A physiologically-based pharmacokinetic modeling approach to assess the impact of chronic kidney disease

Eduard Schmulenson[1,2], Jan-Frederik Schlender[1,2], Sebastian Frechen[2], Ulrich Jaehde[1]

[1] Institute of Pharmacy, Clinical Pharmacy, University of Bonn, Bonn, Germany
[2] Systems Pharmacology & Medicine, Bayer AG, Leverkusen, Germany

Background and objectives

Chronic kidney disease (CKD) is a general term for various irreversible disorders of kidney structure or function. Its progression affects nearly all organs and body systems, revealing the need to characterize its systemic nature.

The aim of the study was to develop a physiologically-based pharmacokinetic (PBPK) modeling approach to understand and predict drug exposure in patients suffering from CKD of different stages.

Methods

- A systematic literature search was conducted to identify pathological conditions of CKD patients.
- Within the Open Systems Pharmacology Suite [1] the parametrization of the identified changes was performed according to the CKD classification [2] by calculating fractional changes along the staging system. An incorporated aging database [3] was used to distinguish between age- and disease-related alterations.
- In order to qualify the parametrization, PBPK models of four paradigm compounds (gentamicin, amikacin, zanamivir, gadodiamide) solely eliminated by glomerular filtration were built.
- The mean prediction error (ME) and the root mean squared prediction error (RMSE) were calculated to assess the predictive performance of the diseased-informed fractional changes. RMSE values were compared to uninformed simulations in which solely the glomerular filtration rate was adjusted.

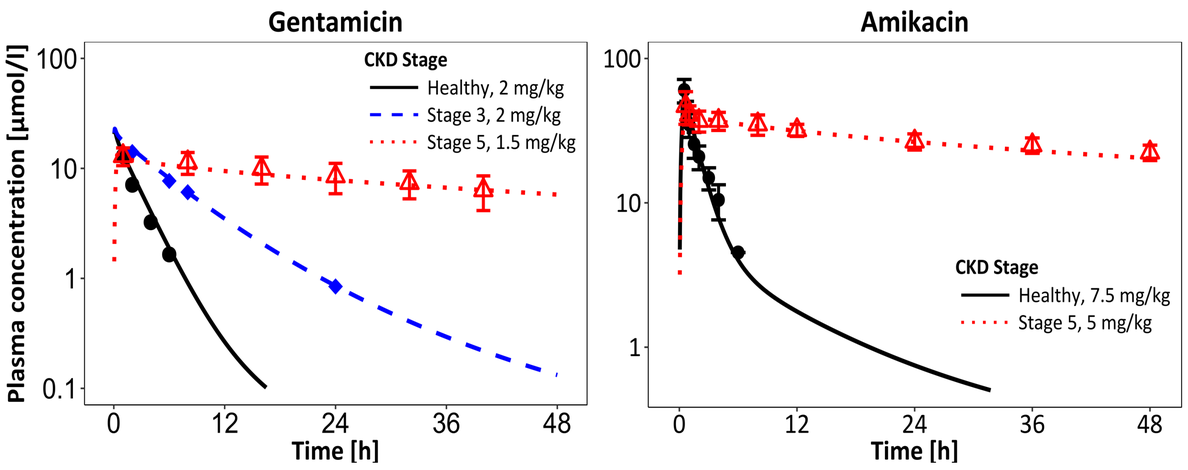
Results I

Weighted fractional changes of the identified parameters during different stages of CKD

Parameter	Mild CKD	Moderate CKD	Severe CKD	ESRD
Renal blood flow	0.843 ± 0.305 (0.662–1.023)	0.616 ± 0.302 (0.557–0.676)	0.566 ± 0.506 (0.326–0.807)	0.146
Kidney volume	0.856 ± 0.245 (0.641–1.071)	0.861 ± 0.357 (0.787–0.936)	0.750 ± 0.346 (0.586–0.914)	0.591 ± 0.277 (0.440–0.742)
Albumin	0.982 ± 0.079 (0.957–1.007)	0.953 ± 0.450 (0.925–0.980)	0.910 ± 0.327 (0.844–0.976)	0.840 ± 0.169 (0.779–0.900)
Alpha-1 acid glycoprotein	NA	1.137 ± 0.282 (0.962–1.312)	1.328 ± 0.341 (1.215–1.441)	2.062 ± 1.272 (1.599–2.525)
Hematocrit	0.942 ± 0.141 (0.870–1.013)	0.901 ± 0.128 (0.877–0.925)	0.816 ± 0.130 (0.782–0.850)	0.625 ± 0.150 (0.586–0.664)
Gastric emptying time	NA	NA	NA	1.671 ± 1.070 (1.371–1.971)

Values are presented as weighted means ± standard deviations with 95% confidence intervals (in parentheses). For renal blood flow in end-stage renal disease (ESRD), no standard deviations were provided in the studies. NA: Not available due to lack of data for these stages.

