A population pharmacokinetic model for creatinine with and without ingestion of a cooked meat meal

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Abstract

A population pharmacokinetic (PPK) model for creatinine was successfully developed using creatinine concentration data from 6 healthy male volunteers with and without ingestion of 225 g boiled beef as an exogenous creatinine source. A model with first-order absorption, zero-order creatinine generation, and first-order elimination was used to describe the pharmacokinetic (PK) data. Creatinine parameters, estimated from the final model were: apparent absorption rate constant (Ka, 1.71 1/h), lag time (0.343 h), renal clearance (equal to systemic clearance) (CL, 7.57 L/h), apparent volume of distribution (Vd, 52.8 L), and creatinine generation rate (CGR, 67.8 mg/h). The CL and CGR estimates were in agreement with the reported values, whereas the Vd estimates were slightly higher than the reported values. The model is a useful starting point for further experimental approaches to improve the understanding of creatinine kinetics, which may involve creatinine "dosing" accompanied by independent methods to assess the glomerular filtration rate.

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What is already known about this subject:

In various creatinine models, the volume of distribution of creatinine was generally assumed as 60% of total human body water. This rough approximation ignores variability, which may lead to biased estimates of other creatinine PK parameters such as creatinine generation rate.

What this study adds:

This study provides reasonable parameter estimates including creatinine generation rate and the volume of distribution from a well-structured dynamic creatinine model. This model provides the basis for further experimental approaches to characterize creatinine kinetics in more detail, which may in turn helps to improve drug dosing in acute renal failure.

Abstract

A population pharmacokinetic (PPK) model for creatinine was successfully developed using creatinine concentration data from 6 healthy male volunteers with and without ingestion of 225 g boiled beef as an exogenous creatinine source. A model with first-order absorption, zero-order creatinine generation, and first-order elimination was used to describe the pharmacokinetic (PK) data. Creatinine parameters, estimated from the final model were: apparent absorption rate constant (Ka, 1.71 1/h), lag time (0.343 h), renal clearance (equal to systemic clearance) (CL, 7.57 L/h), apparent volume of distribution (V_d, 52.8 L), and creatinine generation rate (CGR, 67.8 mg/h). The CL and CGR estimates were in agreement with the reported values, whereas the V_d estimates were slightly higher than the reported values. The model is a useful starting point for further experimental approaches to improve the understanding of creatinine kinetics, which may involve creatinine "dosing" accompanied by independent methods to assess the glomerular filtration rate.

Introduction

Estimated glomerular filtration rate (eGFR) calculated by different equations based on serum creatinine and/or cystatin C is widely used for the estimation of renal function in the clinical setting [1]. Acute changes in renal function take time to become apparent in serum creatinine concentrations; furthermore, these concentrations may be affected by factors other than renal function [2]. Therefore, commonly used equations which are based on steady-state assumptions regarding creatinine formation and elimination are less suitable in patients with unstable renal function [2-4].

In contrast, a compartmental creatinine model allows description of dynamic changes in creatinine parameters over time and provides estimates of residual error arising from the measurements. A compartmental model based on serum and urine creatinine concentration data from critically ill patients has been previously introduced by Ullah *et al* . to estimate creatinine clearance [5]. Covariates, including fat-free mass, plasma urea concentration, age, liver transplantation, sex, and body weight were assessed and incorporated into the published model, contributing to more accurate estimates compared to standard approaches [5]. However, the model assumed a volume of distribution (V_d) of creatinine of 60% of total body weight. This rough approximation ignores variability, which may lead to biased estimates of other PK parameters [5]. Therefore, there is a need to enrich the estimates of creatinine PK parameters with experimental data, in the case of $V_d$including the exogenous administration of creatinine.

Creatinine PK profiles from healthy subjects with and without ingestion of a cooked meat meal as a creatinine source were previously reported by Mayersohn *et al.* [6]. Significant increases in plasma creatinine concentration (mean 52%) and urinary excretion (mean 13%) were reported between 1.5 and 3.5 hours after ingestion of boiled beef, while no changes in clearance were observed [6]. Re-analysis of the data from this study using a population pharmacokinetic (PPK) approach was conducted to estimate the PK parameters of creatinine to refine the dynamic creatinine model and to reduce bias in estimates of other kinetic parameters.

Materials and methods

1.

Data acquired

The PK data for creatinine were captured from the publication by Mayersohn *et al* . [6] using the "getdata" software (version 2.26) [7]. Both plasma and urine data during 24 hours following a breakfast containing 225 g boiled beef or no beef ingestion in 6 healthy male subjects were obtained to establish the model.

