Thrice-weekly temocillin administered after each dialysis session is appropriate for the treatment of serious Gram-negative infections in haemodialysis patients

Stefaan J. Vandecasteele [a,1], Ana C. Miranda Bastos [b,c,d,1], Arnaud Capron [e,f], Anne Spinewine [d], Paul M. Tulkens [b,c], Françoise Van Bambeke [b,c,*]

[a] Nephrology and Infectious Diseases Department, AZ Sint-Jan Brugge-Oostende AV, AV Ruddershove 10, 8000 Brugge, Belgium
[b] Pharmacologie cellulaire et moléculaire (LDRI/FACM), Av. E. Mounier 73, bte B1.73.05, B-1200 Brussels, Belgium
[c] Center for Clinical Pharmacy, Université catholique de Louvain, Av. E. Mounier 73, bte B1.73.05, B-1200 Brussels, Belgium
[d] Clinical Pharmacy Research Group (LDRI/CLIP), Av. E Mounier 72, bte 01.72.02, B-1200 Brussels, Belgium
[e] Clinical Chemistry Department, Cliniques Universitaires St Luc, Av. Hippocrate 10, B-1200 Brussels, Belgium
[f] Louvain Center for Toxicology and Applied Pharmacology, Université catholique de Louvain, Av. E. Mounier 53, Box B1-52-12, B-1200 Brussels, Belgium

ARTICLE INFO

ABSTRACT

In patients with end-stage renal disease (ESRD) treated with intermittent haemodialysis, a limited number of antibiotics have been studied for their suitability for parenteral administration after dialysis sessions only in a thrice-weekly regimen. Temocillin is a β-lactam antibiotic with a long half-live and enhanced activity against most Gram-negative bacteria, including extended-spectrum β-lactamase-producers, thus making it an ideal candidate for use in this setting. This study aimed to evaluate the reliability of thrice-weekly parenteral temocillin in haemodialysis patients by characterising the pharmacokinetics of total and free temocillin. Free and total temocillin concentrations were determined with a validated HPLC method in 448 samples derived from 48 administration cycles in 16 patients with ESRD treated with intermittent haemodialysis and temocillin. Pharmacokinetics were non-linear partly due to saturation in protein binding. Median clearance and half-life for the free drug during intradialysis and interdialysis periods were 113 mL/min vs. 26 mL/min and 3.6 h vs. 24 h, respectively, with dialysis extracting approximately one-half of the residual concentration. The free temocillin concentration remained >16 mg/L (MIC_{90} threshold for most Enterobacteriaceae) during 48%, 67% and 71% of the dosing interval for patients receiving 1 g q24h, 2 g q48h and 3 g q72h, respectively, suggesting appropriate exposure for the two latter therapeutic schemes. Temocillin administered on dialysis days only in a dosing schedule of 2 g q48h and 3 g q72h is appropriate for the treatment of serious and/or resistant Gram-negative infections in patients with ESRD undergoing intermittent haemodialysis. These doses are higher than those previously recommended.

