

A Physiologically-Based Quantitative Systems Pharmacology (PB-QSP) Model for Individualized Prediction of Treatment Outcomes with Alogliptin in the Renal Impairment Population



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Introduction

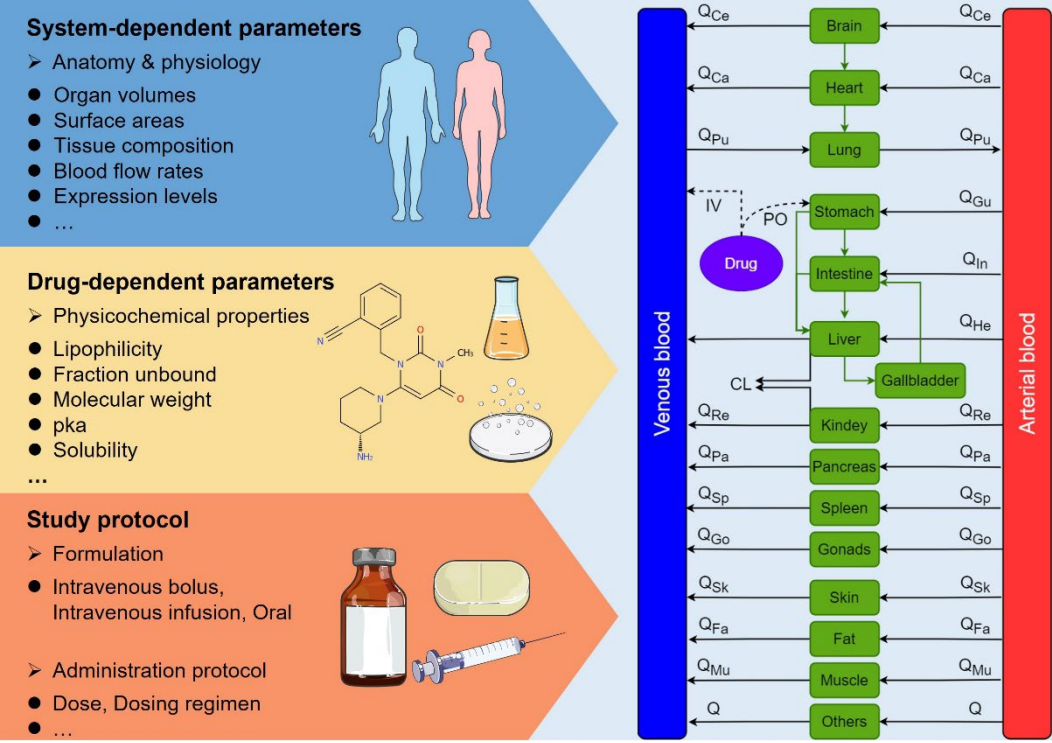
Type 2 diabetes is considered to be one of the most significant health problems affecting the world, and prolonged hyperglycaemia predisposes to chronic damage and dysfunction of various tissues [1]. Alogliptin is a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor that elevates glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) levels to restore glucose-dependent insulin secretion for glucose-lowering effects [2]. Since 60-71% of the dose of alogliptin is excreted as unchanged drug in the urine, making people with renal impairment susceptible to drug accumulation in the body and increasing the risk of serious adverse effects such as hypoglycaemia, acute pancreatitis and abnormal liver function [3, 4]. Therefore, prior modelling of potential exposure and clinical outcomes of alogliptin in individuals with renal impairment may help to ensure the efficacy and safety of the treatment.