Population pharmacokinetic modelling

The model was developed using the nonlinear mixed-effects model software NONMEM (version 7.4.0, ICON Development Solutions, USA) and Perl-speaks-NONMEM (PsN, version 5.3.0, Uppsala University, Sweden). Statistics and plotting were performed using R (version 4.2.0) and R studio (version 2021.09.1+372).

The structural model for creatinine was initially parameterized in terms of Ka, CL, V_d, and CGR. Creatinine in boiled beef entered from the depot compartment (A_1) into the central compartment (A_2), while the creatinine produced in the body entered the central compartment directly with zero-order CGR. Finally, creatinine was eliminated into the urine compartment (A_3) with first-order elimination. The model was developed using first-order conditional estimation with interaction, where a decrease of >3.84 in the objective function value (OFV) (P = 0.05) upon the inclusion of a parameter was used as statistical criteria. Addition of a peripheral compartment as well as various absorption models were tested. No other elimination pathways for creatinine were considered because of obvious lack of identifiability. Interindividual variability (IIV). Different error models were evaluated separately, including additive-only, proportional-only error models, and the combination thereof. Individual creatinine "dose" for each subject was estimated using a pre-defined arbitrary population dose (180 mg) which is the average increased amount of creatinine excreted in urine after ingestion of boiled beef. The post-hoc estimated apparent bioavailability (F1) was used as the individual correction factor for this estimated dose (F1×180 mg).

The final model was validated and diagnosed based on goodness-of-fit (GOF) plots, individual plots, and 95% confidence intervals (CIs) of the estimated parameters from a non-parametric bootstrap (n = 1000).

Results

1.

Model development and assessment

The PPK model was constructed based on the dataset containing 133 serial plasma values and 11 urine values. A one-compartment PK model with linear elimination, first-order absorption, and zero-order creatinine generation fitted creatinine PK data well. Introducing a lag time in the base model resulted in a 28.359 reduction in OFV, indicated a delay in the absorption of creatinine from boiled beef. Finally, exponential and proportional models were used to describe IIV and residual variability, respectively. The scheme of the final model is displayed in Figure 1.

GOF plots (Figure 2) of plasma and urine creatinine show no trends of conditional weighted residuals over the range of predicted values, but slight underestimation of creatinine concentrations at 24 h.

Creatinine parameter estimates

Table 1 lists the PK parameters including Ka and lag time, CL, V_d, F1, and CGR, estimated from the final creatinine model and the 95% confidence intervals derived from 991 successful bootstrap-samples. Point estimates were similar to median values from the bootstrap, and relative standard errors were acceptable. This indicated that the final model is stable.

Discussion

During the model development, one- and two-compartment model were tested separately, and there was no change in OFV upon inclusion of a peripheral compartment. At the same time, estimates of the peripheral compartment volume and inter-compartmental clearance were 0.00364 L and 0.0218 L/h, respectively, which are negligible. Even though there were two-compartment creatinine models reported before, but minor differences between one-compartment and two-compartment models were found [8,9]. Therefore, a one-compartment structure model was applied to fit the data.

Based on the individual plots [6], the creatinine concentration in subject 6 at 24 h after beef ingestion abruptly and markedly increased compared to that of the previous time point, which is unreasonable; on the other hand, creatinine intake from beef may not be completely eliminated by 24 hours. These observations may cause the underestimation of creatinine concentration at 24 hours after beef ingestion.

The introduction of IIV on V_d only resulted in a 0.259 drop in OFV, and therefore it was not included in the final model. This may be a result of the low variability of individual weights (65 – 82 kg) in this study since the V_d of creatinine is usually assumed to be a fraction of total body water [9,10], which is approximately 60% of total body weight. From this model, the V_d of creatinine was estimated to be 52.8 L (72.3% of the total body weight), which is similar to but slightly higher than the fraction of total body water [9,10].

The typical value for creatinine generation rate in healthy volunteers was 67.8 mg/h, which is in agreement with the value of 65.8 mg/h (male, 31 years, 73 kg) calculated based on the equation: baseline CGR, mg/h = (27 – 0.173 × age in years) × weight in kg / 24 [10], but higher than the value of 42.8 mg/h (1183 mg/day) and 43.8 mg/h in patients reported by Ullah *et al* . and Daugirdas *et al* ., respectively [5,11]. The values for estimated individual creatinine renal clearance were similar to those that have been reported [6]. However, the estimated dose (290 ± 74.3 mg, n = 6, based on the equation: F1 × 180 mg) for each subject was not fully consistent with the increased creatinine amount excreted in urine after beef ingestion (180 ± 101.8 mg, n = 5, data from one subject was missing). This does not exclude the possibility that these discrepancies are related to the accuracy of the raw data, furthermore, no demographic information is available in the publication to better define the PPK model.

