Population pharmacokinetic model of cefotaxime encompassing time-varying physiopathology: exploration of intra-individual variability of the renal function

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BACKGROUND

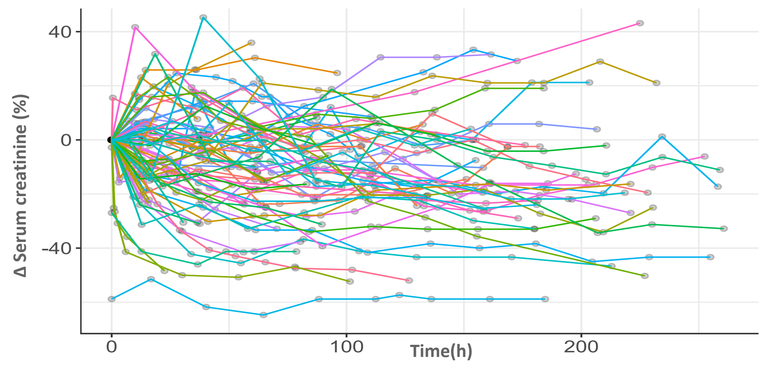
Critically ill patients → Patho-physiological modifications

→ High inter- and intra-individual pharmacokinetic (PK) variability

➡ Supra- or sub-therapeutic concentrations[1]

➡ Need for a personalized drug dosing regimen

***Aim**: To perform a priori dosing adjustment of cefotaxime based on a biomarker model of renal function*



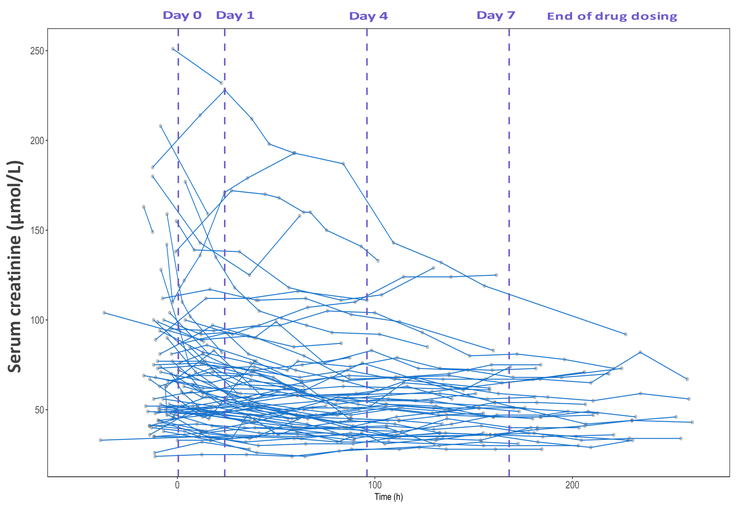
Serum creatinine evolution $\Delta Serum\ creatinine = \left(\frac{Serum\ creatinine_t - Serum\ creatinine_{Baseline}}{Serum\ creatine_{Baseline}}\right) x\ 100$

Grey dots: observed data. Lines: One color per individual

METHODS

STUDY DESIGN

- Prospective, multicenter, observational study (Oct. 2015 - May 2017) in Intensive Care Units (ICU) of Marseille.
- Cefotaxime dosing regimen: loading dose (2g-4g/0.5h) followed by continuous infusion (1-24g/24h) over 7 days



Constant covariates: median [Range] or number

Age (years)	57 [19 – 86]
Male/Female	45/31
Height (cm)	170 [150 - 190]
Weight (kg)	73 [48 – 125]
Body surface area (BSA, m²)	1.87 [1.44 – 2.60]
Body mass index (BMI, kg/m²)	25.25 [16.61 – 44.08]
SAPS_II score	39 [12 – 105]

Time-varying covariates

Hematocrit
Indexed clearance (iCLcr)
SOFA score
Serum albumin
Serum Creatinine
Serum urea
Estimated clearance (eCLcr)

Covariates: Constant covariates collected at inclusion; Time-varying covariates collected every 24h

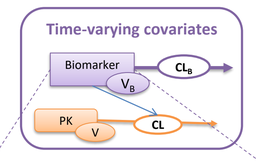
BSA: body surface area determined using the Dubois and Dubois formula, Severity score: SAPS_II Simplified Acute Physiology Score 2; SOFA: Sepsis-related Organ Failure Assessment, estimated creatinine clearance determined using the Cockcroft and Gault formula, indexed clearance creatinine : $iCLcr = \frac{1.73}{BSA} x \left(\frac{Urine\ creatinine\ x\ Urine\ volume}{Serum\ creatine}\right)$

