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PHARMACOLOGY

Modelled Target Attainment after Temocillin Treatment in Severe Pneumonia: Systemic and Epithelial Lining Fluid Pharmacokinetics of Continuous versus Intermittent Infusions

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ABSTRACT The objective of this article is to describe the population pharmacokinetics (PK) of temocillin administered via continuous infusion (CI) versus intermittent infusion (II) in critically ill patients with pneumonia. Secondary objectives included characterization of epithelial lining fluid (ELF)/plasma penetration ratios and determination of the probability of target attainment (PTA) for a range of MICs. Thirty-two mechanically ventilated patients who were treated for pneumonia with 6 g of temocillin daily for *in vitro* sensitive pathogens were assigned to either the II (2 g every 8 h over 0.5 h) or the CI (6 g over 24 h after a loading dose of 2 g) group. A population pharmacokinetic model was developed using unbound plasma, and total ELF concentrations of temocillin and related Monte Carlo simulations were performed to assess PTAs. The area under the concentration-time curve from 0 to 24 h ($AUC_{0–24}$) ELF/plasma penetration ratio was 0.73, at steady state, for both modes of infusion and whatever the level of creatinine clearance. Monte Carlo simulations showed that for the minimal pharmacodynamic (PD) targets of 50% $T > 1\times$ MIC (II group) and 100% $T > 1\times$ MIC (CI group), PK/PD breakpoints were 4 mg/L in plasma and 2 mg/L in ELF and 4 mg/L in plasma and ELF, respectively. The breakpoint was 8 mg/L in ELF for both modes of infusion in patients with creatinine clearance (CL_{CR}) < 60 mL/min/1.73 m^2. While CI provides better PKPD indexes, the latter remain below available recommendations for systemic infections, except in the case of moderate renal impairment, thereby warranting future clinical studies in order to determine the efficacy of temocillin in severe pneumonia.

KEYWORDS temocillin, epithelial lining fluid, PTA, critically ill patients, nosocomial pneumonia, Monte Carlo simulation, critical illness, pharmacokinetics

Temocillin is a derivative of ticarcillin, which, owing to its 6-α methoxy terminal structural modification, is resistant to most β-lactamases produced by extended-spectrum β-lactamases (ESBLs), excluding nonfermenters such as *Pseudomonas Aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* sp., and some carbapenemases (1). This feature makes it an interesting alternative in an era of highly resistant *Enterobacterales* infections in view of sparing carbapenems, supported by some retrospective study results (2, 3).

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Temocillin is licensed in the United Kingdom, Belgium, France, and Germany for use in urinary tract infections (UTI), bloodstream infections, and lower respiratory tract infections (LRTI) at a posology of 2 g twice daily (4). However, studies have demonstrated higher efficacy with 6 g daily in continuous infusion in critically ill patients in various infectious settings (5). Extended or continuous infusions of β-lactams are being used in daily clinical practice in order to maximize the time that the antimicrobial free concentration remains above the MIC (%fT $>$ MIC), which is the cornerstone of β-lactam therapy efficacy (6–8). For temocillin, although no detailed analysis of its pharmacodynamics (PD) *in vitro* exists, it is assumed that a minimal bacteriostatic target of 40 to 50% should be considered by comparison with other penicillins (9, 10). Furthermore, in patients with severe pneumonia, data about epithelial lining fluid (ELF) pharmacokinetics (PK) and penetration ratio of temocillin are lacking. Currently, only the British Society for Antimicrobial Chemotherapy (BSAC) and the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) have defined temocillin clinical breakpoints (susceptible [S] $\leq$ 8 and resistant [R] $>$ 8 mg/L) for systemic infections (11). Very recently, EUCAST issued clinical breakpoints for urinary tract infections only (S $\leq$ 0.001 and R $>$ 16 mg/L), thereby excluding other sites of infection from its recommendations due to the lack of clinical and PK data (12). The aim of this study is to provide an insight to establishing temocillin PK/PD breakpoints in pneumonia via ELF and plasma samples.

RESULTS

Patient enrollment, exclusions, and adverse events. Forty-four patients were enrolled in the study. Thirty-five patients were treated either in the continuous infusion (CI) group (n = 10) or in the intermittent infusion (II) group (n = 25). Twelve were excluded from the PK and PK/PD analyses for the following reasons. Three patients were under continuous veno-venous hemofiltration (CVVH), and this limited number did not permit their PK characterization with acceptable robustness. Furthermore, in the II group, four patients were extubated before bronchoalveolar lavage (BAL), one patient had undetectable urea-BAL, and one patient died before BAL. In the CI group, one patient had undetectable cells in BAL, another patient was shifted from CVVH to intermittent hemodialysis, and one patient was deemed too unstable by the attending physician to undergo BAL.

Consequently, 32 patients were included in the final PK analyses, 23 in the II group and 9 in the CI group. Temocillin and mini-BAL were well tolerated without any significant adverse events.

