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Population Pharmacokinetics of Metformin in Mexican Patients with Type 2 Diabetes Mellitus

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ABSTRACT
The aim of this study was to develop a Population Pharmacokinetic Model (PPM) for Metformin and to determine the influence of physiologic covariates on its pharmacokinetic variability in patients with Type 2 Diabetes Mellitus (T2DM). Ninety-nine patients with T2DM were included in the study. The clinical and pharmacokinetic data of 81 patients were used to build the population model and validated in others 18 patients. All patients received Metformin at a dose of 500-850 mg every 8 h. Blood samples were obtained at 2, 4, 6 or 8 h after drug administration, levels of drug were assayed by high performance liquid chromatography. The PPM was built using a nonlinear mixed effect program. The PPM was fitted to an open one compartment model, Ka = 2.22 h^{-1} (CV61.5%), CL/F = 26.4 L h^{-1} (CV 50.2%) and V/F = 365 L (CV 34.1%). Creatinine clearance (CLcr) and Lean Body Weight (LBW) correlated significantly with CL/F and V/F, respectively. The inclusion of these covariates in the basic model improved significantly the prediction performance as evaluated by the log-likelihood function. The final model was: CL/F = 16.6×exp (0.00546×CLcr), V/F = 209×exp (0.0112×LBW), with CV of 47 and 31.2%, respectively. In the PPM of metformin in Mexican patients with T2DM here described, the covariates, LBW and CLcr had a significant influence on interindividual variability of V/F and CL/F. Model evaluation suggested that the PPM is robust and its parameters were estimated with good precision. The model may be useful for clinician to design a rational initial dosage regimen in this patient population.

Key words: Diabetes mellitus, metformin, population pharmacokinetics, Mexican patients

INTRODUCTION

The incidence of type 2 Diabetes Mellitus (T2DM) has increased significantly in recent decades. It is estimated that approximately 347 million people worldwide have diabetes mellitus (Danaei *et al*., 2011). In Mexico, the prevalence of T2DM in individuals between 20-79 years old is estimated at 10.7% and represents the main cause of death in our country (INSP., 2012). The macro vascular complications such as myocardial infarction, stroke and peripheral vascular disease are the major contributors to this high mortality. Adequate glycemic control has been reported to be associated with a decrease in the progression of vascular disease in patients with T2DM (Roussel *et al*., 2010). Thus, an important goal of treatment is to achieve optimum control of plasma glucose concentrations.

Metformin is an oral administered anti-hyperglycemic agent which works by reducing hepatic glucose production and by increasing peripheral sensitivity to the action of insulin. A higher decrease in mortality has been reported in overweight

patients with type 2 diabetes mellitus that received metformin when compared with those managed with diet alone. For this, metformin is presently the first line therapy in this patient population (American Diabetes Association, 2013). The pharmacokinetics of metformin has been described in healthy volunteers and small groups of patients with T2DM (Bailey, 2008; Scheen, 1996; Tucker *et al*., 1981; Stratton *et al*., 2000). These studies have reported a wide pharmacokinetic interindividual variability. Moreover, the current standard dosing schemes are empirically determined giving rise to shortcomings in the therapeutic concentration that would yield maximum blood glucose control. Hence, individualization of dosing schemes based on a population pharmacokinetic model may be important for this purpose. Based on this, the aims of this study were to determine the interindividual variability of pharmacokinetic parameters for Metformin in patients with T2DM and the influence of physiological covariates on this variability.

MATERIALS AND METHODS

Patients and data collection: Ninety-nine patients with diagnosis of T2DM treated in the clinic of Diabetes and Metabolic Syndrome were included in the study. Eighty one of them were randomly assigned to the index group and eighteen to the validation group. The study was approved by the ethics committee and informed consent was obtained from each patient prior to their study participation.

