dHealth 2023
B. Pfeifer et al. (Eds.)

doi:10.3233/SHTI230027

Development of a Digital Interface for Personalized Dosing in Renal Impaired Patients: A Case-Study Using the ACE-Inhibitor Benazepril

Valerie REINISCH[a], Amrit PAUDEL[a,b] and Joana T. PINTO[a,1]
[a] *Research Center Pharmaceutical Engineering GmbH, Graz, Austria*
[b] *Institute for Process and Particle Engineering, University of Technology Graz, Austria*

Abstract. Background: Personalized dosing regimens have great potential to improve the standard level of care from "one-fits-all" to the "right dose, to the right patient at the right time". Objectives: Development of a digital interface that can inform healthcare professionals on the dosing of an ACE inhibitor on an individual basis. Methods: A physiologically based pharmacokinetic (PBPK) model and a one-compartment model were implemented for the prodrug benazepril and its metabolite benazeprilat, respectively. In sequence, to capture inter-individual differences the models were extended to a population based one (PopPBPK). Results: Both models predicted the pharmacokinetic data in the observed ranges. Application of the models help identify the factors influencing drug concentrations in the body and to find subgroups of patients, in which a dose adjustment is recommended, or a higher degree of caution is required. Conclusion: The use of the models via a practical user interface can help inform clinical decisions and design optimal dosing based on the individual anthropometric characteristics and stage of renal impairment.

Keywords. Precision dosing, physiologically based pharmacokinetic (PBPK) model, renal impairment, inter-individual differences, digital interface

1. Introduction

Physiological based pharmacokinetic (PBPK) modeling encompasses the application of mathematical models, which aim to simulate the concentration-time profiles of a given drug by taking into consideration relevant physiological parameters, to mimic the whole body within an in-silico environment [1].

A more particular approach of these models aims to focus specifically on the impact of inter-individual differences on pharmacokinetic drug behavior [2]. On population-based PBPK modeling (PopPBPK), a series of individuals with different physiological and anthropometric characteristics can be digitally generated based on information from realistic populations, and the sensitivity of the drug pharmacokinetics (PK) to these variabilities is evaluated a priori [2]. As PopPBPK models can help to understand the impact of inter-individual differences on drug variability, the mechanistic knowledge

[1] Corresponding Author: Joana T. Pinto, Research Center Pharmaceutical Engineering GmbH, Graz, Austria, E-Mail: joana.pinto@rcpe.at

derived from these can support identifying the occurrence of adverse effects in high-risk cohorts of patients [3], such as renal impaired individuals. Renal disease can alter the ability of the kidney to clear drugs and varies the intended effect of active pharmaceutical ingredients (APIs). Likewise, drug doses should be modified in accordance to the reduced clearance [4]. However, dose adjustments continue to be mainly performed via a trial-and-error approach [5]. Although, some computational software packages (e.g., MWPharm++, DoseMeRx, Tuxuci, InsightRX) provide examples of the developmental efforts made in dose adjustments technologies, their clinical use has been limited mostly to antimicrobials and monoclonal antibodies [6].

Benazepril is a non-sulfhydryl inhibitor of the angiotensin-converting enzyme (ACE) and it is prescribed in the treatment of high blood pressure [7]. Benazepril is metabolized in the liver, where the drug is hydrolyzed into its main metabolite benazeprilat, that will be cleared in the kidneys [7]. Thus, in renal impairment (RI) patients higher benazeprilat concentrations tend to remain in the body, posing a risk for adverse drug reactions to occur. Likewise, in this work we aimed to develop a digital interface that can inform healthcare professionals on the dosing of benazepril on an individual basis, considering patient physiological characteristics (i.e., weight, height, sex, age) and the stage of RI.

2. Methods

2.1. PBPK model development

To simulate the drug within the body, a full PBPK and a one-compartment model was implemented for benazepril and benazeprilat, respectively. The models were implemented in MATLAB *(R2020a) Update 2* (MathWorks, USA). This software was used to create the system itself and adapt it to possible changes and requirements, such as adding or removing compartments or parts of them or generating specific data for further applications. In addition, it has a build-in application AppDesigner, with which user interfaces can be easily designed.

