



A Population Pharmacokinetic Model for Creatinine with and without ingestion of cooked meat

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Background and Objectives

Background: Estimated glomerular filtration rate (eGFR) based on serum creatinine is now widely reported by clinical laboratories, and in most circumstances, estimated GFR is sufficient for clinical decision-making¹. However, commonly used equations are based on steady-state assumptions regarding creatinine formation and elimination and thus are less suitable in patients with unstable renal function²⁻⁴. A population pharmacokinetic model (PPK) based on creatinine data from critically ill patients was introduced to estimate creatinine clearance more accurately compared to standard approaches⁵. However, the volume of distribution of creatinine was assumed as 60% of the total body weight in this model. The latter is only a rough approximation and neglects variability, which may result in biased estimates of other kinetic parameters. The latter is only a rough approximation and neglects variability, which may result in biased estimates of other kinetic parameters⁵.

We report here on the results of one clinical study regarding creatinine pharmacokinetic (PK) profiles with and without ingestion of a cooked meat meal. A significant increase in creatinine plasma concentrations with no clearance change was found after eating boiled beef⁶. The data from this study were used to estimate PK parameters of creatinine using population pharmacokinetic (PPK) analysis, thus helping to refine the creatinine dynamic model and reducing biased estimates of other kinetic parameters.

Objective: This study aimed to obtain creatinine pharmacokinetic parameters including: apparent absorption rate constant (Ka); renal clearance (CL); the volume of distribution (V_d); and creatinine generation rate (CGR) based on the PPK approach.

Methods

Data acquired: The PK data for creatinine were captured using the “getdata” software⁷, which can digitalize the graphs of the original data from the publication by Mayersohn *et al.*⁶. Both plasma and urine data during 24-hours following beef or no beef ingestion were analyzed using NONMEM (version 7.4.0, USA).

Model development: Creatinine PK model with zero-order creatinine generation rate and first-order clearance was estimated and 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 and post-hoc estimates of apparent bioavailability (F1) as an individual correction factor of this dose. The differential equations for the PK model are expressed as follows:

$$\begin{aligned} \frac{dA_1}{dt} &= -K_a * A(1) \\ \frac{dA_2}{dt} &= CGR + K_a * A(1) - \frac{CL}{V_d} * A(2) \\ \frac{dA_3}{dt} &= \frac{CL}{V_d} * A(2) \end{aligned} \quad (1) \quad (2) \quad (3)$$