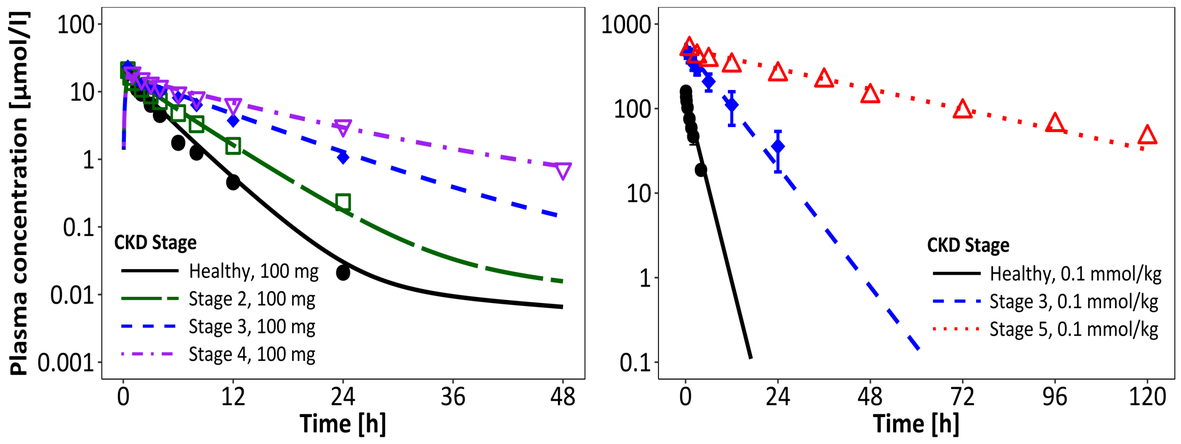
Simulated versus observed plasma concentration-time profiles of gentamicin and amikacin in healthy subjects and CKD patients



Observed data were obtained from [4-7]

Results II

Simulated versus observed plasma concentration-time profiles of zanamivir and gadodiamide in healthy subjects and CKD patients



Observed data were obtained from [8-11].

Predictive performance of the PBPK models

	CKD stage	Gentamicin	Amikacin	Gadodiamide	Zanamivir
ME (Bias)	2	NA	NA	NA	0.175 (-0.246 – 0.596)
	3	-0.006 (-0.017 – 0.004)	NA	0.005 (-0.008 – 0.018)	-0.028 (-0.065 – 0.010)
	4	NA	NA	NA	0.034 (-0.161 – 0.229)
	5	0.008 (0.002 – 0.014)	0.001 (-2×10^{-4} – 0.003)	0.001 (-0.002 – 0.004)	NA
Relative ΔRMSE (Precision)	2	NA	NA	NA	-15%
	3	-18%	NA	-21%	10%
	4	NA	NA	NA	-22%
	5	24%	-2%	-54%	NA

Values are expressed in µmol/l with 95% confidence intervals for ME (in parentheses). NA: Not available

The calculations of ME did not indicate a bias except for the simulation of gentamicin in ESRD patients. Disease-informed simulations of patients with CKD stages 2, 3 and 4 were more precise than the uninformed ones except for one simulation of patients with CKD stage 3 after administration of zanamivir. The precision of the prediction of ESRD patients receiving gadodiamide improved, whereas the simulations of gentamicin and amikacin in ESRD patients did not indicate an improved predictive performance comparing to the respective uninformed simulations.

Conclusions

- The prediction of drug exposure for paradigm compounds eliminated by glomerular filtration for different stages of CKD was mostly accurate and precise.
- The lack of improvement of predictive performance of simulations in ESRD patients suggests that a possible involvement of dialysis and the progression of uremia may require an extension of the model.
- Our PBPK modeling approach provides support for specific considerations regarding clinical trial design and pharmacotherapy for patients suffering from CKD.

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e.schmulenson@uni-bonn.de

Rheinische Friedrich-Wilhelms-Universität Bonn