Plasma concentration of orally administered amoxicillin and clindamycin in patients receiving haemodialysis

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Objectives: In the randomized controlled trial PANTHEM, the prophylactic effect of oral amoxicillin or clindamycin is investigated in patients receiving chronic haemodialysis (HD). However, data on plasma concentrations of these antibiotics during HD are sparse. This study aims to determine if the plasma concentration of amoxicillin and clindamycin is sufficient during HD after oral administration of amoxicillin and clindamycin at three different time intervals prior to the HD procedure.

Methods: Adult patients receiving chronic HD were investigated twice with an interval of at least 7 days starting with either a tablet of 500/125 mg amoxicillin/clavulanic acid or a tablet of 600 mg clindamycin. Patients were randomized to take the antibiotics either 30, 60 or 120 min prior to the HD procedure. Plasma antibiotic concentrations were measured at start, midway and at the end of HD. A lower threshold was set at 2.0 mg/L for amoxicillin and at 1.0 mg/L for clindamycin. In addition, a population pharmacokinetic (PK) analysis was performed, assessing PTA.

Results: In the amoxicillin cohort (*n* = 37), 84% of patients and 95% of all plasma amoxicillin concentrations were above or at the threshold throughout the dialysis procedure. In the clindamycin cohort (*n* = 33), all concentrations were above the threshold throughout the dialysis procedure. Further, in all patients, the mean plasma concentration of both amoxicillin and clindamycin across the HD period was well above the threshold. Finally, the PK model predicted a high PTA in the majority of patients.

Discussion: In patients on chronic HD, oral administration of amoxicillin/clavulanic acid (500/125 mg) or clindamycin (600 mg) within 30–120 min prior to HD leads to a sufficient prophylactic plasma concentration across the HD period.

Introduction

Bacteraemia is frequent and often a serious problem in individuals receiving haemodialysis (HD).[1,2] The incidence rate varies between 18/100 and 40/100 patient-years, and according to the Danish National Microbiology Database the most frequent causal bacteria at first-time bacteraemia in HD are *Staphylococcus aureus* (33%), other staphylococci (19%), *Escherichia coli* (14%) and enterococci (7%).[3,4] Many initiatives have been undertaken to decrease the infection rate but so far with limited success.[5] In the on-going PANTHEM study (ClinTrials.gov NCT05248620), the prophylactic effect of oral

amoxicillin and clindamycin (in the case of side effects to amoxicillin) on severe infections in patients receiving chronic HD is investigated. The present study was undertaken as a pilot study prior to PANTHEM in order to document if a single oral dosage of the two antibiotics taken within the time interval of 30–120 min prior to the start of HD provides sufficient prophylactic antibacterial plasma concentration during the HD procedure.

Materials and methods

Study cohort

Patients were recruited from two dialysis centres in Eastern Denmark. All patients aged 18 years or older with end-stage kidney disease (ESKD) treated with chronic HD via a central venous catheter (CVC) or arteriovenous (AV) fistula were screened for participation. Exclusion criteria were inability to give informed consent, known intolerance to β-lactam antibiotics or clindamycin, active infection treated with antibiotics <7 days prior to inclusion, breastfeeding or pregnancy. Data on the cause of kidney failure, HD filter type, HD flow, HD time, height, weight, smoking status, alcohol consumption and comorbidities were recorded.

Study design

The study followed a crossover design. All patients were planned to participate in the study twice, once for each type of antibiotic, with a minimum of 1 week between the two study days. After inclusion, the patients were randomized to one of three time intervals of antibiotic administration: 30, 60 or 120 min prior to the expected start of the dialysis session. The patients were allocated to the same time interval for amoxicillin and clindamycin administration.

Antibiotic administration

The antibiotics were administered orally, and doses were 500/125 mg of amoxicillin/clavulanic acid and 600 mg of clindamycin, consistent with the formulations and dosages used in the PANTHEM study. Doses of antibiotics were based on the national and international guidelines on treatment of infections in HD patients.[6] We aimed to reach a plasma concentration >2.0 mg/L amoxicillin and >1.0 mg/L clindamycin according to breakpoints from EUCAST, and the HPLC method's lower limit of quantification (LOQ).[7,8] Prophylactic plasma concentrations were defined as plasma concentrations above these values.