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1. Introduction

Patients with end-stage renal disease (ESRD) suffer significantly higher mortality than the general population, with values 48 times higher in the 20- to 44-year-old age group and 7 times higher in the over 75 years age group [1]. Infections, especially septicaemia and pulmonary infections, are the second leading cause of death in this population [2]. Historically, Gram-positive infections were predominant in the haemodialysis population [3]. However, in the past few years a concerning rise in infections caused by Gram-negative pathogens with increasing rates of drug resistance in dialysis patients has fuelled a renewed interest in this field [3–5]. Parenteral antibiotics that permit thrice-weekly dosing after each dialysis session are preferable because they can reduce hospitalisation duration and costs as well as enhance quality of life [1]. Whilst this common practice is supported by strong clinical data for the treatment of Gram-positive infections with cefazolin [6] or vancomycin [7], the antibiotics most frequently administered on dialysis days only for the treatment of Gram-negative infections
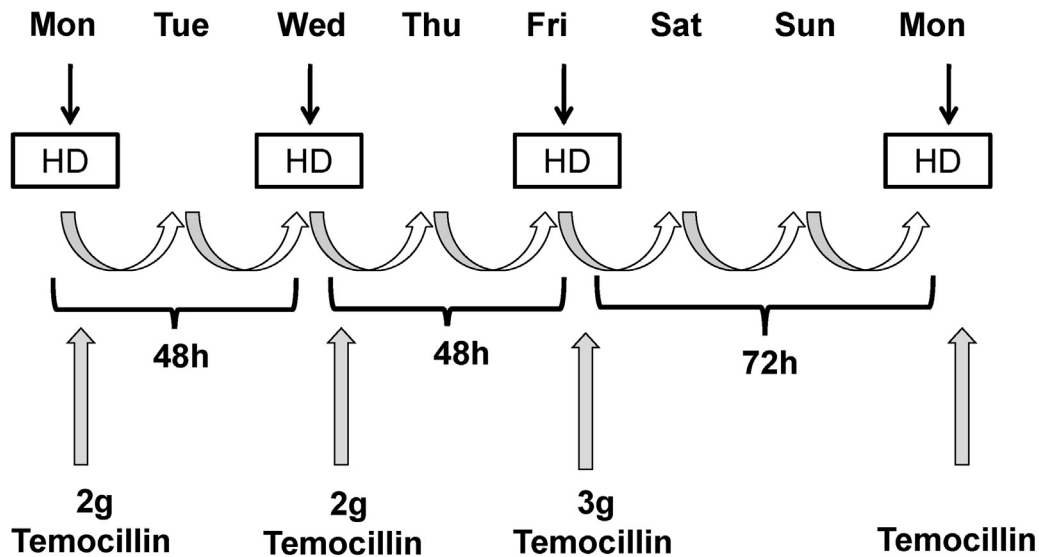
Fig. 1. Study design. Temocillin was administered by intravenous bolus immediately after the haemodialysis (HD) session. This figure represents a typical end-stage renal disease patient who undergoes HD thrice weekly, on Mondays, Wednesdays and Fridays. The study protocol foresaw the administration of 1, 2 or 3 g for a dosing interval of 24 h, 48 h or 72 h, respectively. The 24-h interdialytic period is not represented in this figure.

have been shown to lead to inadequate exposure (ceftazidime) [8] or unacceptable toxicity (aminoglycosides) [9].

In this setting, temocillin (an intravenous β-lactam antibiotic with a long half-life [10]) constitutes a valuable candidate as an anti-Gram-negative agent in settings where *Pseudomonas aeruginosa* can be excluded [11]. Moreover, the remarkable stability of temocillin against most β-lactamases, including AmpC, extended-spectrum β-lactamases and most carbapenemases, fuelled a recent interest in this antibiotic as a carbapenem-sparing agent [12]. For time-dependent antibiotics such as β-lactams, the probability of therapeutic success is related to the proportion of the dosing interval during which their free concentration exceeds the minimum inhibitory concentration (MIC) of the offending organism [13]. Therefore, their elimination rate will be a critical determinant in their overall efficacy and will dictate the frequency of their administration.

Little is known, however, about temocillin pharmacokinetics/pharmacodynamics in ESRD patients as well as its dialysability with contemporary high-flux haemodialysers [11,14]. Its primarily renal elimination (mainly by glomerular filtration in unchanged form) and long serum half-life compared with other β-lactams [10] render it suitable to be administered on haemodialysis days only. This study aimed: (i) to characterise the pharmacokinetics and dialytic clearance of temocillin in patients undergoing intermittent haemodialysis; (ii) to determine the fraction of the dosage interval during which the free concentration exceeds the MIC of target organisms if administered after each haemodialysis session; and (iii) to propose and validate a dosing schedule on dialysis days only.