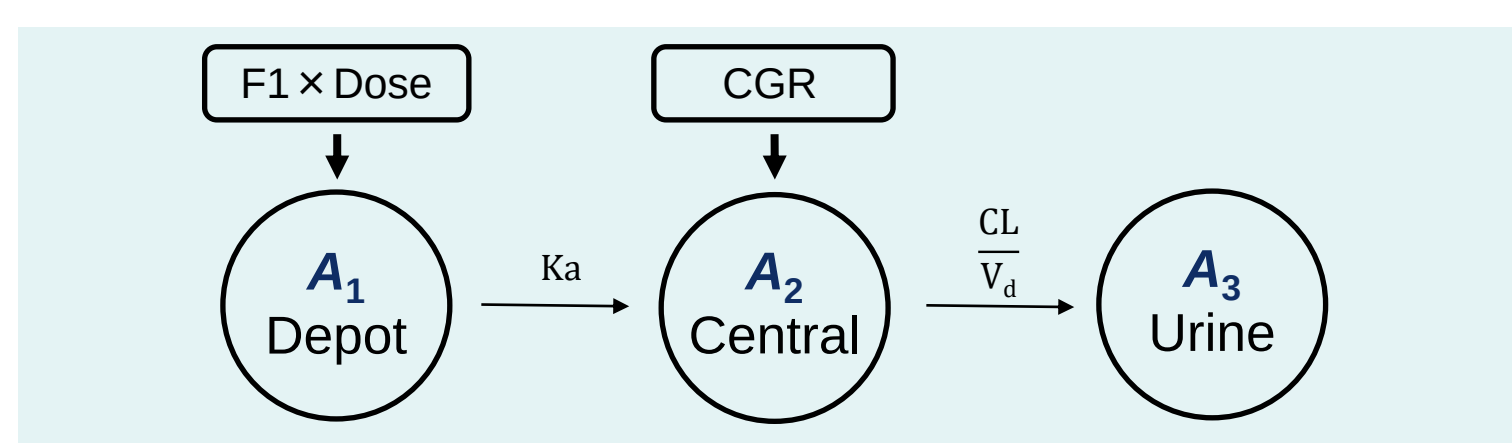


Table Parameter estimates obtained from final model and bootstrap statistics (n = 991).

Parameter	Final model	RSE (%)	Median	95% CI
Ka (1/h)	1.71	27.2	1.53	0.716 – 2.69
CL (L/h)	7.57	6.1	7.53	6.65 – 8.21
V _d (L)	52.8	15.7	49.9	25.9 – 69.3
F1	1.55	16.9	1.50	0.890 – 1.91
CGR (mg/h)	67.8	6.5	67.7	60.0 – 73.0
Lag time (h)	0.343	4.9	0.341	0.289 – 0.372
IIV				
Ka (%)	58.1	35.8	62.8	26.3 – 91.5
CL (%)	14.1	21.7	13.4	7.07 – 18.7
F1 (%)	27.7	23.9	28.5	15.5 – 42.2
CGR (%)	15.3	17.2	14.5	10.0 – 17.9
Residual variability				
Proportional error (plasma and urine, %)	4.0	8.8	3.8	3.2 – 4.5

Conclusion

This study investigated the generation rate and the volume of distribution of creatinine in healthy volunteers using a model-based approach and oral administration of creatinine by boiled meat.

Results

The PPK model was constructed based on the dataset composed of 133 serial plasma values and 11 urine values. A 1-compartment PK model with linear elimination, first-order absorption, and zero-order creatinine generation provided the most robust fit for creatinine PK profiles. Inter-individual variability (IIV) and residual variability were well described by an exponential model and a proportional error model, respectively.