Blood sample management and analysis

Blood samples were collected in EDTA tubes at the start of dialysis, halfway through dialysis and at the end of dialysis. The halfway point was individually set in each dialysis session, based on the patients' most current dialysis times. The exact time of blood sample collection was noted on a label on the EDTA tubes, along with study identification number, type of antibiotic and randomization time. The blood samples were centrifuged within 4 hours from the sample time in a standard laboratory centrifuge at 20°C at a relative centrifugal force (RCF) of 1200 g for 5 min. A minimum of 2 mL of the supernatant plasma was transferred to labelled cryogenic tubes using a pipette, and stored at −80°C until the time of plasma concentration analysis. Samples were stored at the dialysis centres until the end of the study and transported on dry ice in a temperature-controlled vehicle to the Department of Clinical Biochemistry at Aarhus University Hospital, Denmark, for further analysis.

Plasma concentrations of amoxicillin and clindamycin were measured by HPLC with UV detection. The LC was carried out on an Agilent Series 1290 HPLC system with a diode array detector (Agilent Technologies, Denmark). Analytical separation was performed on a Poroshell 120 EC-C18 column (2.7 μm, 2.1×100 mm) (Agilent Technologies,
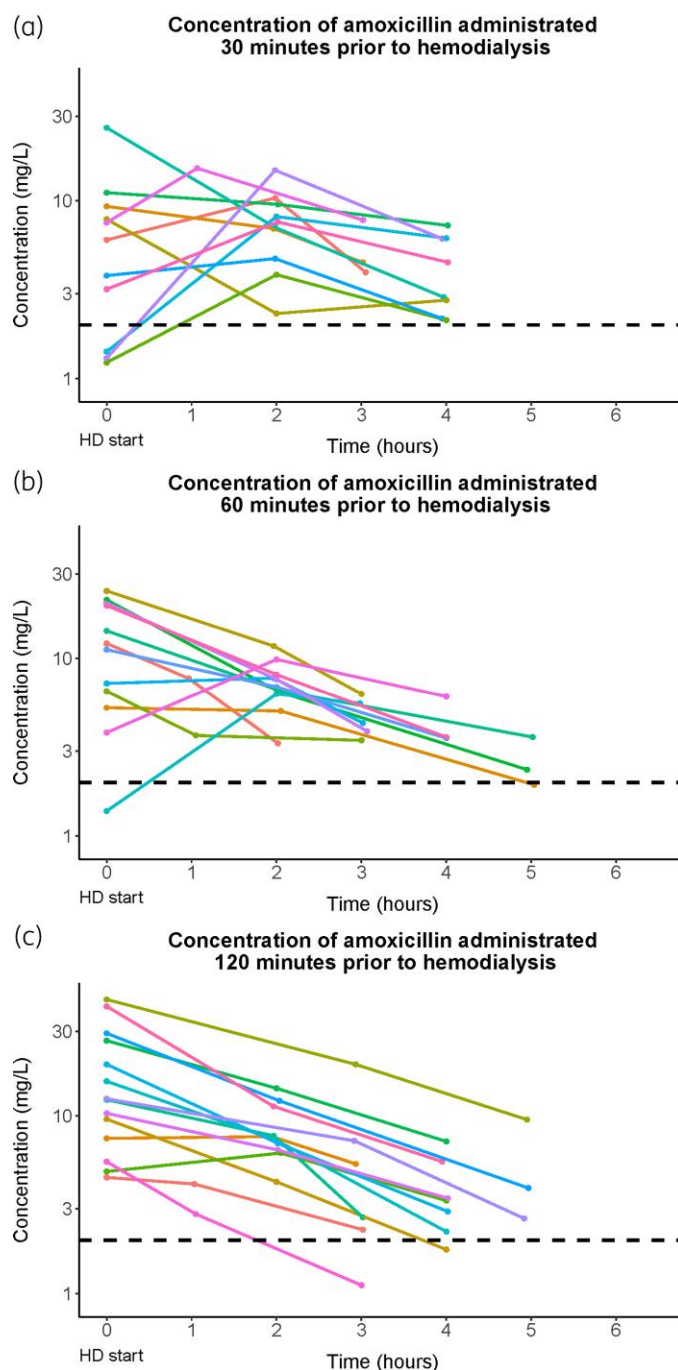

