Poster

[P27-10] P27-10: Pharmacokinetics and pharmacogenetics

Chair: Andrew Somogyi, Australia

Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall)

[P27-10-3] Pharmacokinetics and pharmacogenetics of metformine in patients with type 2 diabetes mellitus

Silvia Romano[1], Miriam Nayeli Morales[2], Susanna Edith Medellin[3], Rosa Milan[4], Perla Niño[5], Jaime Guillermo Rodriguez[6] (1.Universidad Autonoma de San Luis Potosi, 2.Universidad Autonoma de San Luis Potosi, 3.Universidad Autonoma de San Luis Potosi, 4.Universidad Autonoma de San Luis Potosi, 5.Universidad Autonoma de San Luis Potosi, 6.Universidad Autonoma de San Luis Potosi)

Keywords: metformin, pharmacokinetics, pharmacogenetics, diabetes

Background

Metformin is the first line pharmacological treatment for glycemic control in patients with Type 2 Diabetes Mellitus (DM2). However, it is estimated that about 30% of patients do not respond adequately to this treatment which may be related to the high inter-individual variability in the kinetic behavior of this drug and associated to pharmacogenetic factors. The aim of this study was to develop a population-based mixed effects pharmacokinetic model to evaluate the influence of genetic, anthropometric, pathophysiological, clinical and comedic factors on the kinetics of metformin in DM2 patients.

Methods

All procedures were in accordance with esthical standards of the institutional research committee. Patients with DM2 from the Central Hospital "Dr. Ignacio Morones Prieto "in San Luis Potosí (Mexico) under chronic treatment with metformin. The influence of anthropometric, clinical and comedication characteristics of the patients, as well as the presence of genetic polymorphisms OCT2 808 G> T (rs316019), OCT1 1260GAT> (rs72552763) and PMAT 883 -522A> G (rs2685753) on the pharmacokinetic behavior of metformin was evaluated through NONMEM software version 7.3.

Results

For the development of the population model, plasma metformin concentrations were included at the steady state from 70 patients with DM2, which showed a better fit to a one-compartment open model with first order absorption and elimination. The final population pharmacokinetic model obtained was: Clearance (CL) = 15.9 + 0.308 * CLcr for patients with creatinine clearance (CLcr) less than 120 mL/min and CL = 49.3 L/h in patients with CLcr equal to or greater than 120 mL/min. Metformin CL increases 22% in patients with the OCT1 1260 allele, while concomitant administration of clopidogrel decreases metformin CL by 43%. Volume of distribution is described by the following expression: V = 4.37 * Total body weight. Internal validation was performed by bootstrapping, showing the accuracy and the stability of the final model developed.

Conclusions

A final population pharmacokinetic model was successfully developed and demonstrates that metformin dosing criteria for patients with DM2 should consider CLcr, OCT1 genotype and clopidogrel comedication of every person