2. Methods

2.1. Study design and population

This prospective, single-centre (tertiary-care renal unit in Belgium), open-label, non-randomised clinical study characterised the pharmacokinetics of temocillin administered on dialysis days only using a 1-, 2- or 3-day dosing interval. Patients undergoing intermittent haemodialysis for ESRD for whom treatment with temocillin was indicated according to the attending physician were eligible for the study. Exclusion criteria were: (i) age <18 years; (ii) estimated life expectancy of <24 h due to major co-morbid

conditions; (iii) pregnancy; (iv) IgE-mediated allergy to penicillins; or (v) patients not giving informed consent. The attending physician determined the indication for temocillin use as well as its duration. The dialysis schedule was according to clinical state of the art of the study site and was not altered for the purpose of the study. Urea clearance (*Kt/V*) was >1.2; blood flow rates were set as high as possible with a maximum of 400 mL/min and pre-pump pressures not lower than −250 mmHg, unless there was a confirmed disequilibrium syndrome. Blood flow rate, dialysate flow rate, time and other components of the dialysis prescription were determined according to the clinical need by the attending physician. The dialysers used were FX80 and FX10 (Fresenius Medical Care AG & Co., Bad Homburg, Germany).

2.2. Temocillin

Temocillin (Eumedica SA, Brussels, Belgium) was used throughout the study period. Temocillin (1–3 g) was dissolved in 25–75 mL of water for injection and was administered intravenously over a 5-min period directly after dialysis. In analogy with what is done with cefazolin [15], a fixed temocillin dosing schedule of 1 g for a 24-h (1-day) dosing interval, of 2 g for a 48-h (2-day) dosing interval and of 3 g for a 72-h (3-day) dosing interval was used (Fig. 1).

2.3. Sample collection

Blood samples were drawn: (i) just before and at 0.5, 3, 6, 12, 20 (before dialysis) and 24 h (at the end of dialysis) after temocillin administration when patients were dialysed with a 1-day interval; (ii) just before and at 0.5, 3, 6, 12, 24, 36, 44 (before dialysis) and 48 h (at the end of dialysis) after temocillin administration when patients were dialysed with a 2-day interval; or (iii) just before and at 0.5, 3, 6, 12, 24, 36, 48, 68 (before dialysis) and 72 h (at the end of dialysis) after temocillin administration when patients were dialysed with a 3-day interval. Additional blood samples were taken 1, 2, 3 and 4 h after the start of dialysis. All samples were taken from an arterial or venous catheter. Serum samples obtained by centrifugation after blood clotting were frozen at −80 °C immediately after sampling.

2.4. Temocillin assays

Temocillin total serum concentrations were assayed by high-performance liquid chromatography (HPLC) with ultraviolet detection [16]. Free concentrations were determined by HPLC tandem mass spectrometry after ultrafiltration of serum samples ($2000 \times g$, $25\,^{\circ}$C, 20 min) with an Amicon® Ultra-15 device (NMWL 30 K; Merck-Millipore, Merck KGaA, Darmstadt, Germany) as validated previously [17]. In brief, reverse-phase chromatography was performed using as mobile phase a gradient varying linearly from 100% 0.1% formic acid in water to 100% 0.1% formic acid in acetonitrile with a 0.3 mL/min flow rate. Molecular ions were detected in positive electrospray ionisation mode. In addition, the following parameters were also recorded in all patients: time of drug administration; duration of dialysis and of the interdialytic interval; dry body weight (determined at the end of dialysis); mean blood flow; filter used; total volume dialysed; total ultrafiltration; urea and creatinine concentration; patient age; and dialysis vintage (length of time on dialysis).

2.5. Data analysis

Key pharmacokinetic (PK) parameters during the interdialytic period [volume of distribution (V_d), clearance (CL), area under the concentration–time curve (AUC) and elimination half-life ($t_{1/2}$)] were estimated using the non-compartmental 'PK' package (PK version 1.3-2, CRAN) for R 3.0.2 using RStudio 0.98.501 (RStudio, Boston, MA). During the dialysis period, the following parameters were estimated:

$$Fe = (C_{s,pre} - C_{s,post})/C_{s,pre}$$

where Fe is the fraction eliminated by dialysis and $C_{s,pre}$ and $C_{s,post}$ are serum concentrations of temocillin at the beginning and end of haemodialysis, respectively [18];

