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RESEARCH

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

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To the Editor,

Commonly used equations for estimating creatinine clearance (CL) and/or glomerular filtration rate (GFR) from serum creatinine are based on steady-state assumptions regarding creatinine formation and elimination and are therefore less applicable to patients with unstable renal function [1–3]. A compartmental creatinine model that can describe the dynamics in creatinine parameters over time was previously introduced by Ullah et al. to estimate creatinine clearance [4]. In this model, volume of distribution (V_d) of creatinine was fixed at 60% of total body weight, corresponding to total body water (TBW). This approximation ignores variability, which may lead to biased estimates of other pharmacokinetic (PK) parameters [4]. Therefore, there is a need to enrich the estimation of creatinine PK parameters with experimental data, in the case of V_d including exogenous administration of creatinine. Creatinine PK profiles in healthy subjects with and without ingestion of a cooked meat meal as a creatinine source were previously reported by Mayersohn et al. [5]. Data from this study were reanalyzed using a population pharmacokinetic (PPK) approach to estimate PK parameters for creatinine, refine the dynamic creatinine model, and reduce bias in the estimation of other kinetic parameters.

A one-compartment PK model with linear elimination, first-order absorption, and zero-order creatinine generation was constructed based on the dataset composed of 133 serial creatinine plasma concentrations and 11 creatinine amounts excreted in urine during 24 h. Exponential models were most suitable to describe inter-individual variability (IIV), while two separate proportional errors were best to describe residual variability of plasma concentrations and amounts excreted in urine, respectively. The individual bioavailable creatinine dose for each subject was estimated using a pre-defined arbitrary population dose (180 mg) multiplied by individual post hoc estimates for apparent bioavailability (F1). Both the goodness of fit and visual predictive check plots (Supplemental Figs. 1 and 2) and the bootstrap results showed that the final model was reliable and stable.

Table 1 lists the PK parameters estimated from the final model and the 95% confidence intervals derived from 994 successful bootstrap samples. The typical values for CL and V_d of creatinine were estimated to be 7.92 L/h and 53.9 L (73.8% of the total body weight), which were similar to the reported values [5–7]. Incorporating variability on CL and V_d did not significantly improve the model, which may be attributable to the relative homogeneity of the small population studied. As a comparison, when fixing the value of V_d to the estimated TBW, which is 43.8 L (60% of 73 kg), the OFV will increase by 3.230, which does not represent a significant difference, while values of other parameters do not change much. Deciding between various error models was not straightforward due to the limited number of data points, but the point estimates for pharmacokinetic parameters remained essentially unchanged regardless of the error model chosen and are therefore considered as reliable.

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

	Final model		994 successful bootstrap runs	
Parameter	**Estimates**	**RSE (%)**	**Median**	**95% CI**
Ka (1/h)	1.76	26.7	1.60	0.715–3.34
CL (L/h)	7.59	6.4	7.59	6.71–8.48
V_d (L)	53.9	20.0	53.0	31.2–72.0
F1	1.57	21.1	1.60	1.04–2.07
CGR (mg/h)	67.9	6.9	67.9	59.4–76.3
Lag time (h)	0.344	4.7	0.344	0.297–0.370
IIV				
Ka (CV%)	55.3 (1.6%)	37.7	55.4	3.8–83.1
F1 (CV%)	24.6 (0.1%)	20.3	24.0	15.0–30.0
CGR (CV%)	3.9 (0.1%)	25.8	3.5	1.1–4.7
Residual variability				
Proportional error, % (plasma)	3.9 (7.0)	10.0	3.8	3.2–4.5
Proportional error, % (urine)	15.5 (0.2)	21.8	14.7	6.4–19.7

For IIV, the corresponding shrinkage estimates are shown in parentheses

Ka apparent absorption rate constant, *CL* renal clearance, V_d the volume of distribution, *F1* dose correction factor, *CGR* creatinine generation rate

The typical value of the creatinine generation rate (CGR) in healthy volunteers was 68.0 mg/h, which is consistent with the value of 65.8 mg/h (male, 31 years, 73 kg) calculated based on the reported equation [2], but higher than the value of 42.8 mg/h and 43.8 mg/h in patients reported by Ullah et al. and Daugirdas et al., respectively [5, 8]. The estimated dose (293 ± 62.0 mg, $n = 6$) was not fully consistent with the increased creatinine amount excreted in urine after beef ingestion (180 ± 102 mg, $n = 5$). 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 evaluation, a PPK creatinine model was developed using creatinine data with and without ingestion of boiled beef in healthy volunteers. Reasonable parameter estimates including CGR and V_d 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 GFR, e.g., by a test dose of iohexol.

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Author contribution 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.

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

Declarations

Conflict of interest The authors declare no competing interests.

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