Evaluating Metformin Exposure through PBPK Modeling: A Comparative Study between Cancer Patients and Healthy Subjects

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Introduction

- Meta-analysis of clinical studies has demonstrated that pharmacokinetics of drugs may be altered in cancer patients compared to healthy volunteers due to possible change in drug metabolism [1].

- Post hoc analysis from clinical studies have shown that renal clearance of creatinine is altered in cancer population compared to healthy subjects [2].

- Metformin exposure differs between healthy individuals and the cancer population. Metformin is eliminated roughly 80% through renal clearance [3].

We propose using metformin as a case study drug and employing the Simcyp® PBPK platform to evaluate whether we can accurately predict pharmacokinetic differences between healthy and cancer populations due to changes in renal clearance.

Methods

① Literature survey was conducted to collect clinical data in healthy volunteers and cancer subjects. Descriptive meta-analysis was performed to evaluate the differences in PK of metformin in two populations.

② The metformin model from the Simcyp® library including:
First-order absorption model.
Full PBPK model.
Elimination model: renal, biliary and metabolic clearance via CYP3A4.

③ Simulations were conducted for metformin doses of 500 mg and 1000 mg once daily (QD), with 10 trials comprising 10 individuals each, using the default North European Caucasian population for healthy subjects (ages 20-95 years) and the default cancer population (ages 18-95 years) available in Simcyp®.

④ Precision of the models was evaluated by calculating the Average Fold Error (AFE). Area under the concentration-time curve (AUC_{inf}), peak plasma concentration (C_{max}), and drug clearance rate (CL), were analyzed and compared between the healthy subjects and cancer patients to better understand the differences in drug exposure and elimination across these groups.

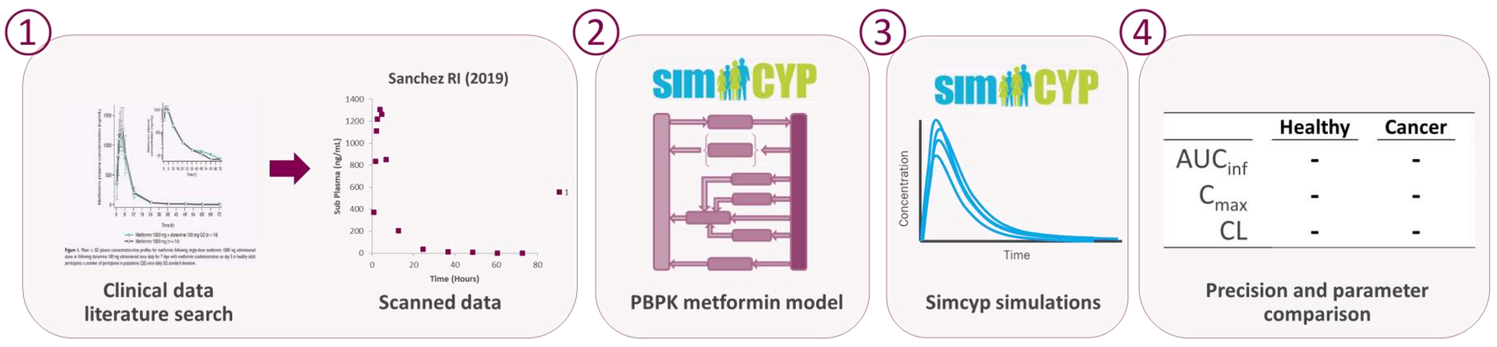

Figure 1 Schematic representation of the modeling strategy. Step 1 involves obtaining clinical data from literature through data digitization. Step 2 entails using metformin model in Simcyp® by including metformin elimination and physicochemical parameters. Step 3 include performing simulations in Simcyp®. Step 4 includes precision model evaluation and parameter comparison

Results

- Meta-analysis from literature studies have demonstrated that metformin exposure is in general higher in individuals with cancer compared to healthy individuals.

- The validated metformin model from the Simcyp® library effectively predicted pharmacokinetic parameters in both healthy and cancer populations. Figure 2 shows model prediction successfully describe the observed data in the different studies.

- Calculated AFE for AUC_{inf} and C_{max} values were between 0.5 and 2, indicating a reasonable precision of both healthy and cancer population PBPK models.

Table 1 includes key parameters comparison between healthy and cancer populations.
- The mean eGFR showed a 32% decrease in cancer patients.
- A notable 25% increase in AUC_{inf} was shown in cancer patients compared to healthy subjects, demonstrating the capability of the model to capture population-specific pharmacokinetic variations.

Table 1: Comparison of Geometric Means of Key Pharmacokinetic Variables Between Healthy and Cancer Populations Based on Simcyp® Predictions.

Dose	1000mg metformin HCL (free 780 mg)			500mg metformin HCL (free 390 mg)		
	Healthy	Cancer	**Ratio**	Healthy	Cancer	**Ratio**
AUC_{inf} (CV) ng·h/mL	21230 (0.53)	26740 (0.59)	**1.25**	10620 (0.53)	13370 (0.59)	**1.25**
C_{max} (CV) ng/mL	2860 (0.52)	3370 (0.54)	**1.17**	1430 (0.52)	1680 (0.54)	**1.17**
CL/F (CV) L/h	47.10 (0.49)	37.40 (0.56)	**0.79**	47.10 (0.49)	37.40 (0.56)	**0.79**
eGFR (CV) mL/min	109.34 (0.45)	74.05 (0.36)	**0.68**	109.34 (0.45)	74.05 (0.36)	**0.68**