The dissolution profile of benazepril HCl [8] was fitted to an exponential cumulative distribution function, with the dissolution rate (k_{diss} = 0.272) directly included in the model. After 30 min of dissolving in the stomach, the drug solubilizes in the fluids of the gastrointestinal tract and permeates the intestinal epithelium to be absorbed and distribute throughout the body [1]. The plasma water partition coefficients (*Kp*) were calculated according to the Rodgers and Rowland method [9]. The values were scaled to the human physiology, based on the volume of distribution of benazepril at steady state (V_{dss} = 0.124 L/kg). The drug was assumed to distribute passively, without saturation, similarly to other ACE inhibitors [10].

Once benazepril reaches the liver it gets converted into benazeprilat, according to Equation (1), where $C_{Ben,liver}$, $CL_{int,liver}$ and Kpu_{liver} is the concentration of benazepril in the liver at time t, the intrinsic liver clearance and the unbound tissue to plasma partition coefficient of the liver, which can be calculated by dividing the Kp_{liver} by the fraction unbound (*fu*). The estimated value of $CL_{int,liver}$ is 1.52 L/h/kg.

After metabolization of benazepril, benazeprilat gets excreted mainly by the kidneys and eliminated from the body with the urine [7]. Based on the latter, a single compartment model was created (Equation (2)) to simulate the time vs. plasma concentration profiles of benazeprilat. The parameters $C_{vein,met}$, V_{vein}, $C_{Met.,liver,max}$,

$CL_{renal,met.}$, fu_{met}, and t_{lag} indicate the concentration of the metabolite in the venous compartment, volume of the vein, maximum concentration of the metabolite in the liver, the renal clearance of the metabolite, fraction unbound of the metabolite and the lag time of 1 h, respectively. The $CL_{renal,met}$ was calculated according to [11] and the excretion factor (k_{ex}) was considered to be 0.28 [12].

$$C_{Met.,liver}(t) = \frac{C_{Ben,liver}(t) \cdot CL_{int,liver}}{Kpu_{liver}} \quad (1)$$

$$C_{vein,met}(t) = \frac{1}{V_{vein}} \cdot \left(C_{Met.,liver,max} \cdot k_{ex} \cdot e^{-\frac{CL_{renal,met.}}{Kp_{renal,met}/fu_{met}}(t+t_{lag})} \right) \quad (2)$$

2.2. Implementation of the Virtual Population

To account for the interindividual differences in the clinical data, an additional population model was implemented [2].

To distinguish between healthy and RI population the glomerular filtration rate (*GFR)* changes according to the impairment level. A distinction was made between three groups: group 1 indicates a normal renal function, group 2 a mild-moderate RI and group 3 a severe RI to kidney failure, with an *GFR* range of 90-120 mL/min/1.73m^2, 30-89 mL/min/1.73m^2 and <30 mL/min/1.73m^2, respectively. To account for the changes of the protein binding to albumin, the serum albumin values for each group were taken to calculate the altering *fu* with the formulation from [13]. The renal blood flow (*BF*), was considered to show a linear relationship with the *GFR* [14], and calculated accordingly.

2.3. Model validation and application

To verify the accuracy of the model, the predictions were compared with data from a clinical trial [12]. By random selection of anthropological parameters from the clinical ranges, 30 plasma vs. time profiles were simulated and the mean values used for comparison.

With the model generated and validated, the differences between the different groups of RI could be determined.To that end, the area under the curve (*AUC*) of the healthy group was divided by the *AUC* of the respective group of RI and compared to the ratios from a clinical study [15]. Since benazepril is a daily medication, steady-state profiles were also simulated over a period of 7 days.

3. Results

3.1. PBPK model development and validation in healthy subjects

Venous plasma concentration versus time profiles are graphically demonstrated in Figure 1. The various curves were the result of the inter-individual variability used in the model.

The PK parameter, i.e., the *AUC* and C_{max} (maximum plasma drug concentration) from benazepril and benazeprilat were calculated and compared to the data from clinical studies (Table 1 and Table 2, respectively). It can be seen that the simulated values were

in the range of the observed ones and the percentage of prediction error (*%PE*), within a reasonable range (< 20%, [16]). Thus, the models were found adequate for further use.