$$CL_{HD} = [(C_{s,pre} - C_{s,post}) \cdot V_d/AUC_{HD}] - CL$$

where CL_{HD} and AUC_{HD} are the haemodialysis clearance and the area under the concentration–time curve during haemodialysis calculated by the trapezoidal rule, respectively [19];

$$t_{1/2HD} = ln(2)V_d/(CL - CL_{HD})$$

where $t_{1/2\,HD}$ is the elimination half-life during haemodialysis [20]; and

$$URR = (BUN_{pre} - BUN_{post})/BUN_{pre}$$

where URR is the urea reduction ratio and BUN_{pre} and BUN_{post} are the pre- and post-dialysis blood urea nitrogen (mg/dL) [19]. Data were pooled by dose and were analysed independently, irrespective of sequence of doses.

The time during which free concentration (fT) stayed above a given MIC was calculated by linear interpolation between measured values for the different dosing regimens. Target attainment rate was calculated considering the fT ensuring a coverage of MIC up to 8 mg/L (temocillin breakpoint for systemic infections from the British Society of Antimicrobial Chemotherapy (BSAC) [21]) and 16 mg/L (presumed MIC for >90% of Enterobacteriaceae [22]).

2.6. Statistical analyses

Multiple comparisons were analysed by analysis of variance (ANOVA). Overall, a *P*-value of ≤0.05 was considered statistically significant. Since two tests were carried out independently, Bonferroni-corrected significance thresholds of $P \leq 0.025$ were used to compensate for the increased type 1 error. Analyses were conducted using R 3.0.2 with RStudio 0.98.501.

Table 1
Patient characteristics ($n = 16$).

Characteristic	Median	Range
Age (years)	68.5	24–91
Follow-up (days)	5.5	2–9
Dosing cycles/subject	3	1–6
Dry body weight (kg)	73.1	41.5–104
Dialysis characteristics		
Vintage (days)	453	4–2475
Q_{Blood} (mL/min)	328	154–396
$Q_{Dialysate}$ (mL/min)	500	500–500
Ultrafiltration (mL)	1800	599–3200
Kt/V	1.51	0.87–1.88
Laboratory parameters		
Albumin (g/dL)	3.3	2.1–4.4
AST (U/L)	19	12–40
$BUN_{Pre-dial}$ (mg/dL)	107	10–169
$Creatinine_{Pre-dial}$ (mg/dL)	6.5	1.26–10.29

Q_{Blood}, blood flow rate; $Q_{Dialysate}$, dialysate flow rate; Kt/V, urea clearance; AST, aspartate aminotransferase; BUN, blood urea nitrogen; pre-dial, pre-dialysis.

3. Results

3.1. Patients and treatment

Sixteen patients were included in the study, including 14 males and 2 females. Their underlying kidney diseases were diabetes ($n = 5$) and/or nephroangiosclerosis ($n = 7$), chronic glomerulonephritis ($n = 2$), interstitial nephritis ($n = 1$), polycystic kidney disease ($n = 1$), congenital reflux or hypoplasia ($n = 2$) and acute tubular necrosis ($n = 2$). All patients were given temocillin as part of regular medical therapy for suspected or documented Gram-negative infection. Sepsis was observed in 44% of patients, and infection diagnosis included vascular necrosis, pyelonephritis, peritonitis, urinary tract infection, abscess, osteomyelitis, prostatitis, pneumonia, endocarditis and cystitis. The causative pathogen identified in 11 (69%) of the patients was a Gram-negative organism from the Enterobacteriaceae family: *Escherichia coli* (36%; $n = 4$); *Klebsiella oxytoca* (27%; $n = 3$); *Klebsiella cloacae* (27%; $n = 3$); and *Klebsiella pneumoniae* (9%; $n = 1$). Further patient characteristics are summarised in Table 1. A total of 48 concentration–time curves (from the administration of temocillin until the end of the following dialysis session) were included in this analysis, including 4 for 1 g every 24 h (q24h), 31 for 2 g every 48 h (q48h) and 13 for 3 g every 72 h (q72h) (the length of the interdialytic interval was determined by the patient's clinical condition). All patients were haemodialysed over 4 h.

