FACULTY OF MEDICINE AND HEALTH SCIENCES

OPTIMISED AMOXICILLIN/CLAVULANIC ACID DOSING IN PATIENTS ON CHRONIC HIGH-FLUX HAEMODIALYSIS

Kelly De Schuyter[1], Pieter J Colin[2], Floris Vanommeslaeghe[1], Sigurd Delanghe[1], Pieter De Cock[3], Peter De Paepe[4], Wim Van Biesen[1], Sunny Eloot[1]

[1]Department of Nephrology, Ghent University Hospital, Belgium [2]Department of Anesthesiology, University Medical Center Groningen, University of Groningen, The Netherlands [3]Department of Pharmacy and Heymans Institute of Pharmacology, Ghent University Hospital, Belgium [4]Heymans Institute of Pharmacology, Ghent University Hospital, Belgium

Background

Amoxicillin/clavulanic acid (AMC) is frequently prescribed to haemodialysis patients, using empirical dosing regimens. The elimination pathway of both compounds differs, making dosing recommendations in end-stage kidney disease challenging.

Pharmacokinetic data of AMC in this patient population are scarce.

The study aim was to optimise dosing regimens of AMC in patients on chronic high-flux haemodialysis.

Methods

- Monocentric prospective observational study including 26 patients on high-flux haemodialysis, receiving different per oral (p.o.) and intravenous (iv) AMC dosing.

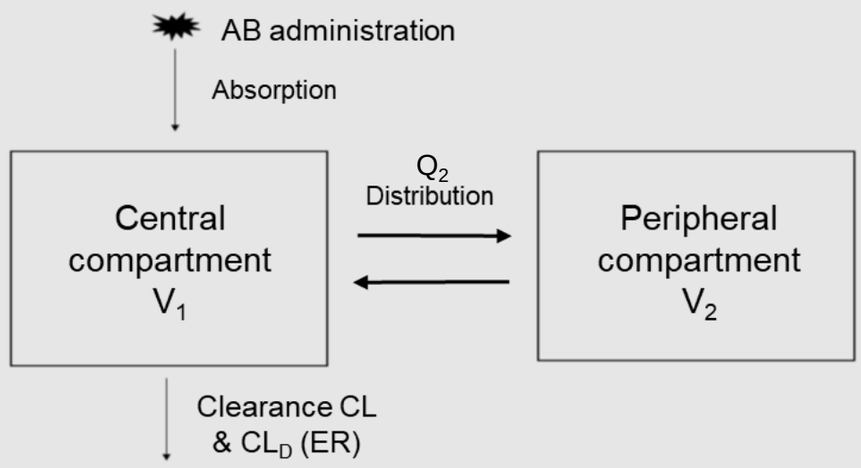
- Blood sampling inter- and intradialytic (n=247) to measure concentrations of amoxicillin (AMX) and clavulanic acid (CLA).

- Development of a population pharmacokinetic (PK) model using non-linear mixed effects fitting the observed time-concentration data. Different covariates were added in a stepwise fashion and, if improving the model, were retained.

- Monte Carlo simulations to simulate different dosing strategies over 1 week. The PK/pharmacodynamic (PD) target of AMX was set at 50%t>MIC=8mg/L. For CLA no PK/PD target is established, thus only occurrence of accumulation was studied.

Results

Measured concentration data for both compounds were best fitted by a two-compartmental model with between-subject variability for distribution volume of central compartment (V_1), total body clearance (CL) and dialysis extraction ratio (ER).



ER was high, 74% and 78% for, respectively, AMX and CLA.

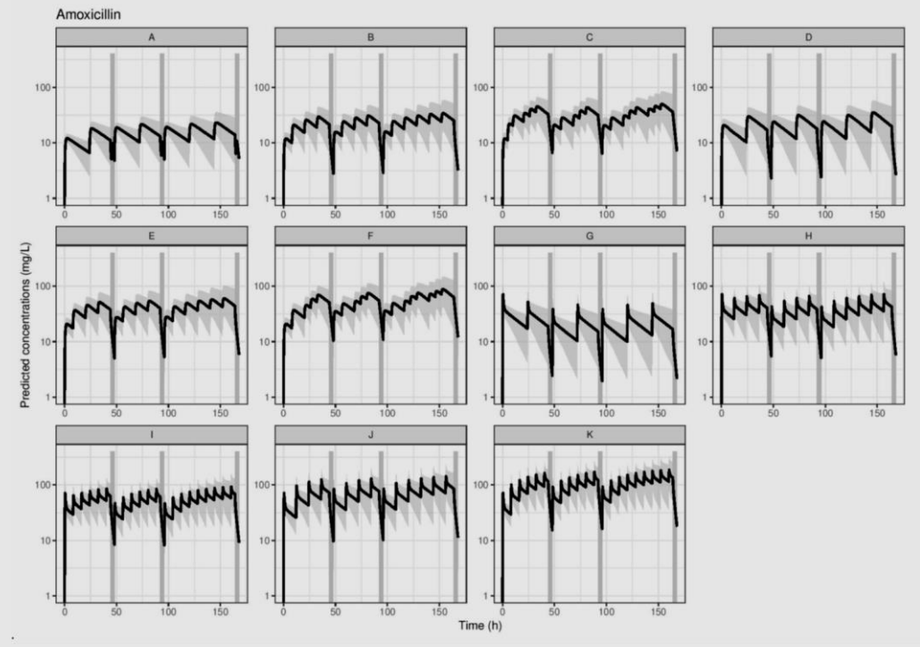
Within an individual patient, estimates for V_1 and ER were highly correlated.