In this study, a PPK model for creatinine was developed using creatinine data with and without ingestion of boiled beef in healthy volunteers. Reasonable parameter estimates including creatinine generation rate and the volume of distribution were obtained from the final well-structured model. The model is a useful starting point for further experimental approaches to improve the understanding of creatinine kinetics, which may involve creatinine "dosing" accompanied by independent methods to assess glomerular filtration rate, *e.g.* , by a test dose of iohexol.

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Conflict of interest

None to declare

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Author Contributions

ZC and CC developed the model and drafted the manuscript; MM performed the clinical trial and provided the data; UF and MT designed and guided the research; all authors contributed to the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table & Figure legends

Figure 1 Schematic flow diagram of the creatinine model.

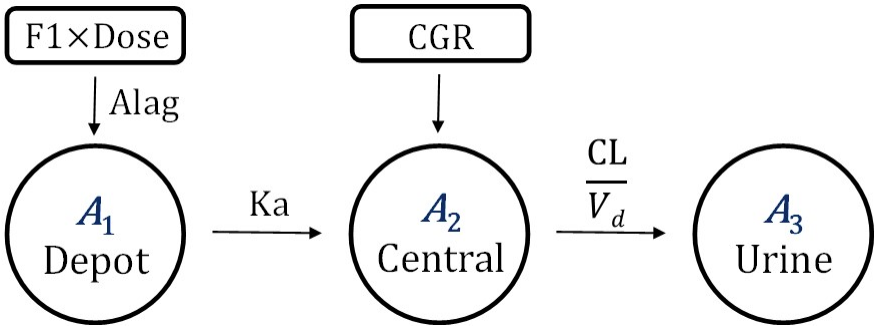
The creatinine in boiled beef entered from the depot compartment (A_1) into the central compartment (A_2) with the apparent absorption rate constant (Ka), while the creatinine produced in the body entered the central compartment directly with zero-order creatinine generation rate (CGR). Finally, creatinine was eliminated into the urine compartment (A_3) with first-order elimination. The post-hoc estimated apparent bioavailability (F1) was used as the individual correction factor for the dose, and a lag time (Alag) was introduced to describe the delay in the absorption of creatinine.

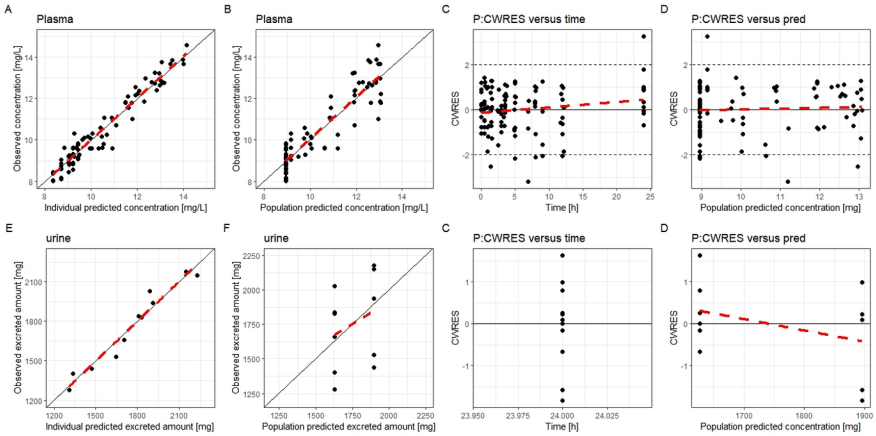
Figure 2 Combined goodness-of-fit plots of creatinine (A – D) plasma concentration and (E – H) urine excreted amount.

CWRES, conditional weighted residuals. A: observed *vs* . individual predicted plasma concentration; B: observed *vs* . population predicted plasma concentration; C: CWRES of plasma *vs* . time; D: CWRES of

plasma *vs* . population predicted plasma concentration; E: observed *vs* . individual predicted amount excreted in urine; F: observed *vs* . population predicted amount excreted in urine; G: CWRES of urine *v* s. time; H: CWRES of urine *vs*. population predicted excreted amount.

Table 1 Parameter estimates obtained from the final model and bootstrap statistics (n = 1000).





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