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Short Communication

Impact of high-flux haemodialysis on the probability of target attainment for oral amoxicillin/clavulanic acid combination therapy

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ABSTRACT

Clearance of small molecules such as amoxicillin and clavulanic acid is expected to increase during high-flux haemodialysis, which may result in lower concentrations and thus reduced efficacy. To date, clearance of amoxicillin/clavulanic acid (AMC) during high-flux haemodialysis remains largely unexplored. Using published pharmacokinetic parameters, a two-compartment model with first-order input was simulated to investigate the impact of high-flux haemodialysis on the probability of target attainment (PTA) of orally administered AMC combination therapy. The following pharmacokinetic/pharmacodynamic targets were used to calculate the PTA. For amoxicillin, the time that the free concentration remains above the minimum inhibitory concentration (MIC) of ≥50% of the dosing period (≥50%$fT_{>MIC}$) was used. For clavulanic acid, the time that the free concentration was >0.1 mg/L of ≥45% of the dosing period (≥45%$fT_{>0.1\ mg/L}$) was used. Dialysis clearance reported in low-flux haemodialysis for both compounds was doubled to represent the likely clearance during high-flux haemodialysis. Monte Carlo simulations were performed to produce concentration–time profiles over 10 days in 1000 virtual patients. Seven different regimens commonly seen in clinical practice were explored. When AMC was dosed twice daily, the PTA was mostly ≥90% for both compounds regardless of when haemodialysis commenced. When administered once daily, the PTA was 20–30% for clavulanic acid and ≥90% for amoxicillin. The simulations suggest that once-daily orally administered AMC in patients receiving high-flux haemodialysis may result in insufficient concentrations of clavulanic acid to effectively treat infections, especially on days when haemodialysis occurs.

1. Introduction

Optimal dosing of antibiotics is vital in the context of antibiotic resistance. In the haemodialysis setting, determining an optimal dosage regimen for many antibiotics can be challenging. Prescribers need to take into account not only the effect of renal failure on antibiotic clearance, but also the potential for enhanced clearance during haemodialysis. Unfortunately, many of the primary studies exploring antibiotic pharmacokinetics in patients receiving haemodialysis were conducted in low-flux haemodialysis. However, low-flux dialysers have now largely been replaced by the more permeable high-flux dialysers [1]. Of concern is the paucity of published data exploring the effects of high-flux dialysers on the clearance of antibiotics, particularly older antibiotics that are still commonly prescribed. One such antibiotic is the β-lactam/β-lactamase inhibitor combination amoxicillin/clavulanic acid (AMC).

In Australia, this antibiotic combination is one of the recommended first-line treatments for mild diabetic foot infection [2], an infection that many patients with end-stage renal disease (ESRD) are at risk of developing. The pharmacokinetics of AMC in ESRD and low-flux haemodialysis have been described previously [3–5]. Amoxicillin is predominantly renally eliminated, with ca. 70% of the administered dose recovered unchanged in the urine [6]. It is therefore not surprising that clearance is decreased in ESRD. However, only 35% of orally administered clavulanic acid is excreted unchanged in the urine [6]. As clavulanic acid undergoes both renal and non-renal elimination, its clearance is affected to a lesser degree in ESRD. However, it is well documented that amoxicillin and clavulanic acid are removed during low-flux haemodialysis [3]. Owing to the increased permeability of high-flux dialysers, it is highly likely that both compounds would be cleared to a greater extent during high-flux haemodialysis, which may impact its therapeutic effect. Therefore, the aim of this study was to evaluate the possible impact of high-flux haemodialysis on the probability of target attainment (PTA) of AMC combination therapy using Monte Carlo simulation.

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2. Methods

2.1. Pharmacokinetics and model specifications

A two-compartment model with first-order input was used both for amoxicillin and clavulanic acid as described previously [7]. The final pharmacokinetic parameters included in the model were non-renal clearance (CL_{NR}), dialysis clearance (CL_D), volume of distribution of the central compartment (V_c), volume of distribution of the peripheral compartment (V_p) and intercompartmental clearance (CL_{IC}). As published data for CL_D in high-flux haemodialysis are not available, this parameter was assumed to be double that reported in low-flux haemodialysis [8]. This assumption was based on reports of other compounds with low protein binding and similar molecular weight exhibiting an approximate two- to three-fold increase in dialysis clearance in high-flux haemodialysis compared with low-flux haemodialysis [9–12]. Bioavailability (F), unbound fraction (fu) and absorption rate constant (k_a) both for amoxicillin and clavulanic acid were also included in the final model. The between-subject variability, reported as a coefficient of variation, was included for CL_{NR}, CL_D, V_c and F. It was assumed that all simulated patients had no residual renal function and a weight of 70 kg. All parameters used in the model are listed in Table 1.

Monte Carlo simulation was performed using Berkeley Madonna v.8.3.13 (http://www.berkeleymadonna.com/). Concentration–time profiles for amoxicillin and clavulanic acid were simulated for 1000 virtual patients over a 10-day period. Across this 10-day period, each patient received 4 h of high-flux haemodialysis occurring on Days 2, 5, 7 and 9 to reflect usual haemodialysis schedules (i.e. haemodialysis occurring thrice weekly). In Berkeley Madonna v.8.3.13, elimination via dialysis was achieved by creating a separate elimination pathway for dialysis that could be turned 'on' and 'off' at the specified time and for a specified duration. The concentration–time profiles were simulated for several clinically prescribed dosage regimens with dialysis occurring at different times in relation to the dose (Table 2). Regimens A–D are often prescribed to patients receiving haemodialysis in Australia, whereas regimens E–G explore 'real-life' scenarios where patients miss certain doses on days when haemodialysis occur. The current recommended dosage regimen for AMC combination therapy in patients receiving haemodialysis in Australia is 500/125 mg twice daily [2].