Patients received Metformin at doses of 500-850 mg every 8 h for the management of their diabetes. In the day of the study, vital signs and glucose levels of the patients were recorded under fasting conditions and subsequently, the usual dose of metformin was administered. Blood samples for determination of metformin concentrations were randomly obtained at 2, 4, 6 or 8 h after dosing. The samples were centrifuged and plasma was separated, stored and kept frozen at -20°C until analysis. For each patient, the following covariates were recorded: body weight, age, gender, height and creatinine.

Methods for analysis of metformin: Plasma concentrations of metformin were measured by using a high performance liquid chromatographic assay previously reported (Cheng *et al*., 2004; Cheng and Chou, 2001). The method was linear over the range of 10-2000 μg mL^{-1} (r = r>0.999). The intra- and inter-day precision (C.V.) was 12% or less and the accuracy was within 6.2% of the nominal concentration.

Population pharmacokinetic analysis: A population pharmacokinetic approach using a nonlinear mixed-effect model was implemented by means of Monolix software program, version 4.0, which combines the Stochastic-Expectation Maximization Algorithm (SAEM) and Markov Chain Monte-Carlo (MCMC) procedure for likelihood maximization. The iteration kernels, k1 and K2, were set to perform a great number of iterations for the purpose of obtaining the best convergence. The MCMC chains were fixed to ten and simulated annealing was used to improve the convergence toward the global maximum of likelihood (Fattinger *et al*., 1995; Aarons, 1991; Sheiner and Beal, 1981).

Model building

Structural model: The concentration-time data of metformin were described using compartmental pharmacokinetic modeling. Models with one and two compartments were compared.

Interindividual and error models: Interindividual variability in PK parameters were ascribed to an exponential model according to the equation: $\theta_j = \theta_p \times \exp(\eta j)$, where θ_j is the estimate for a pharmacokinetic parameter in jth patient as predicted by the model, θ_p is the typical population PK parameter value (CL/F, V/F) and h is a random variable from a normal distribution with zero mean and variance ω^2. Residual variability, which includes intraindividual variability, measurement errors and model misspecification, was estimated using additive and proportional error models; $C_{ij} = C_j + \varepsilon_{add}$ and $C_{ij} = C_j (1+\varepsilon_p)$, where C_{ij} and C_j are the observed and predicted concentrations of metformin for jth patient at the time i, respectively and ε is the error, a random variable with a normal distribution with zero mean and variance σ^2.

Selection of covariates and evaluation of final model: Once the basic model was determined, the relevance of the following covariates was explored: Total body weight (WT), Lean Body Weight (LBW) and creatinine clearance (CLcr) as described by the following equations:

$$\text{LBW}_{\text{males}}\,(\text{kg}) = \frac{9270 \times \text{WT}\,(\text{kg})}{6680 + 216} \times \text{BMI}$$

$$\text{LBW}_{\text{females}}\,(\text{kg}) = \frac{9270 \times \text{WT}\,(\text{kg})}{8780 + 244} \times \text{BMI}$$

$$\text{BMI}\,(\text{kg m}^{-2}) = \frac{\text{WT}}{\text{Height}^2\,(\text{m})}\ \text{(Janmahasatian } \textit{et al}\text{., 2005)}$$

$$\text{CLcr}\,(\text{mL min}^{-1}) = \left(\frac{(140 - \text{age}) \times \text{LBW or WT}}{72 \times \text{Scr}\,(\text{mg dL}^{-1})}\right) \times 0.85 \text{ if female}$$

Each of the potential covariates was incorporated into the basic model to obtain the final model. Maximum likelihood estimates which include: The -2×log-likelihood, Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were used to test different hypothesis regarding the final model, the effect of covariates on pharmacokinetic parameters, the model of residual variability and the variance-covariance matrix of Interindividual variability. The distribution of the Normalized Prediction Distribution Errors (NPDE) and the Visual Predictive Check (VPC) were used as diagnostic tools for assessment of the final model. The external validation was

used to evaluate the predictive performance of the final population model with covariates. The population parameters of the final model were used to estimate the individual parameters in the 18 patients of the validation group.