Figure 1. (a–c) The graphs display the measured plasma concentration of amoxicillin (y-axis, log) in each study patient in the 30 min group (a), 60 min group (b) and 120 min group (c). Each patient has three measured plasma concentration levels, displayed as dots, one at the beginning of HD, one in the middle of HD, and one at the end of HD. The x-axis displays the time from the start of HD. The threshold of 2.0 mg/L of amoxicillin is displayed as a horizontal dashed line. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Denmark) at a temperature of 28°C (amoxicillin) or 40°C (clindamycin) controlled by a column heater. The LOQ was 0.5 mg/L for amoxicillin, with a total imprecision coefficient of variance (CV%) of 18.7%. The

Solli *et al.*

Table 1. Baseline characteristics for patients in each randomization group

Characteristic	Randomization		
	30 min	60 min	120 min
Total (*n*)	12	15	15
AMX (*n*)	11	12	14
CLI (*n*)	9	13	11
Gender (*n*, male)	7	9	10
Age (years), median (IQR)	64.5 (56–80)	63 (58–75)	73 (60–76)
Type of ESKD (*n*)			
Vascular/hypertensive	5	6	3
Diabetic	2	1	2
Glomerulonephritis	2	4	2
Tubulointerstitial	—	2	—
Polycystic	3	1	2
Unknown/other	—	1	6
HD via:			
CVC (*n*)	9	12	9
AV fistula (*n*)	3	3	6
Dialysis time (min)			
AMX dialysis time, median (IQR)	239 (210–240)	238 (180–240)	240 (181–241)
CLI dialysis time, median (IQR)	238 (181–240)	240 (181–241)	240 (237–241)
Blood flow (mL/min)			
AMX blood flow, median (IQR)	300 (295–320)	300 (285–329)	298 (285–314)
CLI blood flow, median (IQR)	299 (280–325)	293 (206–300)	300 (290–310)
Ultrafiltration (mL)			
AMX ultrafiltration, median (IQR)	975 (300–1700)	950 (0–1800)	500 (0–2150)
CLI ultrafiltration, median (IQR)	1100 (550–2403)	1100 (250–1950)	750 (0–1752)
Filter (*n*)			
FX80	—	—	1
FX100	1	4	1
FX1000	4	4	6
Revaclear 400	6	6	5
Polyflux170H	1	—	—
Polyflux210H	—	1	2
Lifestyle			
Alcohol consumption (*n*/week)			
None	6	13	6
1–7	4	—	6
8–14	1	2	2
15–21	1	—	—
Smoking status (*n*)			
Non-smoker	9	13	10
Occasionally	2	2	—
Max. 10 cig./day	1	—	2
Max. 20 cig./day	—	—	2
E-cig.	—	—	1
Comorbidities (*n*)			
MI	2	3	3
CHF	3	6	4
AFLI/AFLU	3	3	6
PVD	2	3	1
Stroke	4	2	—
COLD	1	3	1
Rheumatic disease	—	5	2

Continued

Table 1. *Continued*

Characteristic	Randomization		
	30 min	60 min	120 min
Liver disease	2	—	1
Diabetes	3	4	3
Diabetes complications (*n*)			
Nephropathy	2	3	3
Neuropathy	2	2	1
Retinopathy	2	3	1
PVD	1	—	—
Heart disease	—	—	1

AFLI, atrial fibrillation; AFLU, atrial flutter; AMX, amoxicillin; CHF, congestive heart failure; cig., cigarettes; CLI, clindamycin; COLD, chronic obstructive lung disease; MI, myocardial infarction; PVD, peripheral vascular disease.

LOQ was 1 mg/L for clindamycin, with a total imprecision of 15.6%. The methods are described by Greibe *et al.*[8]

Statistical analysis

Analyses were performed separately for amoxicillin and clindamycin. Each combination of HD timepoint and randomization (oral dose offset 30, 60, 120 min) is defined as a group. The plasma concentrations were log_{10} transformed prior to analysis. Effect across groups were tested with two-way ANOVA (HD timepoint versus randomization including interactions) using repeated measures correction (3 HD timepoints per patient). The residual error of the ANOVA model was used to estimate SD of the mean for each group. Results were back-transformed to non-log when reported and hence reported means are geometric means. The geometric mean concentrations including CI estimates were computed. Furthermore, the lower 20% probability bound for each group assuming log-normal distribution was computed. We used SAS 9.4 for Windows (SAS Institute Inc, NC, USA) and R, version 4.2.2. (R Core Team, 2022, R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses.