Objectives

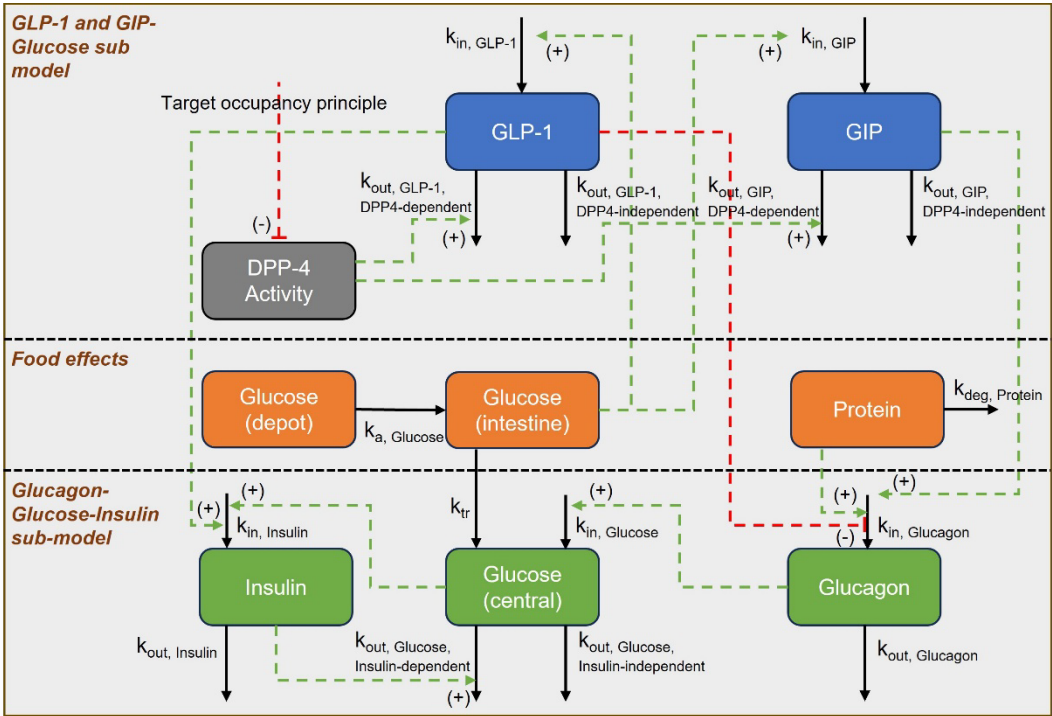
To develop a physiologically-based quantitative systematic pharmacology (PB-QSP) blood glucose control systemic modulation model to predict alogliptin exposure levels in vivo and use blood glucose levels as a clinical endpoint to prospectively understand its therapeutic outcomes in populations with varying renal function.

Methods

● PBPK modelling framework



● DPP4 occupancy-GLP1-GIP-insulin-glucagon-glucose QSP model

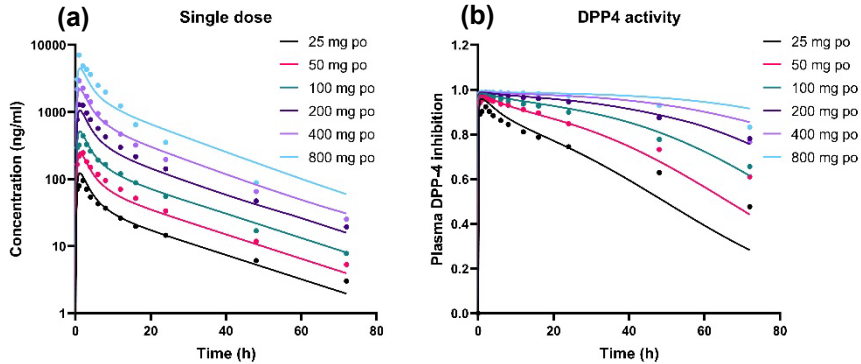


A PB pharmacokinetic (PBPK) model was developed using reported physicochemical properties and clinical data of alogliptin, and the inhibitory effect of alogliptin on DPP-4 was determined based on the principle of target occupancy. The DPP-4-GLP-1-GIP-glucagon-insulin- blood glucose control system was integrated and established, including crosstalk and feedback loops between the components [5].