Table 1
Previously published pharmacokinetic parameters included in the model.

Parameter	Amoxicillin	Clavulanic acid
CL_{NR} (%CV) [3]	0.864 L/h (33%)	2.616 L/h (33%)
CL_D (%CV) [a]	9.26 L/h (13%)	11.14 L/h (15%)
V_c (%CV) [7]	13.7 L (38.7%)	7.6 L (34.7%)
V_p [7]	13.7 L	11.6 L
CL_{IC} [7]	15.6 L/h	10.4 L/h
F (%CV) [4]	0.69 (10%)	0.61 (47%)
fu [8]	0.8	0.7
k_a [6]	1.48 h^{-1}	2.8 h^{-1}

CL_{NR}, non-renal clearance; CV, coefficient of variation; CL_D, dialysis clearance; V_c, volume of distribution of central compartment; V_p, volume of distribution of peripheral compartment; CL_{IC}, intercompartmental clearance; F, bioavailability; fu, unbound fraction; k_a, absorption coefficient.
[a] High-flux CL_D was assumed to be double CL_D reported in low-flux haemodialysis.

Table 3
European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for various micro-organisms for amoxicillin/clavulanic acid [14].

Micro-organism	Susceptible	Resistant
Streptococcus pneumoniae	MIC ≤ 0.5 mg/L	MIC > 2 mg/L
Enterobacteriaceae (including *Escherichia coli*)	MIC ≤ 8 mg/L	MIC > 8 mg/L
Enterococcus spp.	MIC ≤ 4 mg/L	MIC > 8 mg/L
Haemophilus influenzae	MIC ≤ 2 mg/L	MIC > 2 mg/L
Staphylococcus aureus	MIC ≤ 2 mg/L	MIC > 2 mg/L

MIC, minimum inhibitory concentration.

2.2. Pharmacokinetic/pharmacodynamic (PK/PD) indices for amoxicillin and clavulanic acid

Amoxicillin exhibits time-dependent killing where therapeutic outcomes correlate with the amount of time the free drug concentration remains above the minimum inhibitory concentration (MIC) of the causative pathogen ($fT_{>MIC}$), with optimum killing when $fT_{>MIC}$ is ≥50% of the dosing interval [13]. The MICs evaluated for this study were 1, 2, 4 and 8 mg/L as per the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints for AMC for various micro-organisms (Table 3) [14]. Micro-organisms were considered to be resistant to AMC if the MIC was >8 mg/L [14].

Currently, there is no accepted PK/PD index for clavulanic acid. Only one study has suggested that the free concentration of clavulanic acid should be >0.1 mg/L ($fT_{>0.1\ mg/L}$) for ≥45% of a 24-h

Table 2
Probability of target attainment (PTA) of pharmacokinetic/pharmacodynamic targets[a] for amoxicillin and clavulanic acid for different dosage and dialysis regimens.

Regimen	Dosage regimen (amoxicillin/clavulanic acid)	Dialysis prescription	Indication of whether PTA ≥ 90%								
			Amoxicillin				Clavulanic acid	Combined			
			MIC 1 mg/L	MIC 2 mg/L	MIC 4 mg/L	MIC 8 mg/L		MIC 1 mg/L	MIC 2 mg/L	MIC 4 mg/L	MIC 8 mg/L
A	875 mg/125 mg once daily	Dialysis starts 8 h after morning dose is administered (i.e. afternoon dialysis)	✓	✓	✓	✓	✘	✘	✘	✘	✘
B	875 mg/125 mg once daily	Dialysis starts 2 h after morning dose is administered (i.e. morning dialysis)	✓	✓	✓	✘	✘	✘	✘	✘	✘
C	500 mg/125 mg twice daily	Afternoon dialysis	✓	✓	✓	✓	✓	✓	✓	✓	✓
D	500 mg/125 mg twice daily	Morning dialysis	✓	✓	✓	✘	✓	✓	✓	✓	✘
E	500 mg/125 mg twice daily	Morning dose is administered at the end of morning dialysis	✓	✓	✓	✓	✓	✓	✓	✓	✓
F	500 mg/12 5 mg twice daily	Morning dose is administered at the end of morning dialysis, but night dose is missed	✓	✓	✓	✓	✓	✓	✓	✓	✓
G	500 mg/125 mg twice daily	Morning dose is missed on dialysis days	✓	✓	✓	✓	✘	✘	✘	✘	✘

MIC, minimum inhibitory concentration.
Note: ✓ denotes PTA ≥ 90%, ✘ denotes PTA < 90%.
[a] For amoxicillin, the time that the free concentration remains above the MIC of ≥50% of the dosing period (≥50%$fT_{>MIC}$) was used; for clavulanic acid, the time that the free concentration was >0.1 mg/L of ≥45% of the dosing period (≥45%$fT_{>0.1\ mg/L}$) was used.