Population pharmacokinetic (PK) analysis

We developed a population PK model for each antibiotic using non-linear mixed-effects modelling in MATLAB SimBiology (Version 9.13, R2022b, The MathWorks Inc., Natick, MA, USA). Because the concentration–time curves showed a mono-exponential decline [Figures 1(a–c) and 2(a–c)], we evaluated the data using one-compartment models with first-order absorption and first-order elimination. Models were evaluated and compared by goodness-of-fit plots, objective function value (defined as −2× loglikelihood), and accuracy and reliability of the parameter estimates. To investigate the PTA in patients with varying time intervals and HD duration, we performed Monte-Carlo simulations of the final models. First, PK parameters were sampled for 10 000 patients. Second, we simulated the models with the sampled parameters and computed concentration–time curves for each patient. Finally, we determined the PTA, defining the targets as plasma concentrations above 2 mg/L of amoxicillin and 1 mg/L of clindamycin during the entire HD period. Details on the population PK analysis are provided in Appendix S1 (available as Supplementary data at *JAC* Online).

Ethics

The study was conducted in accordance with the Helsinki Declaration of Ethical Principles for Medical Research and approved by the Danish Committee on Health Research Ethics (H-20026735). Written informed consent was obtained from all participants.

Results

Patient characteristics

A total of 42 patients were included [median age 63.5 years (IQR 58–76), 62% male]. Twelve patients were randomized to the 30 min group, 15 patients to the 60 min group, and 15 patients to the 120 min group (Figure 3). In the amoxicillin group, five patients were excluded; one patient withdrew consent to the amoxicillin part, and in four patients, one of the three plasma concentrations could not be determined from the HPLC chromatograms due to unexplained interference around the peak retention time, causing inconclusive outcome. In the clindamycin group, nine patients were excluded; three patients withdrew consent to the clindamycin part, and in six patients, one of the three plasma concentrations could not be determined due to unexplained interference, as outlined above. Consequently, the final dataset used for ANOVA and geometric means consisted of 37 patients with concentration results at all three timepoints for amoxicillin and 33 patients with concentration results at all three timepoints for clindamycin (Figure 3). For the population PK modelling, all available concentrations were included. Thus, 119 concentrations of amoxicillin from 41 patients and 108 concentrations of clindamycin from 38 patients were included in the modelling.

Patient characteristics of the three randomization groups, including HD blood flow, ultrafiltration and comorbidities, can be found in Table 1. In the total study cohort, the main causes of ESKD were vascular/hypertensive disease (*n*=14; 33%), glomerulonephritis (*n*=8; 19%), polycystic kidney disease (*n*=6; 14%) and diabetes mellitus (*n*=5; 12%). The patients were mainly non-smokers (*n*=32; 76%) and had a low level of alcohol consumption of 0–7 units per week (*n*=35; 84%). The most commonly used HD filter types were Revaclear 400 (*n*=19; 46%) and FX1000 (*n*=14; 33%). Technical details on the HD procedure and filters are described in Table S1. Thirty patients (71%) had a CVC and the remaining 12 patients (29%) had an AV fistula. Cardiac disease and diabetes mellitus were the most frequent comorbidities, with 13 (32%) patients with atrial fibrillation or atrial flutter, 13 patients (32%) with congestive heart disease, and 10 patients (24%) with diabetes mellitus.
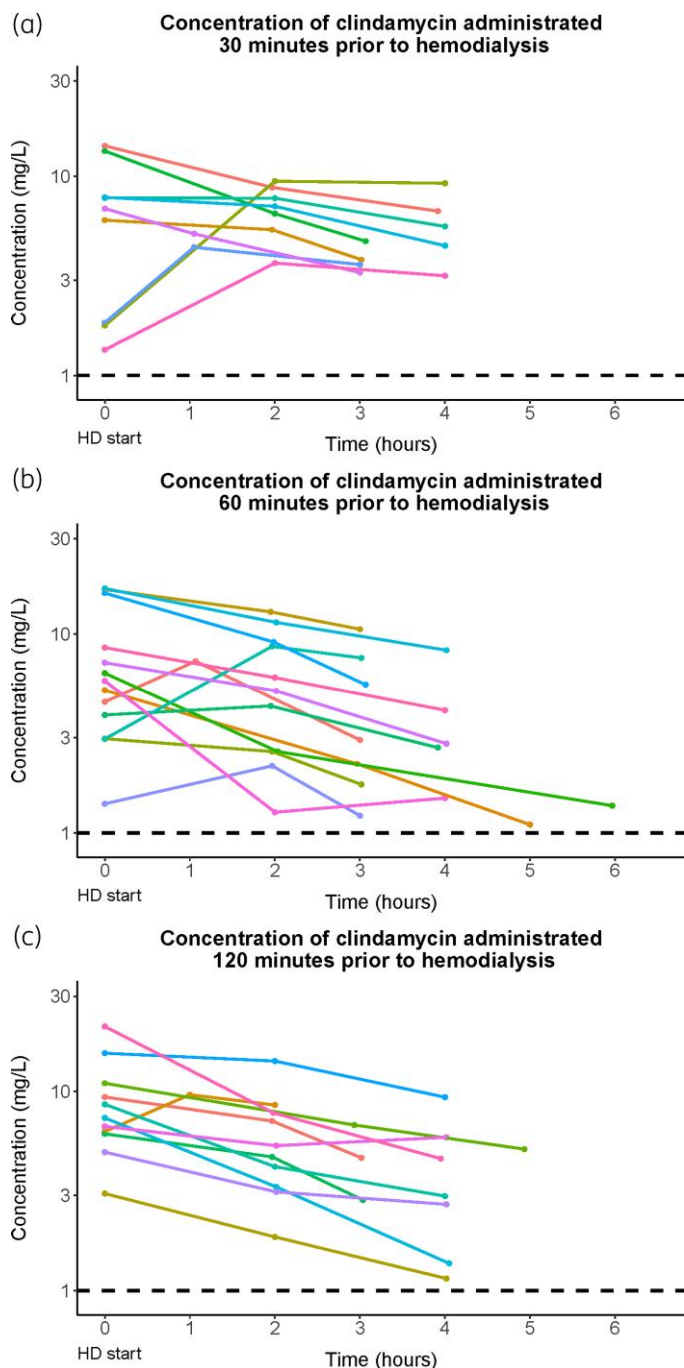
(a)

