other reasons as decided by clinician [9].

Assay of pioglitazone concentrations

Plasma concentrations of pioglitazone were determined by a validated reverse phase high-performance liquid chromatographic method using ultra violet (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 the LT 10AT VP pump, an SPD 10A VP variable wavelength UV visible spectrophotometric detector and a Rheodyne syringe 20 µl loop injector system was used (Rheodyne, Cotati, CA, U.S.A). An INERTSIL ODS-3V C-18, 4.6×250 mm [Shimadzu, Kyoto, Japan] chromatography column was used for analysis [11].

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 (FO) absorption was used as a best structural model. The basic PK parameters were oral clearance (CL/F, L/hr), VD (V/F, L). The FO and first-order conditional estimation (FOCE) was used throughout the analysis. The PPK analysis consisted of several major steps like base PK 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 objective function value (OFV) when compared to the two compartment model. Hence it was used for describing the PKs of pioglitazone.

The inter-individual variability for basic PK parameters was modeled by the log normal distribution as described in equations 1 and 2.

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

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

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 variance of $\omega^2_{CL/F}$.

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

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

Where C_{ij} is the i-th observed plasma concentration of pioglitazone 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° of freedom ($p<0.05$) was considered statistically significant in the model-building process.

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 PKs of pioglitazone were stepwise added to the basic model (addition method) Statistical significance for incorporation of each covariate was judged based upon a change in OFV (ΔOFV). Initially, exponential error models were used to describe the inter-individual variability terms and were included on both PK parameters in the model, and the initial residual error model used consisted of two components: additive and a proportional component. Once an appropriate base PK 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, creatinine clearance, 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 PK parameters were normalized to their corresponding medians and then introduced into the model as shown by equation 4.

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

Where P_k is the PK parameter, θk1 is the typical value of the PK 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 an objective function) was then removed from the model. This entire cycle was repeated in a step-wise 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 Table 1.

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

Parameter	Range	Mean (±SD)
Age (years)	35-70	48.74 (±9.52)
Body weight (Kg)	43-84	62.83 (±9.27)
Dose (mg)	15	15 (±0.00)
Serum level (µg/ml)	0.03-0.336	0.112 (±0.82)
Sampling time (hrs)	0.5-24	10.36 (±8.69)

SD: Standard deviation

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 a steady state, at least 3-7 blood samples (4-5 ml) from each patient during the pioglitazone treatment at 0, 1, 2, 4, 6, 8, 10, 12 and 24 hr before the next dose. These sampling schedules were randomly allocated. Sampling intervals are not fixed for all patients. Blood samples were collected in Ethylenediaminetetraacetic acid coated tubes and immediately centrifuged at 3000×g for 8 minutes at room temperature. The collected samples were stored at −80°C until further analysis was carried out.

Pioglitazone estimation

The mobile phase consisted of ammonium acetate (30 mM; pH 5), methanol with the ratio of 65:35 respectively. The flow rate was 1 ml/minute and the eluent was monitored spectrophotometrically at 247 nm at room temperature. Rosiglitazone (20 µg/ml) was used as an internal standard. Sensitivity of the assay was <50 ng/ml. Intra- and inter-assay variations were <1 and <2% respectively. Recovery of pioglitazone was 98-99%. Using 500 µl of plasma sample, standard curves were linear from 0.05 to 0.5 µg/ml (r^2=0.997) (Figs. 1 and 2).

Model development

A one-compartment open model with FO 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 pioglitazone.

In the preliminary screening phase, no covariate reduced the objective function. In the forward stepwise model-building the cumulative inclusion of WT, age and BSA also does not reduce the OFA. This gave reasonably good output with appropriate estimates of the CL and VD (Tables 2 and 3). But there is no change in the OFVs in covariate models. So the base model itself considered as the final model. Scatters were improved and PRED versus DV and WRES plot(s) pattern suggested that the model is complete.

The final structural model was:

FO Method:

CL=θ1*EXP ([η1])

V=θ2*EXP ([η2])

FOCE Method:

CL=θ1*EXP ([η1])

V=θ2*EXP ([η2])

The PPK model parameter estimates obtained by using the final model are given in Table 4.

