PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING OF EMPAGLIFLOZIN IN PEDIATRIC POPULATIONS WITH HEALTHY AND OBESE WEIGHTS

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease affecting adults and children. Treating T2DM in children poses a challenge due to the difficulties in conducting clinical trials in this special population. Empagliflozin (EMPA) is an antidiabetic drug belonging to the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors and reversibly inhibits glucose reabsorption in the proximal tubules of the kidneys. This drug is a great candidate for treating T2DM in children due to its action on diabetes and other effects such as cardio- and nephroprotection, without causing hypoglycemia as an adverse effect. Despite its therapeutic advantages, the most appropriate dose for T2DM treatment in children is still unknown. In this context, new methodological approaches (NAM) are necessary to overcome these obstacles. Physiologically-based pharmacokinetic modeling (PBPK) emerges as a promising and regulatory-accepted approach that can predict the most suitable dose for children. The PBPK model is a computational tool that divides the body's organs and tissues into compartments and connects them through blood flow. It allows for a mechanistic description of a drug's pharmacokinetic behavior by applying mathematical models that use the drug's physiological, physicochemical, and pharmacological parameters.Therefore, the aim of this study was to construct the PBPK model for oral administration of EMPA in children with healthy and obese weight, and predict the best doses for this population.

Material and Methods

Following a literature search, pharmacokinetic and physicochemical parameters of the drug, along with physiological characteristics from selected studies for validation, were obtained for the model development. A PBPK model of empagliflozin was developed using the PK-Sim® v.11.3 program and verified in the adult population, by comparing the simulated plasma exposure with the observed data, and further scaled to the pediatric populations with normal and obese body weight. Statistical tools like sensitivity analysis and parameter identification were used to determine which input data most influenced the parameter under study and to find the best input values to align with clinical studies. Sensitivity analysis was employed throughout the model development to assess the impact on AUC (Area under the curve), Cmax (maximum concentration) and Tmax (time to reach maximum concentration). A virtual population was created based on demographic and physiological data from selected articles, and simulations were performed for validation. Model validation involved comparing simulated concentration-time profiles to clinical data, ensuring observed data fell within the 90% confidence interval and that pharmacokinetic parameters (AUC, Tmax, Cmax) had predicted/observed ratios between 0.5 and 2.

Results and Discussion

The study aimed to develop and validate a PBPK model for empagliflozin in healthy adults, and scale it for healthy children, adolescents, and those with obesity. The goal was to evaluate the pharmacokinetic profile of EMPA in these populations and determine whether dose adjustments were necessary compared to adult dosing ranges, particularly regarding Cmax and AUC parameters. The model was constructed using the drug's physicochemical properties along with pharmacokinetic and anthropometric data from Seman et al. (2013) and was subsequently validated with other clinical studies. During the model construction and initial graphical observations, discrepancies were identified between the pharmacokinetic profile of the simulated curve and the data from clinical studies. Sensitivity analysis revealed that the parameter most influencing Cmax and AUC values was the logP (octanol-water partition coefficient). Consequently, the model was refined, and the logP value was adjusted during validation, resulting in a more accurate pharmacokinetic profile, as confirmed by graphical comparisons and observed/predicted ratio analysis. After the validation for healthy adults, the model was scaled for children with healthy and obese weight. The parameters that showed the most significant changes were Cmax and AUC. In children with healthy weights, Cmax was 1.93 and 1.39 times higher in the 10-12 years old and 13-14 years old groups respectively, compared to adults receiving a 10mg dose. Similarly, AUC increased by 1.81 and 1.48 times in the 10-12 years old and 13-14 years old groups respectively, among healthy children. In obese children aged 10-12, Cmax and AUC were altered, showing an increase of 1.77 and 1.81 times respectively.

Conclusion

PBPK models of empagliflozin were created for adults, children, and adolescents to predict pharmacokinetic profiles and parameters in these populations. The study confirmed the accuracy of the developed PBPK model in replicating observed pharmacokinetic profiles. It provided a robust basis for extending the research to pediatric populations. Simulations indicated the need for dose adjustments in pediatric patients, particularly for healthy children aged 10-14 and obese children aged 10-12. These adjustments are essential to minimize adverse effects, ensuring the safe and effective use of empagliflozin in these age groups.

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