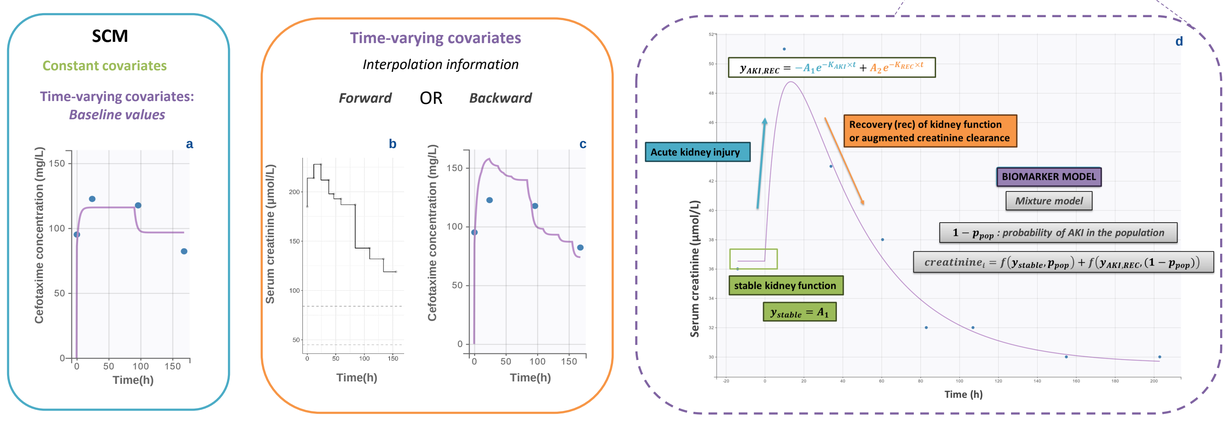
POPULATION PK ANALYSIS PLAN

251 cefotaxime concentrations — **523 serum creatinine concentrations**

BASE MODEL — Structural model (without covariates); Data below the limit of quantification: left-censored

BASELINE COVARIATES → **REGRESSOR COVARIATES** → **BIOMARKER MODEL**





Analysis: MONOLIX® 2023R1 software. a) Cefotaxime concentrations: representative individual fit with baseline serum creatinine. b) Serum creatinine: representative individual fit with backward interpolation. c) Cefotaxime concentrations: representative individual fit with backward interpolation. d): Serum creatinine: representative individual fit with a biomarker model

SCM: stepwise covariate model procedure with forward (α =0.05) and backward steps (α =0.01), power and exponential covariate relationships tested
Purple line: individual prediction, blue dot: observed data, black line: backward interpolation, blue dot: observed data, dashed grey line: normal values

RESULTS

POPULATION PK MODEL OF CREATININE

Parameter	Base model Estimates	Base model RSE (%)[SHR](%)	Final model Estimates	Final model RSE (%)[SHR](%)
		Fixed effects		
A_1 (µmol/L)	**72.7**	6.09	**75.67**	4.88
A_2 (µmol/L)	**114**	10.8	**105**	7.28
K_{AKI} (1/h)	**0.021**	30.7	**0.025**	22.1
K_{REC} (1/h)	**0.022**	18.7	**0.023**	13.9
P_{pop}	**0.77**	2.08	**0.73**	2.47
Covariate effects				
βA_1_urea			**0.39**	24.1
βA_2_urea			**0.91**	14.8
		Random effects		
IIV A_1	**0.41**	11.4 [-9.01]	**0.35**	11.4 [-6.4]
IIV A_2	**0.81**	10.4 [3.24]	**0.51**	10.4 [0.406]
IIV K_{AKI}	**1.47**	19.3 [11.7]	**1.1**	19.3 [13.6]
IIV K_{REC}	**0.99**	18.2 [7.37]	**0.84**	18.2 [-7]
IV P_{pop}	**0.26**	16.1 [3.59]	**0.28**	16.1 [-5]
ε	**0.075**	4.23	**0.075**	4.49

Parameter estimates
RSE relative standard error
SHR shrinkage
AKI: Acute kidney injury
REC: recovery of kidney function
Green: baseline covariates
IIV inter-individual variability,
ε proportional residual error