Statistical method: Based on this individual parameters, the concentrations were calculated at the observed times and compared with the actual concentrations to determine the Mean Squared Error (MSE) and the Root Mean Squared Error (RMSE). These values with 95% confidence interval for the true mean were estimated according to the methodology suggested by Sheiner and Beal (1981) and Akaike (1974), where difference exits if $p<0.05$ by U Mann-Wihtney test between predicted and observed concentrations.

RESULTS

The clinical and demographic characteristics of the index and validation groups of patients are shown in Table 1. No differences were observed between the groups. A total of 370 plasma concentrations were available for analysis, an average of 3.7 per patient with a range of 2-5.

The concentration-time data was best fitted for a one compartment model with parameters ka, CL/F and V/F with its associated variability modeled exponentially. Population typical values for ka, CL/F and V/F were 2.22 h^{-1}, 26.4 L h^{-1} and 382 L, respectively. The variability between subjects was 61.5, 51.7 and 29.9% for ka, CL/F and V/F, respectively. The residual error was best described by a proportional error model, $\sigma = 0.191$ mg L^{-1}.

Among the covariates analyzed, LBW showed a significant correlation with V/F, CL_{creat} with CL/F and no covariate correlation were observed with ka. Therefore, LBW and CL_{creat} were included in the forward stepwise analysis. In this analysis the covariate with the highest significance was first inserted to the model followed by other less significant covariates. If the covariate significantly reduces the objective function criteria then it is integrated into the model, otherwise it is removed. As a result, in forward stepwise analysis, both covariates were introduced into the model because they led to a significant reduction in -2LL, AIK and BIC when compared with the basic model. These were confirmed by backward elimination. The interindividual variability was also reduced from 25.9-21.2% for V/F and from 51.7-41.2% for CL/F. Figure 1 shows the scatter plot of

Table 1: Characteristics of the patients

	Modeling group		Validation group	
Characteristics	Mean	Range	Mean	Range
Age (years)	59.0	39-77	61.0	40-79
Height (cm)	153.0	139-174	154.0	138-175
Weight (kg)	71.6	50.5-106	70.4	45.7-98.3
Lean body weight (kg)	48.2	30.3-81	47.6	31.4-79.8
Body mass index (kg m^{-2})	33.0	23-43	31.0	24-41
Creatinine clearance (mL min^{-1})	97.6	49-152	98.4	45-149