DISCUSSION

PPKs of pioglitazone in Indian Type-II diabetic patients using NONMEM was undertaken the first time in India (perhaps also in the world). The principal aim of this study was to account for the inherent kinetic variability in Indian population in terms of readily identifiable factors.

A better understanding of the intra and inter individual variabilities associated with the PK and pharmacodynamic behavior of the therapeutic agents can lead to a more efficacious and safer drug use [13]. These include physiologic, pathologic, and treatment characteristics (e.g.: Age, weight, renal, hepatic function, etc.). This information can be used to design rational dosage guidelines that would result in therapeutic concentrations, based on sound

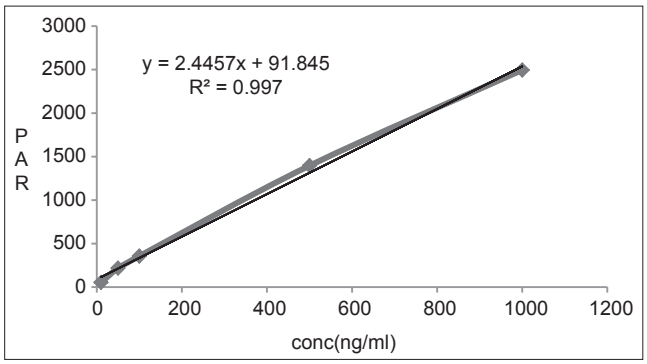

Fig. 1: Standard graph of pioglitazone

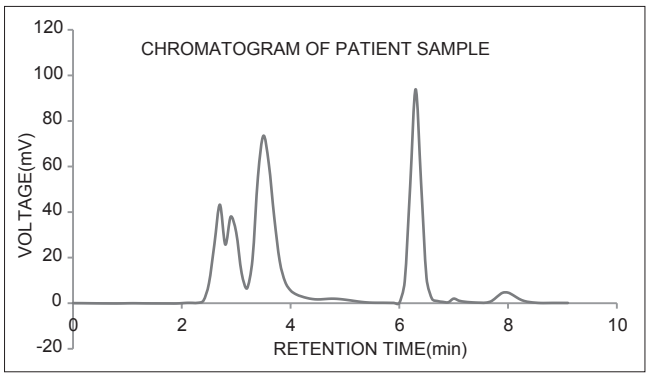

Fig. 2: Typical chromatogram of pioglitazone 100 ng/ml in plasma

Table 2: Analysis of covariate effect for CL

Hypothesis	Equation	Objective function	Change in OFV	p value
Base model		968.237		
	θ2 (BSA)	968.053	0.184	N.S
Age influence CL	θ2	963.868	4.369	N.S

CL: Clearance, BSA: Body surface area, N.S: Non-significant, OFV: Objective function value

Table 3: Analysis of covariate effect for VD

Hypothesis	Equation	Objective function	Change in OFV	p value
Base model		968.237		
BSA influence VD	θ3	965.822	2.415	N.S
Age influence VD	θ3	967.263	1.026	N.S

BSA: Body surface area, N.S: Non-significant, VD: Volume of distribution, OFV: Objective function value

Table 4: Estimation of pharmacokinetic parameters by FO and FOCE model

Parameter	Meaning	Estimation
θ1	Coefficient (K)	2.18 E+05
θ2	Coefficient (CL)	1.49 E+06
θ3	Coefficient (V)	3.25 E+00
ω1	Inter-patient variability (CL)	1.71 E+10
ω2	Inter-patient variability (V)	4.68 E+07
ε1	Residual proportional error	1.61 E+02

CL: Clearance, FO: First-order, FOCE: First-order conditional estimation

quantitative analysis rather than on purely empiric considerations, in the majority of the patients. The main application of population models is to establish dosage regimen. Apart from this it is also possible to estimate the variability of the concentrations achieved, which for any dosage regimen, should permit calculation of the proportion of patients at risk of attaining toxic or ineffective concentrations. Estimation of PK parameters in target population rather than in healthy volunteers is highly desirable in obtaining therapeutic benefit [14].