(b)

(c)

Figure 2. (a–c) The graphs display the measured plasma concentration of clindamycin (*y*-axis, log) in each study patient in the 30 min group (a), 60 min group (b) and 120 min group (c). Each patient has three measured plasma concentration levels, displayed as dots, one at the beginning of HD, one in the middle of HD, and one at the end of HD. The *x*-axis displays the time from the start of HD. The threshold of 1.0 mg/L of clindamycin is displayed as a horizontal dashed line. This figure appears in colour in the on-line version of *JAC* and in black and white in the print version of *JAC*.

Plasma concentration of amoxicillin

In patients administered oral amoxicillin 30 min prior to the HD procedure, plasma amoxicillin concentration was <2.0 mg/L in

three patients at the start of HD, but then increased and stayed above the threshold for the remainder of HD. In the other patients, plasma amoxicillin was above the threshold level throughout the HD [Figure 1(a)]. In patients, administered oral amoxicillin 60 min prior to the HD procedure, plasma amoxicillin concentration was <2.0 mg/L at the start of HD in one patient, but then increased and stayed above the threshold for the remainder of HD. In one patient, plasma concentration was at the threshold at the end after 5 h HD. All other concentrations were ≥2.0 mg/L throughout HD [Figure 1(b)]. In patients administered oral amoxicillin 120 min prior to the HD procedure, plasma amoxicillin concentration at the start of HD was well above 2.0 mg/L [Figure 1(c)]. A decreasing concentration slope was observed in all patients and two patients had a concentration <2.0 mg/L at the end of HD. In 84% of patients, all plasma amoxicillin concentrations were above the threshold throughout the dialysis procedure, and 95% of all amoxicillin concentrations were above the threshold.

The overall geometric mean amoxicillin concentration was well above the threshold level in all three randomization groups, with a geometric mean of 5.21 mg/L (SD±1.59) in the 30 min group, 6.33 mg/L (SD±1.42) in the 60 min group and 6.92 mg/L (SD±1.77) in the 120 min group (Figure 4). Overall, a large variation in obtained plasma concentrations was observed. The HD blood flow ranged from 219 to 395 mL/min and the geometric mean amoxicillin concentration decreased by 0.023 mg/L (95% CI −0.057 to 0.011 mg/L, $P = 0.17$) for every 1 mL/min increase in HD blood flow (Figure S1). Still, none of the individual geometric mean concentrations were below the threshold of 2 mg/L.