For AMX, residual diuresis and blood flow were kept as covariates, and residual diuresis was associated with CL (p=0.027), which was 12mL/min and 22mL/min for a residual diuresis of respectively <500mL/24h and ≥500mL/24h.

AMX	CLA
$CL\ (mL\ min^{-1}) = \begin{cases} 12.1\ (18) \cdot e^{\omega_2} & Urine\ volume\ (mL\ 24h^{-1}) < 500 \\ 21.5\ (17) \cdot e^{\omega_2} & Urine\ volume\ (mL\ 24h^{-1}) > 500 \end{cases}$	$CL\ (mL\ min^{-1}) = 64.4\ (21) \cdot e^{\omega_4}$
$V1\ (L) = 11.3\ (12) \cdot e^{\omega_1}$	$V1\ (L) = 16.2\ (14) \cdot e^{\omega_1}$
$ER\ (\%) = \frac{e^{1.96\ (12) - 0.488\ (25) \cdot \frac{FLOW\ (mL\ min^{-1}) - 115}{100}}}{1 + e^{1.96\ (12) - 0.488\ (25) \cdot \frac{FLOW\ (mL\ min^{-1}) - 115}{100}}} \cdot e^{\omega_3}$	$ER\ (\%) = \frac{e^{1.29\ (17)}}{1 + e^{1.29\ (17)}} \cdot e^{\omega_3}$
$V2\ (L) = 12.5\ (7.0)$	$V2\ (L) = 7.35\ (26)$
$Q2\ (mL\ min^{-1}) = 180\ (27)$	$Q2\ (mL\ min^{-1}) = 66.7\ (67)$

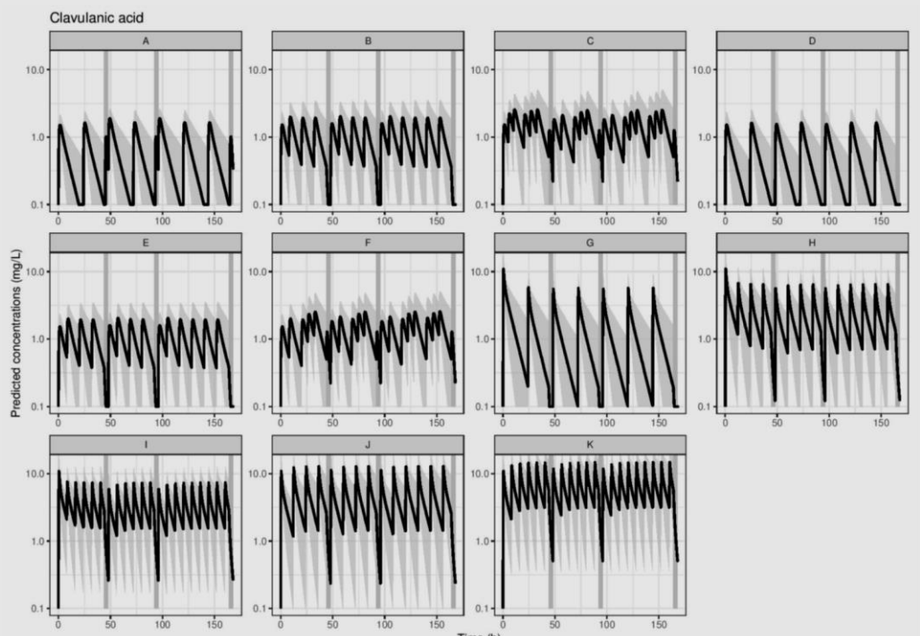
All **simulated AMX dosing** regimens achieved adequate PD target attainment.

Accumulation of AMX was observed in all simulations.



all with administration post HD
A: 500mg/125mg p.o. q24h (plus 500mg/125mg during HD); **B:** 500mg/125mg p.o. q12h; **C:** 500mg/125mg p.o. q8h (administration pre- and post-HD); **D:** 875mg/125mg p.o. q24h; **E:** 875mg/125mg p.o. q12h; **F:** 875mg/125mg p.o. q8h (administration pre- and post-HD); **G:** starting dose 1000mg/200mg iv, maintenance dose 500mg/100mg iv q24h; **H:** starting dose 1000mg/200mg iv, maintenance dose 500mg/100mg iv q12h; **I:** starting dose 1000mg/200mg iv, maintenance dose 500mg/100mg iv q8h; **J:** 1000mg/200mg iv q12h; **K:** 1000mg/200mg iv q8h.

CLA simulations showed only minor accumulation.



CONCLUSION: We propose a dosing strategy of p.o. 500mg/125mg q8h or iv 500mg/100mg q8h after an iv loading dose of 1000mg/200mg to achieve adequate exposure of CLA while minimising AMX accumulation. Considering high dialyser clearance, dosing should be scheduled post-dialysis.

Contact

sunny.eloot@ugent.be

Universiteit Gent
@ugent
Ghent University

GHENT UNIVERSITY

UZ GENT