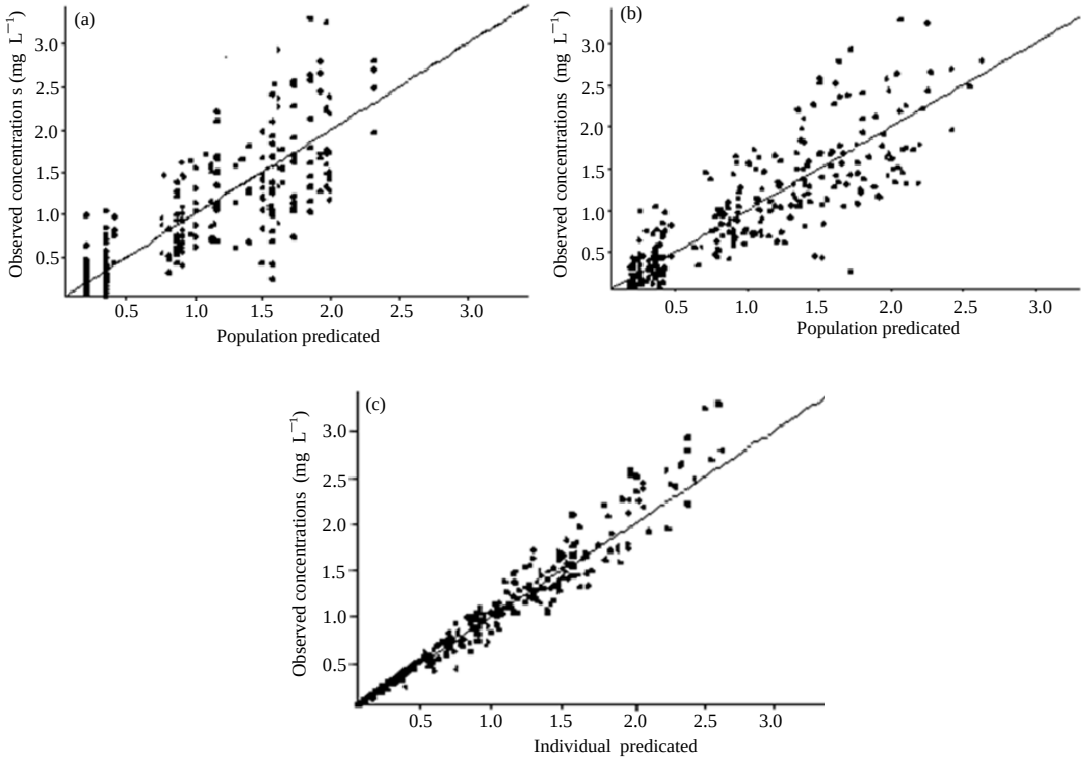

Fig. 1(a-c): Scatter plot of observed versus predicted plasma metformin concentrations indicated by a closer distribution around the line of unity for (a) Basic model, (b) Covariates model versus and (c) Individual predictions using the final model

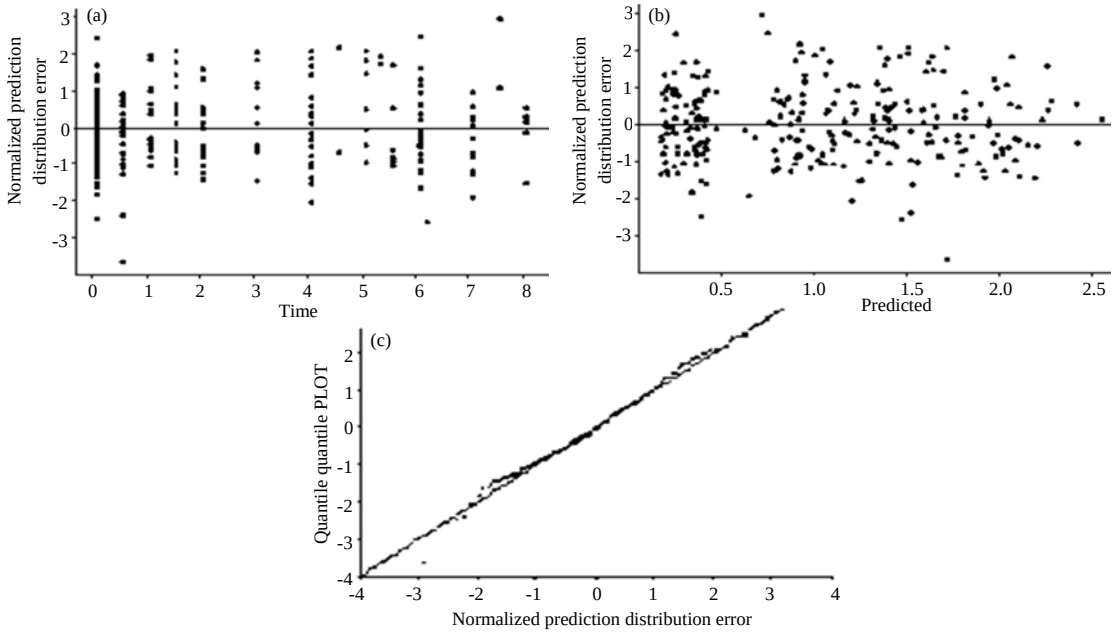

Fig. 2(a-c): Diagnostic plots for the final model including the covariates LBW and CLcr. (a, b) Normalized prediction distribution error versus time and predictions and (c) Normal quantile plot for Normalized prediction distribution error