Plasma concentration of clindamycin

The plasma concentrations of clindamycin administered orally 30 min [Figure 2(a)], 60 min [Figure 2(b)] or 120 min [Figure 2(c)] prior to the HD procedure were all >1.0 mg/L ($n = 33$; 100%).

The overall geometric mean clindamycin concentration was also well above the threshold level in all three randomization groups, with a geometric mean of 5.26 mg/L (SD±1.52) in the 30 min group, 4.36 mg/L (SD±1.97) in the 60 min group and 5.41 mg/L (SD±1.72) in the 120 min group (Figure 4). Also for clindamycin, a large variation in obtained plasma concentrations was observed. The HD blood flow ranged from 250 to 348 mL/min and the geometric mean concentration of clindamycin decreased with 0.0017 mg/L (95% CI −0.048 to 0.045, $P = 0.94$) for every 1 mL/min increase in HD blood flow (Figure S2). None of the individual geometric mean concentrations were below the threshold of 1 mg/L.

Population PK analysis

Population PK models with first-order absorption and first-order elimination adequately described the data, and the parameter estimates are presented in Table 2. The Monte-Carlo simulations confirmed that oral administration of amoxicillin/clavulanic acid (500/125 mg) or clindamycin (600 mg) within 30–120 min prior to HD leads to sufficient prophylactic plasma concentrations in most patients (Tables 3 and 4). Goodness-of-fit plots and visual predictive check plots are shown in Figures S3–S5.
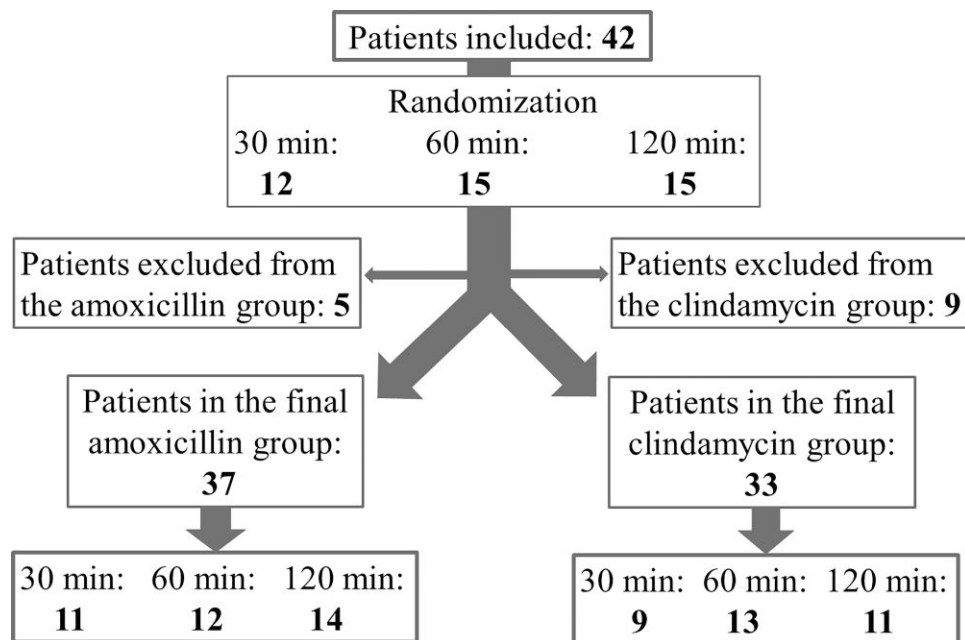
Figure 3. The flowchart shows the inclusion and randomization of study subjects as well as the final study cohort in each study arm.

Table 2. Population PK estimates

		AMX	CLI
Population mean (95% CI)	V/F (L)	20.6 (12.6–33.6)	57.7 (45.3–73.4)
	CL/F (L/h)	10.3 (8.6–12.5)	14.2 (11.1–18.2)
	K_a (h^{-1})	0.97 (0.55–1.73)	1.92 (1.27–2.92)
Inter-individual variability (%CV)	V/F	90.1	61.4
	CL/F	55.1	64.8
	K_a	NE	NE
Correlation	η_V, η_{CL}	0.67	0.60
Residual variability (mg/L)	SD[a]	1.91	1.50

All estimated PK parameters are log-normally distributed.
AMX, amoxicillin; CLI, clindamycin; F, bioavailability; K_a, absorption rate coefficient; NE, not estimated.
[a]SD of the additive residual error.