Our study population was representative of the Type-II diabetic patient population in India [15]. Hence, the population parameters obtained in the present study can be used in optimizing the dosage of pioglitazone for individual patients in India. This will not only reduce the incidence of adverse drug effects, but also aid in cost-effective long-term drug therapy. A major feature of the population approach is that sparse kinetic data from a large number of patients can be used successfully analyzed in conjunction with factors (covariates), which may influence drug disposition.

Investigation on the influence of various fixed effects parameters on pioglitazone CL and V of distribution in Indian population was performed using both FO and FOCE (in both ADVAN2 TRASNS2) methods, and it resulted in possible final regression models related to population values of CL and V.

The range of pioglitazone concentrations obtained in different patients was 0.03-0.336 (μg/mL), and these values are higher than the values previously reported study conducted in healthy volunteers. As the pioglitazone 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 two-fold increase in CL/F was observed in patients with moderate renal failure [16]. 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 PPK model for pioglitazone has been developed based upon the data obtained in the Indian diabetic patient population. Using NONMEM software, PPK parameter estimation was performed by FO and FOCE methods. Final PK models were developed, and influences of various covariates on CL and V studied.

REFERENCES

1. Hanefeld M. Pharmacokinetics and clinical efficacy of pioglitazone. Int J Clin Pract Suppl 2001;121:19-25.
2. Eckland DA, Danho M. Clinical Pharmacokinetics of pioglitazone. Exp Clin Endocrinol Diabetes 2000;108:234-42.
3. Collste P, Haglund K, Von Bahr C. Plasma levels and effects of pioglitazone after single and multiple oral doses. Clin Pharmacol Ther 1980;27:441-9.
4. Borg KO, Carlsson E, Hoffmann KJ, Jönsson TE, Thorin H, Wallin B. Metabolism of pioglitazone in man. Acta Pharmacol Toxicol 1975;36 (Suppl V):125-35.
5. Sheiner LB, Ludden TM. Population pharmacokinetics/dynamics. Annu Rev Pharmacol Toxicol 1992;32:185-209.
6. Martín-Jiménez T, Riviere JE. Population pharmacokinetics in veterinary medicine: Potential use for therapeutic drug monitoring and prediction of tissue residues. J Vet Pharmacol Ther 1998;21(3):167-89.
7. Sun H, Fadiran EO, Jones CD, Lesko L, Huang SM, Higgins K, *et al.* Population pharmacokinetics. A regulatory perspective. Clin Pharmacokinet 1999;37(1):41-58.
8. Whiting B, Kelman AW, Grevel J. Population pharmacokinetics. Theory and clinical application. Clin Pharmacokinet 1986;11(5):387-401.
9. Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm 1977;5(5):445-79.
10. Mamidi RN, Chaluvadi MR, Benjamin B, Ramesh M, Katneni K, Babu AP, *et al.* HPLC method for the determination of rosiglitazone in human plasma and its application in a clinical pharmacokinetic study. USA: John Wiley & Sons; 2003. p. 65-8.
11. Brahmaiah B, Sujana K, Prameela Rani A. Development and validation of RP-HPLC method for simultaneous determination of ramipril and valsartan in bulk and pharmaceutical dosage forms. Asian J Pharm Clin Res 2013;6(1):23-5.
12. Harish KK, Vijay SK, Satish BK, Reddy NY, Raghavaiah VK, Devarakonda KR. Population pharmacokinetics of cisplatin in Asian Indian cancer patients. Clin Res Regul Aff 2009;26(4):84-92.
13. Mahender V, Arun Kumar M, Devender K, Narsimha Reddy Y. Population pharmacokinetics and clinical response of metoprolol in South Indian hyperternsive patients. Asian J Pharm Clin Res 2014;7(2):140-3.
14. Aarons L, Balant LP, Mentre F, Morselli PL, Rowland M, Steimer JL, *et al.* Practical experience and issues in designing and performing population pharmacokinetic/pharmacodynamic studies. Eur J Clin Pharmacol 1996;49(4):251-4.
15. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, *et al.* Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. BMJ 2000;321(7258):412-9.
16. Budde K, Neumayer HH, Fritsche L, Sulowicz W, Stompôr T, Eckland D. The pharmacokinetics of pioglitazone in patients with impaired renal function. Br J Clin Pharmacol 2003;55(4):368-74.