3.2. PBPK model application in renal impaired subjects

Since the objective of this study was to determine the changes in benazeprilat concentrations in RI individuals, the model was extended to these patient strata. After an initial dose of 10 mg of benazepril HCl, and a simulation time of 24 h for 7 days, the resulting plasma concentrations in the different groups can be observed in Figure 2. Depending on the RI group being simulated, very notable, important differences could be observed on the concentration-time profiles of benazeprilat. To understand the ability of the model to predict benazeprilat plasma concentration profiles in renally diseased patients, the $AUC_{0\text{-}t}$ in the different impairment stages to healthy $AUC_{0\text{-}t}$ ratios were compared to the ones from clinical data. The ratios from literature are 1.5 and 4.3 for Group 2 and Group 3, respectively [15]. In comparison, the ratios of the simulations with this model were 1.69 and 4.13 for Group 2 and Group 3, respectively. This indicates that the model was able to capture well the plasma differences of benazeprilat in renal impaired patients.

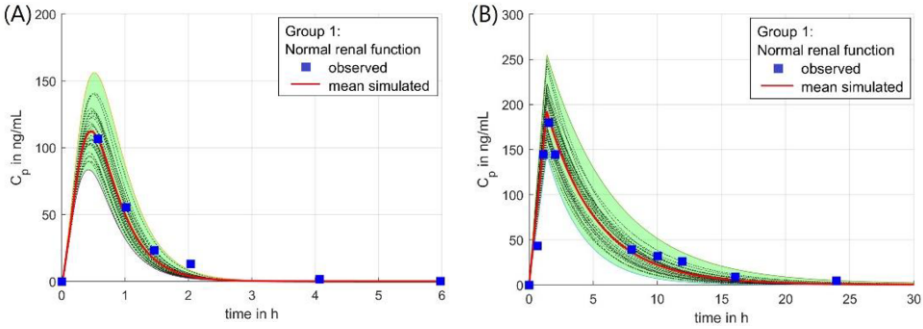

Figure 1: Plasma concentration profiles (in ng/mL) Group 1 (normal renal function) with simulation length of 72h, (A): benazepril (zoomed plot with timespan 0-6h), (B): benazeprilat (zoomed plot with timespan 0-30h). blue dots: observed data, red line: mean simulated profile, green shaded area: simulations of the individuals.

Table 1: PK-Parameter benazepril of Group 1 (normal renal function) Simulation and Observed data. Arithmetic Mean ± SD (min-max), %PE: percentage prediction error = |(observed-simulated)/observed|·100

PK-parameter (unit)	**Group 1 Simulation**	**Observed data** [12]	**%PE**
$AUC_{0\text{-}72h}$ (ng·h/mL)	97.55 ± 18.79 (69.49-149.47)	106.5 ± 42.15	8.40
$AUC_{0\text{-}inf}$ (ng·h/mL)	97.55 ± 18.79 (69.49-149.47)	110 ± 41.48	11.32
C_{max} (ng/mL)	112.48 ± 16.66 (83.589-156.16)	110.97 ± 47.15	1.36

Table 2: PK-Parameter benazeprilat of Group 1 (normal renal function) Simulation and Observed data. Arithmetic Mean ± SD (min-max), %PE: percentage prediction error = |(observed-simulated)/observed|·100

PK-parameter (unit)	**Group 1 Simulation**	**Observed data** [12]	**%PE**
$AUC_{0\text{-}72h}$ (ng·h/mL)	901.13 ± 231.34 (512.22-1557.30)	1001 ± 358.2	9.98
$AUC_{0\text{-}inf}$ (ng·h/mL)	902.88 ± 233.37 (512.26-1569.80)	1102 ± 367.8	18.07
C_{max} (ng/mL)	192.09 ± 29.583 (144.78-255.07)	180.25 ± 56.4	6.57