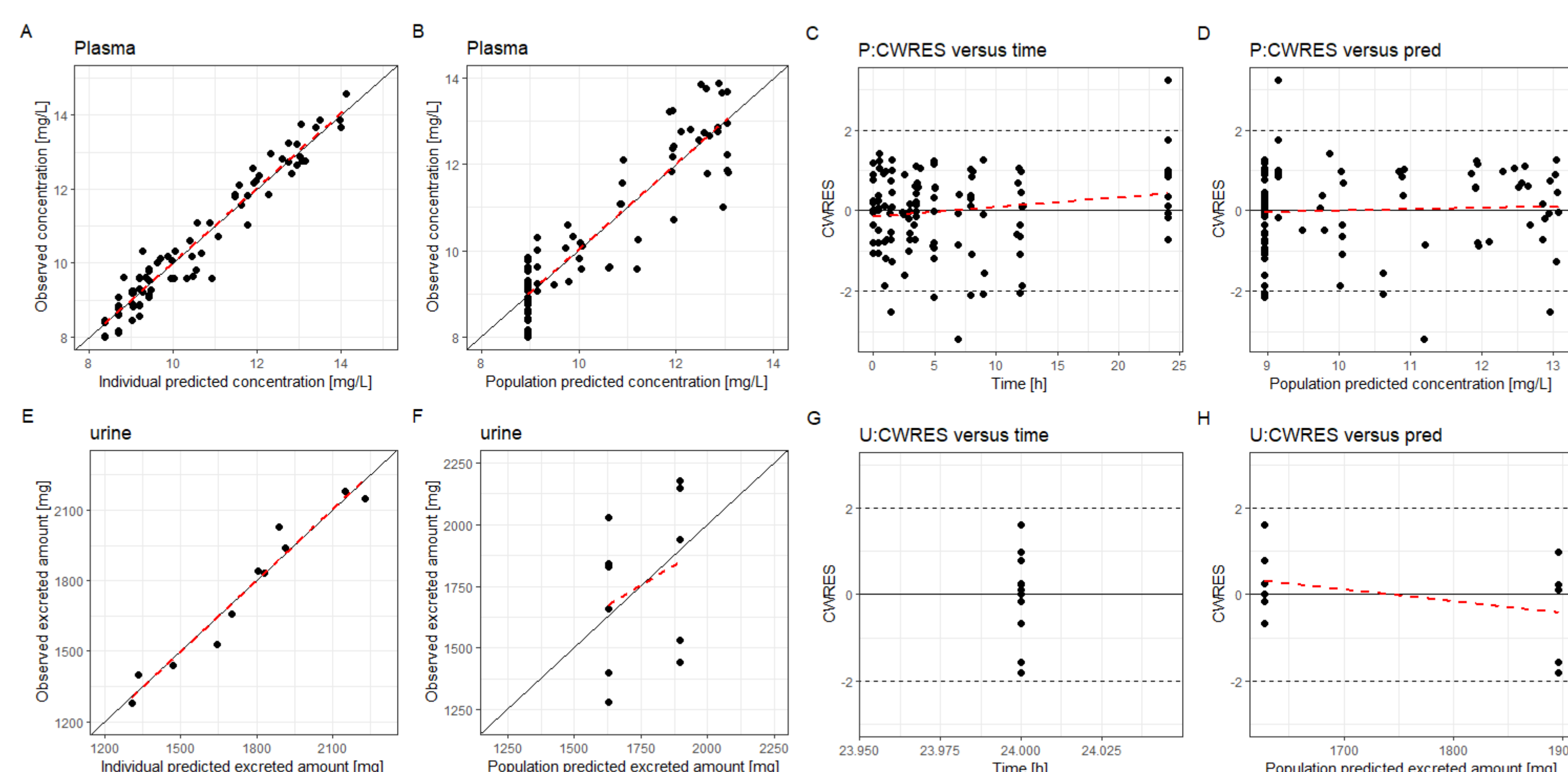


Figure 1 Combined goodness-of-fit plots of creatinine (A – D) plasma concentration and (E – H) urine excreted amount. CWRES, conditional weighted residuals.