Table 3. PTA for amoxicillin during the entire HD period

	Dialysis duration (%)		
Time interval (min)	3 h	4 h	5 h
30	96.0	85.5	62.9
60	94.0	75.7	52.2
120	75.7	52.2	31.9

Table 4. PTA for clindamycin during the entire HD period

	Dialysis duration (%)		
Time interval (min)	3 h	4 h	5 h
30	99.2	96.3	90.4
60	98.2	93.7	86.6
120	93.7	86.6	77.6

Discussion

The principle finding of this study was that oral administration of standard doses of both amoxicillin/clavulanic acid and clindamycin administered in the time interval 30–120 min before the start of HD provides a sufficient prophylactic antibacterial plasma concentration of both amoxicillin and clindamycin during the dialysis procedure.

Infections are persistently a major risk factor in patients receiving chronic HD.[9] Contamination of the vascular access can cause serious infections with severe complications, including sepsis, endocarditis, osteomyelitis and spondylodiscitis.[1] Patients receiving dialysis are predisposed to infections due to several factors such as old age, diabetes, accumulation of uraemic toxins, and an impaired immune system.[10] Additionally, the use of temporary or permanent catheters as vascular access and the frequent skin perforation in the use of AV fistulae are acknowledged as the most likely port of entrance for bacteraemia and sepsis.[11] Amoxicillin/clavulanic acid and clindamycin are frequently used antibiotics in patients in need of chronic HD, mainly to treat respiratory infections and wound infections.

Gram-positive bacteria are found as the microbial agents in more than 65% of bacteraemias in patients on chronic HD, and the highest risk of bacteraemia is found during the first 6 months
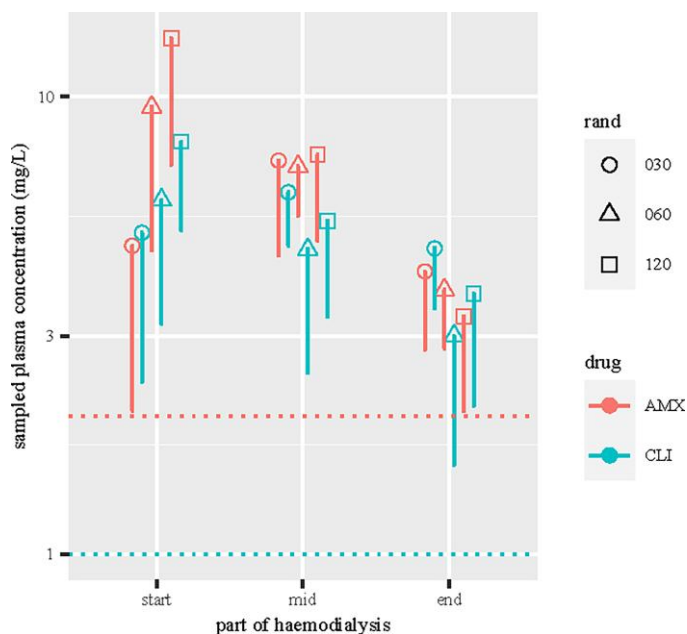
Figure 4. Geometric mean of amoxicillin (red lines, displayed first in each pair of lines) and clindamycin (blue lines, displayed second in each pair of lines) with the lower 20% probability bound for each randomization group (30, 60 and 120 min). The minimum threshold levels are shown in dotted lines, red is the amoxicillin threshold of 2 mg/L (the higher dotted line) and blue is the clindamycin threshold of 1 mg/L (the lower dotted line).