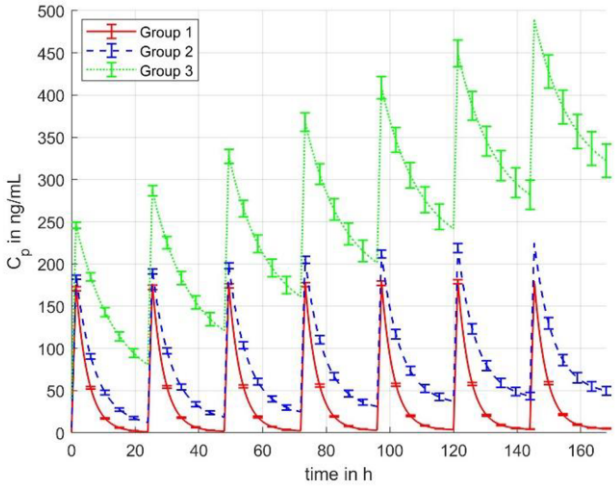

Figure 2: Mean plasma concentration profiles (in ng/mL) and error bars with the standard error of the mean (SEM) of Group 1 (normal renal function; solid red), Group 2 (mild-moderate RI; dashed blue) and Group 3 (severe RI-kidney failure; dotted green).

3.3. Model application and operation in clinical settings

Products aimed to be used within a digital medical framework, target to support the practice of medicine, promoting positive health outcomes on individuals and across populations [17]. Consequently, a platform that could allow the characterization of the drug pharmacokinetics under different physiological scenarios and pathological conditions could be invaluable in informing clinical decisions. Thus, a generation of a user-friendly platform for health professionals, to be able to use benazepril PopPBPK, as easily and conveniently as possible was also included within the objectives of the work. Figure 3 exemplifies a first translation of the model into a graphical user interface (GUI).

In the population tab the user can input the individual-related data (Figure 3, left). After clicking on the chosen drug in the drop-down menu, which are stored based on the different classes and types of medication, all input parameters are displayed on the screen in the parameter section, which can be modified (Figure 3, middle). So far just benazepril can be selected. Results are visually and in form of PK parameter shown in the simulation-tab (Figure 3, right). In future, together with feedback from the end-users (healthcare personnel) the GUI could be improved to provide a more intuitive experience.

In this study the interface generated exemplifies how this could be used to stratify patients and analyze their individual response to different doses on multiple days. Likewise, the final GUI could be used to inform the dose adjustment of benazepril in patients with mild to moderate impairment (for end-stage RI, as the patients do dialysis, and this is not accounted for in the model, the application is limited).

Therefore, more simulations were performed for group 2 (mild to moderate RI) individuals to identify factors that may also lead to dose adjustment. Thus, subgroups were created, first female and male, and then further subdivided into body mass index (*BMI*) ranges. From the model results, it can be concluded that for the male population, dose adjustment should also be considered in the case of obesity (*BMI* >30 kg/m^2). In the female population, the maximum recommended dose of 40 mg appears adequate to

achieve a therapeutic effect in severe thinness individuals (*BMI* <16 kg/m^2). In overweight individuals (*BMI* = 25-30 kg/m^2), dose adjustment is again recommended. In general, the higher the weight or *BMI* in a group of RI patients, the lower the dose required.

Likewise, the framework demonstrated shows how a PopPBPK model can be developed into a GUI that can account for individual patient characteristic, and easily and quickly inform healthcare personnel about the risk of drug accumulation and possible dose adjustment necessary to avoid any adverse effects in different at risk-cohorts of patients (e.g., renal impaired, obese, renal impaired and obese patients).

4. Conclusion

Our work demonstrated that the use of simulations of a validated pharmacometric model can help identify the factors influencing drug concentrations in the body and identify subgroups of patients, in which a dose adjustment is recommended, or a higher degree of caution is required and can in turn take into consideration by designing a dosing regimen. By combining the latter with an easy to use interface we aim to better inform clinical decisions, involve patients in the disease process and detect possible risk factors at an early stage.

In future, to further improve our interface, we aim to develop an automated decision system, through machine learning (ML). For this, we will use our PopPBPK model to generate large amounts of data and use this as input.