CV, Coefficient of variation; AUC_{inf}, area under the concentration vs time curve; C_{max}, maximum concentration; CL/F, Clearance/Bioavailability at steady state; eGFR, estimated Glomerular Filtration Rate

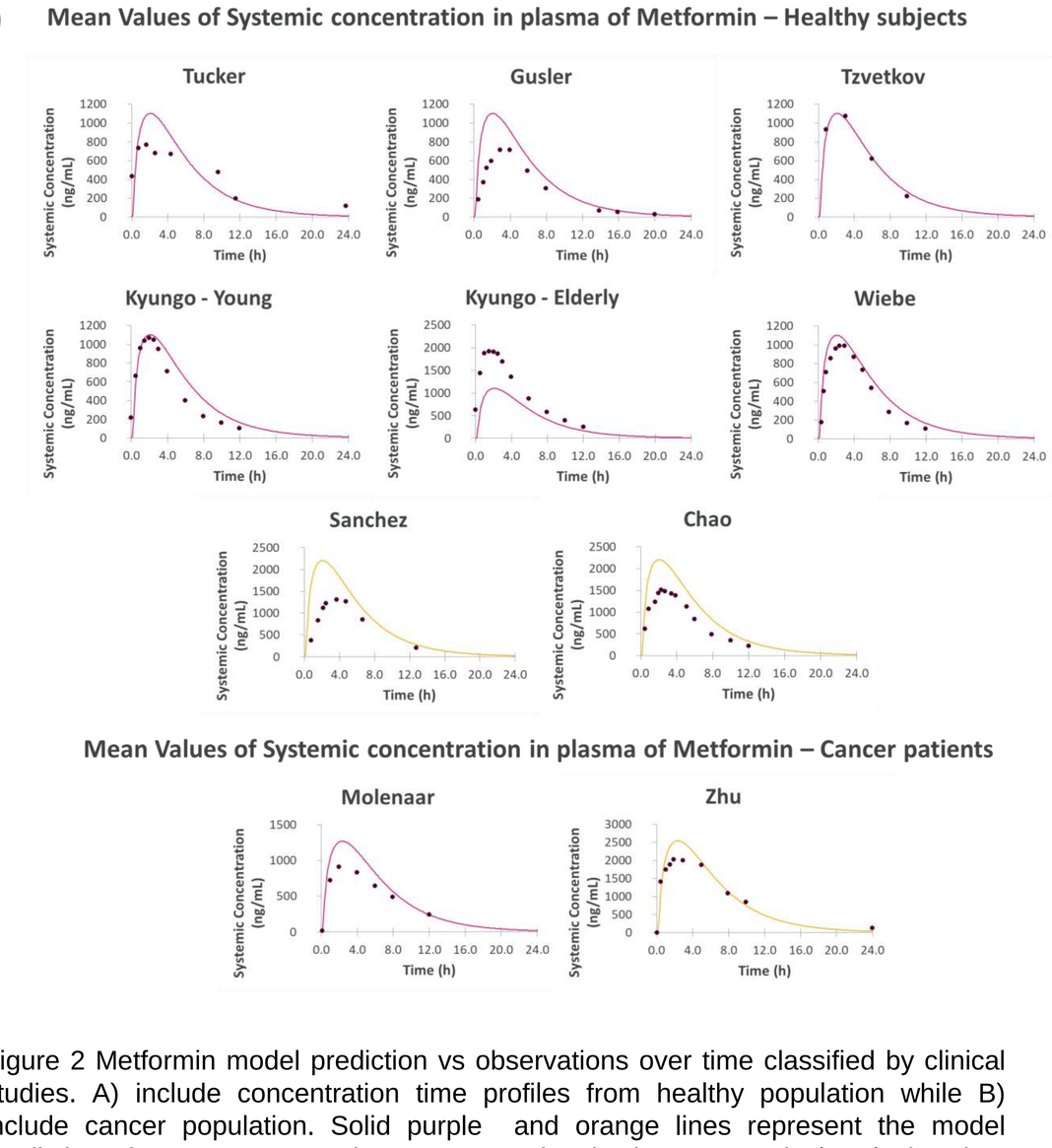

Figure 2 Metformin model prediction vs observations over time classified by clinical studies. A) include concentration time profiles from healthy population while B) include cancer population. Solid purple and orange lines represent the model predictions for a 500 mg and 1000 mg metformin dose respectively. Black points represent the data observations.

Conclusions

- Using metformin as a case study, we demonstrated that PBPK modeling can reasonably predict drug clearance in cancer patients by considering changes in renal clearance due to the disease.
- Future work with more drugs which are cleared by renal clearance will further strengthen our conclusions.
- This approach highlights the importance of incorporating disease-specific physiological alterations for better pharmacokinetic predictions in clinical settings.

References

1. Schwenger E, Reddy VP, Moorthy G, Sharma P, Tomkinson H, Masson E, Vishwanathan K. Harnessing Meta-analysis to Refine an Oncology Patient Population for Physiology-Based Pharmacokinetic Modeling of Drugs. Clin Pharmacol Ther. 2018 Feb;103(2):271-280. doi: 10.1002/cpt.917. Epub 2017 Nov 20. PMID: 29063606.
2. Wright J, Boddy A, Highley M, Fenwick J, McGill A, Calvert A. Estimation of glomerular filtration rate in patients. Br J Cancer. 2001;84(4):452–9.
3. Graham GG et al 2011. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50(2):81-98. doi:10.2165/11534750-000000000-00000. 2011;50(2):81–98. Available from: https://pubmed.ncbi.nlm.nih.gov/21241070/

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