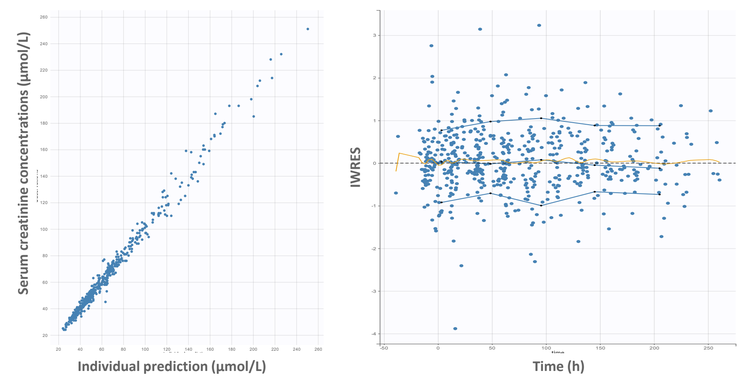
➔ Intra-individual variation of probability of constant or first order model

- Detection of changes between normal renal function and AKI
- Detection of changes between AKI and recovery of renal function

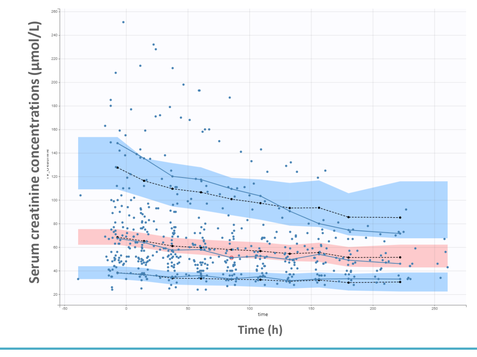
➔ Serum urea concentration explains part of the IIV of creatinine levels

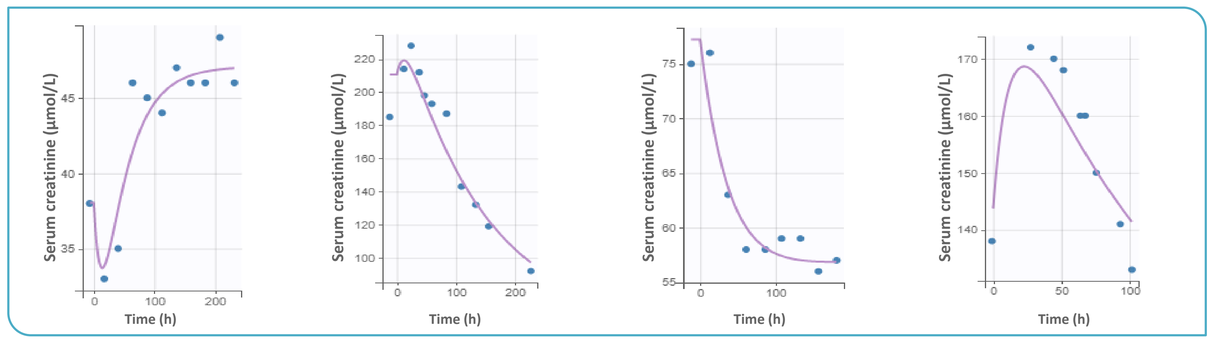
MODEL EVALUATION

Goodness of fit plots
Orange line: spline, dashed black line: 90% prediction interval, IWRES: individual weighted residuals, dashed line: theorical mean, blue line: empirical percentiles



Visual Predictive Check
blue solid lines: 5th,50th and 95th percentiles of observed data, shaded areas: 95% confidence interval of the simulated 50th (red), 5th and 95th(blue) percentiles respectively





Representative individuals for creatinine with biomarker model
a,b,c,d: purple line: individual prediction of serum creatinine model, blue dot: observed data

➔ Good fit, no bias
➔ Prediction of next creatinine concentrations

CONCLUSION

- **High inter- and intra-variability of renal function in ICU patients was partly explained by time-varying creatinine covariate**
- **A predictive model of serum creatinine evolution has been developed**
- **We will combine a cefotaxime Pop-PK model with the creatinine biomarker model**

Contact
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[1] Smekal, A.-K.; Furebring, M.; Eliasson, E.; Lipcsey, M. Low Attainment to PK/PD-Targets for β-Lactams in a Multi-Center Study on the First 72 h of Treatment in ICU Patients. Sci. Rep. 2022, 12 (1), 21891. .
[2] Waikar, Sushrut S., et Joseph V. Bonventre. « Creatinine Kinetics and the Definition of Acute Kidney Injury ». Journal of the American Society of Nephrology : JASN 20, no 3 (mars 2009): 672 79.