3.2. Pharmacokinetics

The mean serum concentration–time profiles of temocillin are shown in Fig. 2. Both the actual total and free temocillin concentrations were measured because (i) only the free concentration is anticipated to be pharmacologically active and (ii) there are huge variations in protein binding in patients with advanced renal failure [23], which makes reference to standard populations for extrapolating free concentrations from measured total concentrations inadequate. Data analysis was carried out independently for the interdialytic and intradialytic period. Key PK parameters during the interdialytic period are summarised in Table 2 both for the total and free temocillin concentrations.

Exposure to total or free temocillin, determined by the area under the concentration–curve up to the last measurable concentration (excluding dialysis) (AUC_last), was not proportional to the dose ($P \leq 0.025$), suggesting non-linear pharmacokinetics. Comparison of PK parameters for total and free drug showed that the AUC_last for the free concentration was 3-fold lower than for the
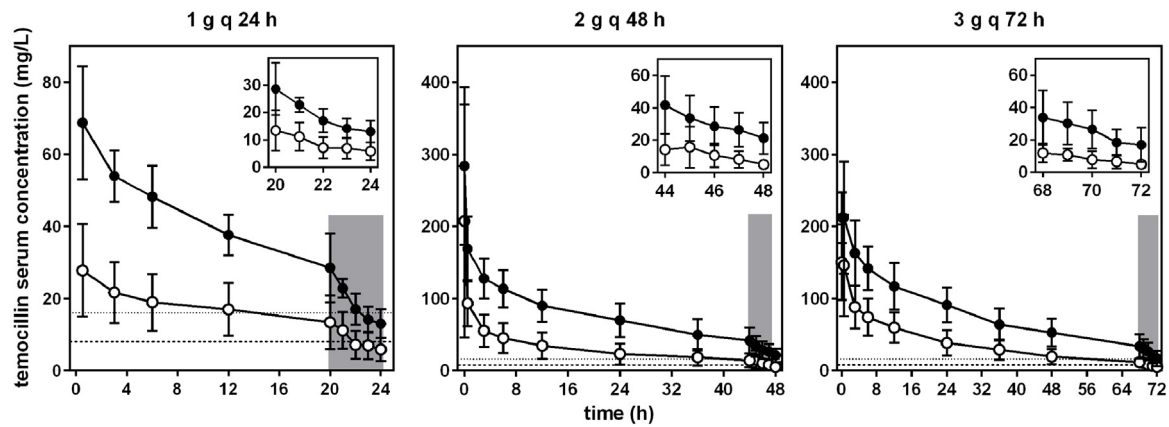
Fig. 2. Serum concentration–time profiles of temocillin. Mean ± standard deviation of total (●) and free (○) temocillin concentrations for the 1 g (left panel), 2 g (middle panel) and 3 g (right panel) dosing regimens. Greyed areas correspond to the haemodialysis period (4 h), with data shown in details in the inset.

Table 2
Pharmacokinetic (PK) parameters[a] for total and free temocillin concentrations for the three dosing regimens during the interdialytic period.

PK parameter	Total concentrations			Free concentrations		
	1 g q24h	2 g q48h	3 g q72h	1 g q24h	2 g q48h	3 g q72h
AUC_{last} (mg h/L)	781 (83)	3352 (895)	5484 (1661)	276 (127)	1257 (651)	2677 (858)
AUC_{inf} (mg h/L)	1749 (813)	5088 (1978)	7621 (2925)	713 (620)	1805 (988)	3122 (1024)
V_d (L)	17.7 (4.2)	15.6 (5.5)	20.7 (5.4)	60.6 (28.1)	43.9 (19.4)	33.3 (10.3)
V_d/W_t (L/kg)	0.26 (0.09)	0.23 (0.10)	0.31 (0.10)	0.8 (0.3)	0.6 (0.2)	0.5 (0.1)
CL (mL/min)	11.2 (5.1)	7.6 (2.9)	7.5 (3.1)	43 (39)	26 (16)	18 (6)
CL/W_t (mL/min/kg)	0.16 (0.07)	0.11 (0.06)	0.12 (0.06)	0.6 (0.4)	0.4 (0.2)	0.3 (0.1)
$t_{1/2}$ (h)	22.5 (14.0)	26.0 (8.9)	35.8 (16.9)	23.6 (14.8)	24.1 (13.4)	22.8 (6.0)