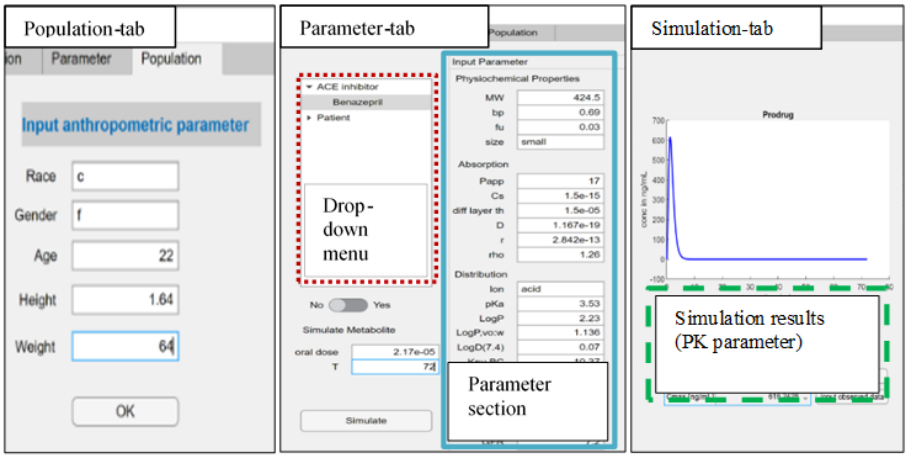

Figure 3: Graphical user interface, left: population-tab, middle: section of the parameter-tab, right: section of simulation-tab.

References

[1] S. A. Peters, Evaluation of a generic physiologically based pharmacokinetic model for lineshape analysis, *Clinical Pharmacokinetics* **47**(4) (2008), 261–275

[2] S. Willmann et al., Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs, *Journal of Pharmacokinetics and Pharmacodynamics* **34**(3) (2007), 401–431

[3] M. Krauss et al., Translational learning from clinical studies predicts drug pharmacokinetics across patient populations, *npj Systems Biology and Applications* **11** (2017),

[4] M. P. Doogue and T. M. Polasek, Drug dosing in renal disease, *Clinical Biochemist Reviews* **32** (2011), 69–73

[5] T. M. Polasek et al., Precision dosing to avoid adverse drug reactions, *Therapeutic Advances in Drug Safety* **10** (2019),

[6] W. Kantasiripitak et al., Software Tools for Model-Informed Precision Dosing: How Well Do They Satisfy the Needs?, *Frontiers in Pharmacology* **11** (2020), 620

[7] J. A. Balfour and K. L. Goa, Benazepril: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Hypertension and Congestive Heart Failure, *Drugs* **42**(3) (1991), 511–539

[8] S. Li et al., Correlation and prediction of moisture-mediated dissolution stability for benazepril hydrochloride tablets, *Pharmaceutical Research* **21**(4) (2004), 617–624

[9] T. Rodgers and M. Rowland, Physiologically Based Pharmacokinetic Modelling 2: Predicting the Tissue Distribution of Acids, Very Weak Bases, Neutrals and Zwitterions, *Journal of pharmaceutical sciences* **95**(6) (2006), 1238–1257

[10] D. G. Levitt and R. C. Schoemaker, Human physiologically based pharmacokinetic model for ACE inhibitors: Ramipril and ramiprilat, *BMC Clinical Pharmacology* **6** (2006), 1–27

[11] C. G. Regårdh, Factors Contributing To Variability in Drug Pharmacokinetics. Iv. Renal Excretion, *Journal of Clinical Pharmacy and Therapeutics* **10**(4) (1985), 337–349

[12] E. V. Mishina, Clinical Pharmacology / Biopharmaceutics Review Lotensin, *Clinical Pharmacology Review NDA* **19**(851) (2003),

[13] L. Sun et al., Application of Physiologically Based Pharmacokinetic Modeling to Predict the Effect of Renal Impairment on the Pharmacokinetics of Olanzapine and Samidorphan Given in Combination, *Clinical Pharmacokinetics* **60**(5) (2020), 637–647

[14] L. P. Li et al., Evaluation of Renal Blood Flow in Chronic Kidney Disease Using Arterial Spin Labeling Perfusion Magnetic Resonance Imaging, *Kidney International Reports* **2**(1) (2017), 36–43

[15] G. Kaiser et al., Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations, *American Heart Journal* **117**(3) (1989), 746–751

[16] B. Davit et al., International guidelines for bioequivalence of systemically available orally administered generic drug products: A survey of similarities and differences, *AAPS Journal* **15**(4) (2013), 974–990

[17] L. Yardley et al., The person-based approach to intervention development: Application to digital health-related behavior change interventions, *Journal of Medical Internet Research* **17**(1) (2015), e30