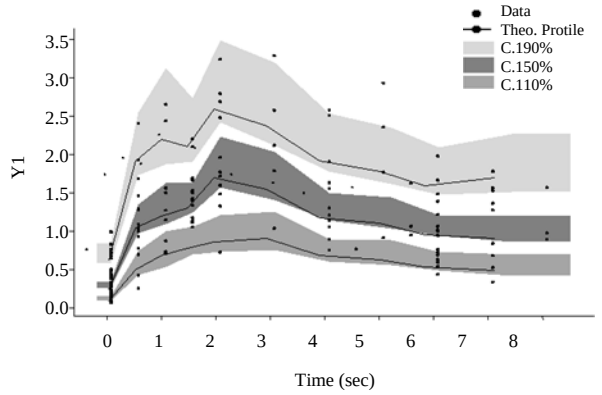

Fig. 3: Visual predictive check (VPC) for metformin concentrations versus time for the final model including LBW and CLcr based on 200 Monte Carlo simulated concentrations. Solid lines represent the median, 10th and 90th percentiles and its confidence intervals

observed concentrations and the predicted concentrations of the basic and covariate models.

The diagnoses for the evaluation of the final model are shown in Fig. 2 and 3. NPDE values are found randomly distributed with normal distribution. The results of visual predictive check of the model were based on 200 simulations. The majority of observed values lie within the 5 and 95% percentiles while, less than 10% of the observations were outside these percentiles. To validate the model, data from one

Table 2: Estimate pharmacokinetic parameters

	Basic model		Covariate model	
Parameters	Mean	RSE (%)	Mean	RSE (%)
Fixed parameters				
Ka (h^{-1})	2.22	8	2.14	8
V/F (L)	382	4	198	15
β_V (LBW)	-		0.013	23*
CL/F ($L \times h^{-1}$)	26.4	10	17.5	23
β CLcr	-		0.00499	38*
Interindividual variability (%)				
ω_{ka}	61.5	8	61.8	9
$\omega_{V/F}$	25.9	9	21.2	16
$\omega_{CL/F}$	51.7	13	41.2	19
Intraindividual variability				
σ (mg L^{-1})	0.191	10	0.190	9
Log-likelihood				
-2×log-likelihood	101.15		76.36	
AIC	115.15		94.36	
BIC	133.17		117.53	

*Significant at p<0.0001, RSE: Relative standard error, AIC: Akaike information criteria, BIC: Bayesian information criteria, LBW: Lean body weight

sample of eighteen patients was used, whose clinical and demographic characteristics were not different from those of patients used to build the model (Table 2). The final model with covariates was used for predictions. The mean prediction error (me) as an estimate of the magnitude of the systematic component of error or bias was -0.011 mg L^{-1} with 95% Confidence Interval (CI) of -0.107-0.086 mg L^{-1}. Meanwhile, the root mean squared prediction error as a measure of precision was 0.398 mg L^{-1} with 95% CI of 0.284-0.485 mg L^{-1}. The scatter plot of observed against predicted concentrations in the validation group are shown in Fig. 4.

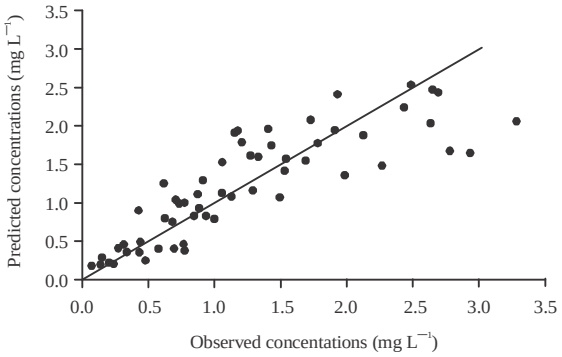

Fig. 4: Scatter plot of observed versus predicted concentrations of validation group

DISCUSSION

A population approach was used to determine the pharmacokinetic parameters of metformin in Mexican patients with T2DM along with their inter and intraindividual variabilities by a non-lineal mixed effects model implemented in Monolix program software (version 4.0).