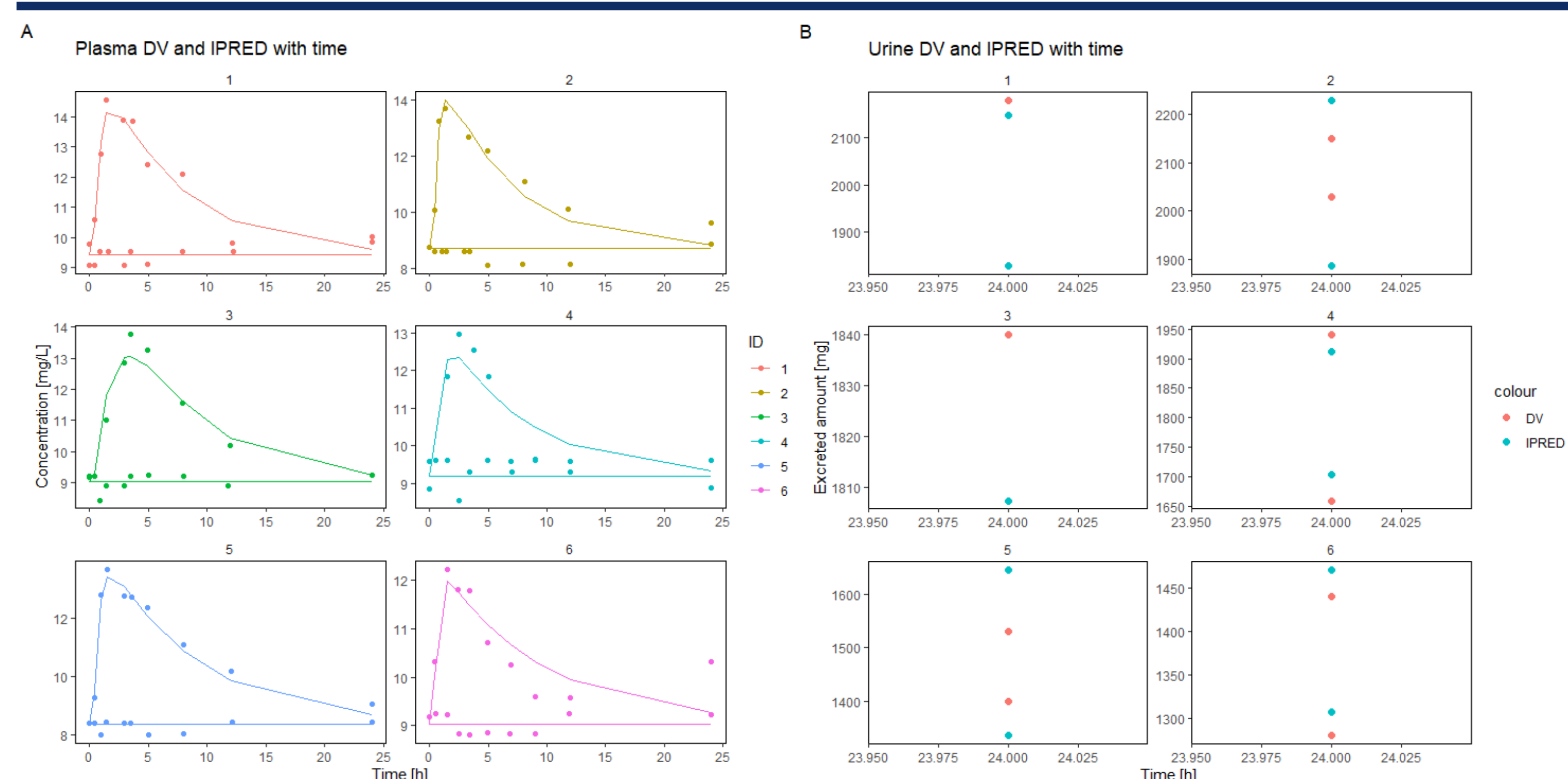


Figure 2 Individual observed and predicted creatinine (A) plasma concentration plots and (B) urine excreted amount.

DV, dependent variable (observation); IPRED, individual prediction.

Finally, the PK parameters including CL, V_d, F1, CGR, and lag time were estimated from the creatinine model (Table). The IIV of V_d was removed as it did not contribute to model improvement. 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 water⁸, which is approximately 60% of the 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 also close to but slightly higher than the fraction of total body water.

The typical value for creatinine generation rate in healthy volunteers was 67.8 mg/h, which is 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^{5,9}. The values for estimated individual creatinine CL were similar to those that have been reported⁶. However, the adjusted “dose” (F1 × 180 mg) for each subject was not consistent with the increased creatinine amount excreted in urine after beef ingestion. This does not exclude the possibility that these discrepancies are related to the accuracy of the raw data; also, no demographic information is available in the publication to better define the PPK model.

Reference

- 1 Stevens LA, Levey AS. J Am Soc Nephrol. 2009, 20(11):2305-13.
- 2 Cockcroft DW, Gault MH. Nephron. 1976, 16(1):31-41.
- 3 Bragadottir G, *et al.* Crit Care. 2013, 17(3): R108.
- 4 Scappaticci GB, Regal RE. World J Hepatol. 2017, 9(3):131-138.
- 5 Ullah S, *et al.* Clin Pharmacol Ther. 2021, 110(5):1240-1249.
- 6 Mayersohn M, *et al.* Br J Clin Pharmacol. 1983, 15(2):227-30.
- 7 <http://getdata-graph-digitizer.com/download.php>
- 8 Pickering JW, *et al.* Crit Care. 2013,17(1): R7.
- 9 Daugirdas JT, Depner TA. Nephrol Dial Transplant. 2017, 32(11):1926-1933.