q24h, every 24 h; q48h, every 48 h; q72h, every 72 h; AUC_{last}, area under the concentration–time curve up to the last measurable concentration (excluding dialysis); AUC_{inf}, area under the concentration–time curve from zero to infinity (excluding dialysis); V_d, volume of distribution; V_d/W_t, volume of distribution per dry body weight; CL, clearance; CL/W_t, clearance per dry body weight; $t_{1/2}$, elimination half-life.

[a] Values are given as the mean (standard deviation).

total concentration for patients having received 1 g or 2 g, but was only 2-fold lower for those having received 3 g. The median V_d across dosing regimens for free concentrations was 0.5 L/kg, which is approximately two times higher than the corresponding V_d for the total concentrations. Median free temocillin clearance was 0.4 mL/min/kg, which is approximately four times higher than the total temocillin clearance. Note that free clearance was highest in patients having received a 1 g dose and appears to reduce with increasing dosage. The elimination half-life (median, 24–26 h) was prolonged in ESRD patients and was similar across free and total temocillin concentrations.

3.3. Haemodialysis efficacy

Summaries of the haemodialysis efficacy for temocillin are shown in Table 3. Residual median temocillin concentrations before starting dialysis were 13.4 mg/L and 40 mg/L for free and total concentrations, respectively. They were markedly reduced during haemodialysis across the three dosing regimens so as to reach median concentrations of 6.5 mg/L (free) and 16 mg/L (total). Median haemodialysis clearance for free temocillin was 113 mL/min, which is approximately double the value found for the total concentration. The interdialytic (4 h) and intradialytic (>20 h) elimination half-lives were significantly different ($P \leq 0.025$). The estimated fraction eliminated by dialysis for the free concentration varied from 48% to 59%. The URR was ca. 70% across all dosing groups.

3.4. Pharmacodynamics

The causative infectious pathogen was identified in 11 patients (69%) and it belonged to the Enterobacteriaceae family. A recent

Table 3
Temocillin dialysis efficiency.[a]

Parameter	1 g q24h	2 g q48h	3 g q72h
URR (%)	63.3 (12.1)	72.4 (7.9)	71.1 (9.2)
Total concentrations			
CL_{HD} (mL/min)	67 (22)	39 (18)	77 (26)
$t_{1/2\ HD}$ (h)	3.0 (0.5)	4.3 (1.5)	3.0 (1.1)
Fe (%)	58.9 (7.2)	48.6 (9.2)	58.5 (11.0)
$C_{s,pre}$ (mg/L)	29 (11.7)	45 (20)	40 (19)
$C_{s,post}$ (mg/L)	12 (4.4)	23 (10)	16 (8)
Free concentrations			
CL_{HD} (mL/min)	106 (9)	136 (83)	113 (61)
$t_{1/2\ HD}$ (h)	4.1 (0.3)	3.6 (2.1)	3.2 (1.2)
Fe (%)	48.3 (4)	59 (15)	58 (12)
$C_{s,pre}$ (mg/L)	3.4 (7.4)	13 (8.7)	15.1 (6.6)
$C_{s,post}$ (mg/L)	7.1 (4.4)	4.7 (2.9)	6.5 (3.5)

q24h, every 24 h; q48h, every 48 h; q72h, every 72 h; URR, urea reduction ratio; CL_{HD}, dialysis clearance; $t_{1/2\ HD}$, elimination half-life during haemodialysis; Fe, fraction eliminated by dialysis; $C_{s,pre}$ and $C_{s,post}$, serum concentrations of temocillin at the beginning and end of haemodialysis, respectively.