after initiation of HD with CVC as vascular access.[4,10,11] Therefore, the PHANTEM study was initiated to explore if prophylactic oral administration of amoxicillin/clavulanic acid and clindamycin can diminish the risk of severe infections during this initial time interval in patients on chronic HD. The antibiotic tablets are administered as a single oral dose before each HD. However, information on plasma amoxicillin and clindamycin concentration during HD in relation to the time of oral amoxicillin/clavulanic acid and clindamycin administration before the procedure remains largely unexplored. In one study, the influence of various degrees of renal insufficiency i.e. glomerular filtration rate (GFR) <5 to 75 mL/min/1.73 m^2 on the pharmacokinetics of amoxicillin and clavulanic acid was assessed after one tablet of amoxicillin/clavulanic acid 500/125 mg or IV 1000/200 mg was given 6 h prior to a standard HD of 4 h.[12] At the end of the HD period, 10 h after the administration of antibiotics, no clavulanic acid was measurable, but amoxicillin was. However, in the time intervals of the present study, both antibiotics were clearly within the prophylactic range. Additionally, systemic availability was independent of renal function. In another older study, 150 mg clindamycin was given orally to four patients just before HD started.[13] Peak plasma concentration was reached after 45 min, and after 6 h, plasma concentration varied between 0.29 and 0.59 mg/L. In contrast to these older investigations, the present study was carried out using updated dialysis methods including high blood flow, i.e. ≥300 mL/min, in more than 40% of the patients, which is known to yield a higher extraction rate of amoxicillin.[14] Although there was a slight decrease in geometric mean amoxicillin concentration with increasing HD blood flow in our study, as expected

from a drug with mainly renal elimination, it was not a statistically significant decrease, and more importantly none of the geometric mean concentrations were below the predefined lower threshold level. Nevertheless, our data align with these older studies. We demonstrate that plasma concentration of both amoxicillin and clindamycin are well above the threshold level after oral administration 30–120 min before HD. To our knowledge, this is the largest study on plasma amoxicillin and clindamycin concentrations during HD after oral administration, and the only study providing real data within decades.

Finally, our results are in accordance with those found in a recent study by Schuyter *et al.*[15] They also used Monte-Carlo simulations using varying dosing regimens of amoxicillin (dosed at least twice a day orally or IV), demonstrating high PTAs. In our study, most patients received HD lasting 3–4 h, during which PTAs were acceptable, but PTA decreased to <50% for 5 h HD in patients administered amoxicillin with the time interval of 120 min. For clindamycin, PTA was 78%–99% for all HD durations, and for all time intervals. Since no prophylactic breakpoints for amoxicillin or clindamycin are known in patients on chronic HD, we used clinical breakpoints. Prophylactic breakpoints will be lower, and may actually be substantially lower. This only provides further evidence for a sufficient prophylactic dosage regimen in the PANTHEM study.

Limitations

Due to limited data in the absorption phase, the inter-individual variability of the absorption parameters could not be estimated. In cases of slow individual absorption, the PTA by administration 30 min prior to HD may decrease, and the PTA by administration 120 min prior to HD may increase. Another limitation is that dialysate was not collected for drug determination. However, it should be kept in mind that the primary goal of our study was to establish that the oral prophylactic standard doses of amoxicillin/clavulanic acid and clindamycin achieved the predefined target concentration coverage with the predefined time lag between administration and the beginning of the HD sessions.

Conclusions

In patients receiving chronic HD with either a CVC or an AV fistula as vascular access, oral administration of a single tablet of amoxicillin/clavulanic acid (500/125 mg) or clindamycin (600 mg) taken within the time interval of 30–120 min prior to the start of HD, provided sufficient prophylactic plasma concentrations of the antibiotic throughout the whole HD period.

Funding

Transparency declarations

We declare that the results presented in this paper have not been published previously in whole or part. The authors declare no conflict of interest directly related to the content of this paper. H.B. reports grants from

Author contributions

Conception or design: N.E.B., E.G., H.P.H., L.B., R.B., E.H.L., C.M., E.F., L.Ø., C.T.P., H.B., K.I,. M.C. Acquisition, analysis, or interpretation of data: M.B., L.B., R.B., C.N.S., K.P.K., J.H.K., N.E.B., A.C.F., E.H.L., E.G. Drafting: N.E.B., C.N.S., K.P.K. Revision for important intellectual content: M.B., J.H.K., E.G., H.P.H., L.B., R.B., M.C., E.H.L., C.M., A.C.F., E.F., L.Ø., C.T.P., H.B., K.I. Final approval of the version to be published: M.B., N.E.B., C.N.S., K.P.K., J.H.K., E.G., H.P.H., L.B., R.B., M.C., E.H.L., C.M., A.C.F., E.F., L.Ø., C.T.P., H.B., K.I. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: N.E.B., C.N.S., K.P.K., J.H.K., E.G., H.P.H., L.B., R.B., M.C., E.H.L., C.M., A.C.F., E.F., L.Ø., C.T.P., H.B., K.I., M.B.

Supplementary data

Appendix S1, Figures S1 to S5 and Table S1 are available as Supplementary data at *JAC* Online.

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