The pharmacokinetics of metformin was appropriately described by one-compartment model with the estimated parameters: ka, V/F and CL/F. More complex models of 2 or 3 compartments have been used to describe the pharmacokinetics of metformin. However, when the data was fit to a two-compartment model, the standard error of the parameters estimated increased as well as the value of the objective function reason why it was not selected. A more extensive sampling would have allowed characterization of other compartments. However, this model proved to be useful to describe and predict the metformin concentrations. One-compartment model has also been reported by Bardin *et al*. (2012), which is more accessible to the clinicians in their daily practices.

The introduction of significant covariates to the basic model decreased the magnitude of interindividual variability. For V/F, CV of 25.9% in the basic model decreased to 21.2 % after LBW was included as a covariate. Of the body size descriptors evaluated, only LBW significantly influenced the parameter V/F. This relationship is consistent with the distribution of metformin in the extracellular fluid and its poor lipid solubility. Furthermore, LBW has been used as a useful predictor of pharmacokinetic behavior of highly water soluble drugs and it was the best predictor for V/F in a large population of obese patients studied by Bardin *et al.* (2012). Thus, our results support previous recommendations for dosing metformin based on LBW and not on other descriptors of the body size (Bardin *et al*., 2012; Han *et al*., 2007).

For CL/F, CV of 51.7% in the basic model decreased to 41.2% after the creatinine clearance, used as a surrogate marker of glomerular filtration, was included as a covariate. This is expected because metformin is not metabolized and is eliminated unchanged by renal excretion. However, although the relationship was significant, CLcr explains only a small percentage of the metformin CL/F. This implies that other factors, such as organic cation transporters, whose activity is genetically controlled, could contribute significantly to its elimination in different populations (Bardin *et al*., 2012; Hong *et al*., 2008; Sambol *et al*., 1995).

The mean CL/F of Metformin in our population of patients with T2DM was 26.4 L h^{-1} with a variability of 51.7%. Previous studies in smaller populations of healthy volunteers with normal renal function reported a population CL/F of 30.4 L h^{-1} with a variability of 24.6%. These differences reflect different kinetic dispositions and the risk of extrapolating this information to implement a dosage regimen in a specific population with T2DM.

More recently, Bardin *et al*. (2012) studied a group of T2DM patients with a wide range of body weight and BMI values with CL/F and mean population of 56 L h^{-1} 60 kg^{-1}. The model that best described the CL/F included the covariates age, LBW and serum creatinine. The inclusion of these covariates decreases the interindividual variability from 55% to 39%, an absolute reduction of 16%. The mean population CL/F in our patients was 26.4 L h^{-1} and the final model only included the covariate CLcr. The inclusion of this covariate reduced the interindividual variability from 51.7-41%, an absolute reduction of 10.7%. Age, LBW and serum creatinine were not included in the model because CLcr contained these covariates and its inclusion should produced problems of multi-collinearity. Therefore, our results are consistent with those reported by Bardin *et al*. (2012) and emphasized the importance of considering LBW to quantify the influence of body composition on kinetic dispositions of metformin in a population of T2DM patients with a wide range of body weight.

CONCLUSION

In conclusion, the pharmacokinetic parameters of metformin and the factors influencing their variability were established in Mexican patients with T2DM noting a wide range of body weight. Model evaluation suggested that the model is robust and its parameters were estimated with good precision. The model may be useful for designing a rational initial dosage regimen in this population of patients by clinicians.

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