[a] Values are given as the mean (standard deviation).

Belgian survey reported $MIC_{50/90}$ values of 8/16 mg/L for temocillin against these organisms [22]. Table 4 summarises the proportion of the dosing interval during which the free temocillin concentration remains above an MIC of 8 mg/L ($fT_{>MIC8}$) or 16 mg/L ($fT_{>MIC16}$) taken as tentative susceptibility breakpoint values for temocillin [21,24]. These values ranged from 78% to 90% and from 48% to 71% when considering $fT_{>MIC8}$ and $fT_{>MIC16}$, respectively.

4. Discussion

This study is the first to substantiate with robust PK data that temocillin is a reliable option to treat serious Gram-negative

Table 4
Percentages of the dosing interval that serum levels of temocillin are above clinically relevant minimum inhibitory concentrations of pathogens.[a]

PK/PD criterion[b]	1 g q24h	2 g q48h	3 g q72h
%fT > 8 mg/L	78 (33)	88 (18)	89.5 (20)
%fT > 16 mg/L	48 (37)	67 (30)	71 (24)

PK/PD, pharmacokinetic/pharmacodynamic; q24h, every 24 h; q48h, every 48 h; q72h, every 72 h.
  [a] Values are given as the mean (standard deviation).
  [b] Percentage of the dosing interval that free serum temocillin concentrations are >8 mg/L and >16 mg/L, respectively.

infections in ESRD patients when administered thrice weekly on dialysis days only. Previous research on temocillin during haemodialysis was limited to two studies conducted in the 1980s with a small number (n = 5–7) of patients and using older and less efficient low-flux dialysers. The performance of these dialysers in eliminating temocillin is inferior to that of contemporary high-flux dialysers, and modern pharmacokinetic/pharmacodynamic (PK/PD) insights about parameters predicting the activity of β-lactams were not yet fully developed [11,25]. The applicability of these outdated data to current practice is therefore questionable.

The pattern of Gram-negative organisms observed in this study is similar to that typically seen in haemodialysis patients, with *E. coli* and *Klebsiella* spp. being the most frequent organisms isolated [4]. The incidence of Gram-negative bacteraemia in dialysis patients has increased during recent years and it is associated with an unfavourable prognosis with a 3-month mortality of 28.6% as well as non-dialysis access-related infection such as diabetic foot ulcer or urinary and intra-abdominal infection [5]. There is a worrisome increase in antibiotic resistance in Gram-negative organisms with resistance percentages of >30% for fluoroquinolones, trimethoprim/sulfamethoxazole and conventional β-lactams such amoxicillin/clavulanic acid, forcing clinicians to resort to broad-spectrum drugs such as carbapenems [3]. Temocillin is a strategically important alternative to carbapenems in this context [12].

We observed a consistently high systemic exposure to temocillin. The total volume of distribution is in agreement with literature data [25] and does not appear to be significantly affected by renal insufficiency, as previously reported [11,14]. Free AUC reaches 35–50% of total AUC depending on the dose, which is in the same range as recent observations in severely ill patients hospitalised in intensive care units [24]. Both types of patients frequently experience lower drug protein binding than healthy volunteers [23,26], for whom temocillin free concentrations account for only 15% of total temocillin serum concentrations [10].

We demonstrate that temocillin pharmacokinetics are markedly different during haemodialysis compared with the interdialytic interval, with a clearance of 113 mL/min vs. 26 mL/min and a serum half-life of 3.6 h vs. 24 h, respectively. This emphasises the need to administer the drug after the dialysis session to accommodate for intradialytic losses.

