PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING AND SIMULATION (PBPK) FOR DOSE PREDICTION OF TIRZEPATIDE FOR HEALTHY ADULTS

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Introduction

Type II diabetes mellitus (T2DM) is a multifactorial disease and the most common form of diabetes. It is characterized by insulin resistance and primarily affects adults and the elderly. Treatment in special populations is challenging due to low treatment adherence and a high frequency of drug interactions, as well as difficulties in conducting clinical studies in these populations and the use of off-label medications. Tirzepatide (TZP) is the first antidiabetic drug to act as a dual agonist of the GIP/GLP-1 receptors, mediating insulin secretion. This drug stands out as a potential option for treating T2DM in special populations due to its efficacy in disease control, as well as weight reduction and improvement of cardiovascular risk factors, without hypoglycemia as an adverse effect. The PBPK model is a computational tool, with regulatory acceptance, that divides the organs and tissues of the body into compartments, connecting them through blood flow. Using this model, it is possible to mechanistically describe the pharmacokinetic behavior of a drug, employing mathematical models that incorporate physiological, physicochemical, and pharmacological parameters specific to the drug. To evaluate the pharmacokinetic profile of tirzepatide in special populations and possible dose adjustments, it is necessary to first build a model in healthy adults. This work aims to construct a PBPK model for subcutaneous administration of TZP in healthy adults, which will later be scaled to special populations.

Materials and Methods

For the construction of the PBPK model, a literature search was conducted to obtain the necessary physicochemical and pharmacokinetic parameters, along with physiological characteristics from selected studies by Feng et al. (2023), Furihata et al. (2021), and Urva et al. (2021) for the development and validation of a PBPK model in healthy adults using the PKSim v.11.3 program. To evaluate the robustness of the model, pharmacokinetic parameters such as AUC (Area Under the Curve), Cmax (maximum concentration), and Tmax (time to reach Cmax) were assessed. They were considered acceptable if the ratio between the predicted and observed values was between 0.5 and 2. The pharmacokinetic profiles from the chosen articles were compared with the concentration versus time curve generated in the constructed model to ensure that the model was adequately developed. The parameterization step was carried out for model refinement and calibration, using statistical tools like sensitivity analysis and parameter analysis to identify the qualitative and quantitative influence of each input on the pharmacokinetic parameters. After the parameterization and validation steps, a virtual population was created for final validation based on the observation of the pharmacokinetic simulation curves and the ratio between predicted and observed values, which was between 0.5 and 2.

Results and Discussion

With the aim of developing and validating a PBPK model in healthy adults, physiological data extracted from clinical studies such as those by Feng et al. (2023), Furihata et al. (2021), and Urva et al.

(2021) were used through the WebPlotDigitizer program to evaluate the curves extracted from the studies against the curves obtained in the analysis of pharmacokinetic parameters. During the development of the model, it was essential to carefully consider various pharmacokinetic stages, particularly the metabolism and elimination of tirzepatide. Adjustments were needed regarding elimination, such as renal clearance and the drug's glomerular filtration rate. Additionally, the pharmacokinetics of the subcutaneous administration route were evaluated, along with the particularities of this route. The increase in doses described in the articles was also evaluated, along with the construction of a dosing regimen to monitor drug exposure. Subsequently, parameter sensitivity analysis was performed, with values between 0.5 and 2 for the ratio between predicted and observed values, confirming the model's validation. Thus, it was possible to construct and validate the PBPK model for healthy adults, as the pharmacokinetic parameters AUC (Area Under the Curve), Cmax (maximum concentration), and Tmax (time to reach Cmax) were within the range of 0.5 to 2, thereby validating the model.

Conclusion

The development and validation of the PBPK model for tirzepatide in healthy adults demonstrated its accuracy and robustness in predicting pharmacokinetic parameters such as AUC, Tmax, and Cmax. Therefore, based on the construction of the model for the healthy adult population and the evaluation of pharmacokinetic profile curves, it will be possible to scale the model to special populations to evaluate pharmacokinetic parameters and potential dose adjustments.

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