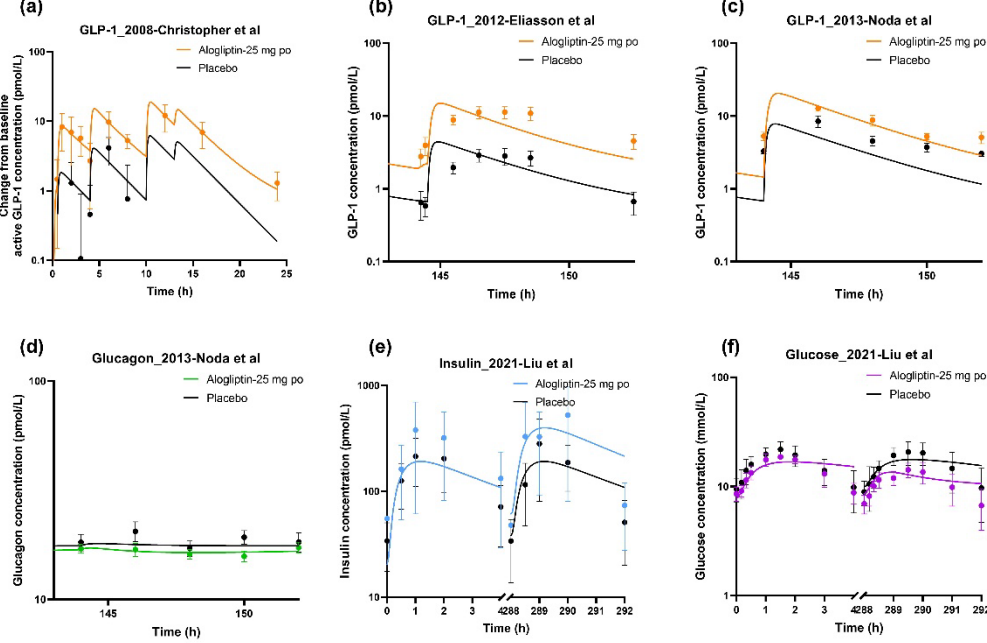
Results

The PB-QSP model contains five indirect response models as a “skeleton” structure and contains 12 feedback loops that adequately characterized the PK of alogliptin, the time course of DPP-4 inhibition, and the kinetics of GLP-1, GIP, glucagon, insulin, and blood glucose simultaneously in humans. Compared with clinically observed values, 97.62% of predicted plasma concentrations of alogliptin, 100% of DPP4 inhibition, 76.19% of GLP-1, 100% of glucagon, 70% of insulin, and 100% of blood glucose were within 2-fold error of the corresponding observed concentrations. In a virtual oral glucose tolerance test (OGTT) performed before and after oral administration of 25 mg of alogliptin, the AUC_{0-∞} in stage 3, 4, and 5 renal impairment groups was 2.05, 2.99, and 3.77 times higher than in healthy groups, and the maximum blood glucose level after 72 hours was reduced by 2.26, 3.48, and 4.18 mmol/L, respectively. But the minimum blood glucose level was not significantly different between the groups.

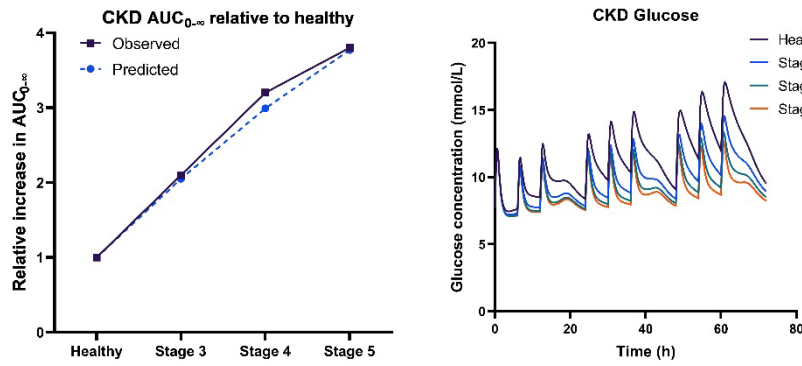
● Alogliptin PBPK model and DPP4 inhibition



● GLP-1, glucagon, insulin, blood glucose concentrations



● Prediction of AUC ratios and OGTT test blood glucose levels in renal impairment population



Conclusions

Our model provided valuable insights PK/pharmacodynamics (PD) and complicated glucose homeostasis of alogliptin in populations with different renal functions. In addition, since the glucose regulation modelling framework in the QSP model is “drug-independent”, our model can be further extended to predict the effects of other such drugs on blood glucose.

References

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