Temocillin has an extensive dialysability due to its low molecular weight (<500 Da) and its high degree of water solubility, which is further enhanced by the low serum albumin levels frequently observed in sick dialysis patients, as illustrated in this study [23]. During the interdialytic period, temocillin exhibits complex, non-linear pharmacokinetics, which can partly be attributed to saturable protein binding [27]. Binding sites for temocillin have not been identified, but it has been suggested that proteins other than albumin could be involved especially at high temocillin concentrations [28]. This could be of importance, particularly in inflammatory situations where the serum concentration of albumin tends to decrease while those of other proteins such as α-1-acid glycoprotein tend to increase. Non-linear pharmacokinetics may also

be partly explained by an increasing extrarenal elimination with decreasing glomerular filtration (likely biliary secretion), which may become the main elimination pathway in patients with ESRD [14]. Interestingly, the current data suggest a decrease in clearance of free drug with increasing dose (only borderline statistically significant, probably due to the limited sample size), which is the hallmark of a mixed-order elimination process. This explains the subtherapeutic drug exposure observed with the lowest dose of 1 g per 24-h interval. It could correspond to a saturation of biliary secretion at high antibiotic concentrations because this process requires the intervention of active transporters [27].

Regarding temocillin pharmacodynamics, its overall efficacy is best predicted, as for all β-lactam antibiotics, by the time during which the free concentration remains above the MIC of the offending bacteria ($fT_{>MIC}$) [13]. There is, however, no clear consensus on the fraction of the dosing interval during which the free concentration has to remain above this MIC value. Animal models suggest that a $fT_{>MIC}$ of 29–34% is required to achieve bacteriostasis against most susceptible organisms when using discontinuous administration [13].

Mathematical models based on Monte Carlo simulations using a cut-off $fT_{>MIC}$ of 40% suggest for temocillin a clinical PK/PD breakpoint of 8–16 mg/L [24], a value of the same order of magnitude as the MIC_{90} for most Enterobacteriaceae [22]. This target was reached for the 2 g q48h and 3 g q72h dosing regimens and only partially reached for the 1 g q24h regimen when considering an MIC of 16 mg/L. In order to maximise bacterial killing and thus therapeutic efficacy, values of $fT_{>MIC}$ as high as 50–100% have also been proposed when dealing with more complicated infections in immunocompromised patients [22,29]. This goal could not be achieved for patients receiving 1 g q24h for whom temocillin $fT_{>MIC16}$ was <50%. Conversely, this value was obtained for the majority of patients receiving 2 g q48h or 3 g q72h, with free concentrations remaining above an MIC of 8 mg/L or 16 mg/L during ca. 90% and 70% of the dosing interval, respectively. However, still higher exposure may be needed in order to prevent the emergence of more resistant mutants, with trough values for free concentrations as high as four times the MIC being recommended to avoid selection of resistant subpopulations [30]. Based on these considerations, it is obvious that the doses of temocillin recommended in the Summary of Product Characteristics, being 0.5 g q24h and 1 g q48h, will lead to subtherapeutic drug exposure in the majority of patients [10], which may call for revision of these recommendations. Noteworthy, temocillin was well tolerated in this ESRD population.

This study has several limitations. First, we did not evaluate whether rebound occurred in temocillin concentrations after haemodialysis. If so, the half-life might be overestimated. Second, the patients were not all at steady state, thus the potential for drug accumulation with multiple dosing exists. However, haemodialysis was highly efficient at removing temocillin. Therefore, any drug accumulation can be considered insignificant compared with other sources of variability, and we estimated it to be less than one-half of the accuracy of the analytical method (15%) used. Lastly, and in a more global context, further studies are needed to more definitely establish the optimal PK/PD target for β-lactams in general, and for temocillin in particular, in order to better define adequate dosing regimens.

5. Conclusion

This study demonstrates that temocillin is a safe, effective, strategically interesting, and easy-to-use therapeutic option in ESRD patients undergoing intermittent haemodialysis provided close attention is given to its proper dosing. The approach followed

in this study could also be used to assess the reliability of other β-lactams for the treatment of ESRD patients undergoing intermittent haemodialysis. For the three dosing schedules studied, temocillin trough levels before dialysis were relatively independent of the dosing schedule, leaving room to explore the use of higher doses in order to achieve a higher percentage of $fT_{>MIC16}$, and decreasing the risk of the emergence of bacterial resistance while patients are undergoing treatment. In addition, the proposed regimen allows for treatment of both inpatients and outpatients.

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