Patient demographics. Patient demographics and clinical characteristics are described in Table 1. The two groups were clinically and demographically similar. Thirty-one percent of patients had augmented renal clearance (ARC) defined as $>$120 mL/min/1.73 m^2 (7/23 in the II versus 3/9 in the CI group, respectively) (13). The mean creatinine clearance was 107.2 $\pm$ 49.5 mL/min/1.73 m^2.

Clinical PK and microbiology. A high PK interindividual variability was observed in the serum and ELF concentrations in both groups as illustrated in Fig. S1 in the supplemental material. Mean observed concentrations in plasma and ELF are displayed in Fig. 1.

Forty-six pathogens were isolated from the 32 patients (11 in the CI group; 35 in the II group), among which were 33 nonfermenter *Enterobacterales* (data not shown). Based on Vitek 2, the majority (85%) of pathogens had an MIC of $\leq$4 mg/L for temocillin, and 15% had an MIC of 8 mg/L. Based on Etest, 10 (30.3%) pathogens had an MIC of $\leq$4 mg/L, 12 (36.4%) had an MIC of 4 to 8 mg/L, and 11 (33.3%) had an MIC of $>$8 mg/L, mainly *Escherichia coli* and *Serratia Marcescens*, corresponding to resistant strains according to BSAC recommendations. Four strains (12.1%) were extended-spectrum β-lactamase (ESBL) producers, one in the II group and three in the CI group. None were carbapenemase producers. Based on Etest, the mean MIC was 9.94 mg/L ($\pm$ 7.86 mg/L), and the median was 8 mg/L (interquartile range [IQR], 4 to 13 mg/L).

Population PK model building and internal validation. A two-compartment model best fitted the plasma unbound concentrations, and an additional compartment was added to describe ELF concentrations. Creatinine clearance was retained as a

TABLE 1 Demographic and clinical characteristics of patients

Demographic and clinical data	All (n = 32)	CI group (n = 9)	II group (n = 23)	P value
Age (yr)	64.9 ± 11.4	66.1 ± 7.0	64.4 ± 12.8	0.71
Male (no. [%])	24 (75.0)	8 (88.9)	16 (69.6)	0.39[a]
Wt (kg)	74.4 ± 13.7	75.6 ± 16.7	73.9 ± 12.8	0.76
BMI (kg/m^2)	25.1 ± 4.6	25.1 ± 4.5	25.1 ± 4.7	0.99
Hospital stay before onset of pneumonia (days)	15.6 ± 15.0	18.3 ± 13.9	14.5 ± 15.6	0.33[b]
ICU stay before onset of pneumonia (days)	10.3 ± 10.1	13.8 ± 12.9	9.0 ± 8.8	0.35[b]
Simplified CPIS	7.8 ± 1.0	8.1 ± 1.2	7.7 ± 0.93	0.25
SAPS III	72.2 ± 12.7	74.8 ± 11.9	71.3 ± 13.2	0.49
SOFA score	9.7 ± 3.3	10.0 ± 3.7	9.6 ± 3.2	0.77
APACHE II	28.6 ± 8.6	28.3 ± 9.6	28.7 ± 8.4	0.92
Septic shock (no. [%])	12 (37.5)	5 (55.6)	7 (30.4)	0.24
Concomitant bacteremia with the targeted bacteria (no. [%])	5 (15.6)	3 (33.3)	2 (8.7)	
Cl_{CR} (mean ± SD)[c]	115.6 ± 51.7	119.2 ± 33.2	114.2 ± 58.0	0.81
>120 mL/min/1.73 m^2	14 (43.7)	6 (66.7)	8 (35.8)	
90–119 mL/min/1.73 m^2	8 (25.0)	2 (22.2)	6 (26.1)	
60–89 mL/min/1.73 m^2	3 (9.4)	0 (0.0)	3 (13.0)	
30–59 mL/min/1.73 m^2	7 (21.9)	1 (11.1)	6 (26.1)	
CVVH	0 (0.0)	0 (0.0)	0 (0.0)	

[a]Fisher's exact test.
[b]Kruskal-Wallis test.
[c]Using urine output collection over 24 h.

significant covariate on clearance (power relationship). According to the model, the plasma free fraction increases on average from 10% to about 75% when the total concentration increases from 10 mg/L to 400 mg/L, with quite high interindividual variability (coefficient of variation [CV] = 36%).

Total temocillin concentrations were related to unbound concentrations according to the following equation: $Ct = Cu + \frac{Cb_{max} \times Cu}{BC_{50} + Cu}$. Parameter estimates and related covariate are summarized in Table S1 in the supplemental material. The ratio of area under the concentration-time curve (AUC) between concentration of total temocillin in ELF (Celf) and plasma concentration of unbound (free) temocillin (Cu) (R_{AUC}) was estimated to be 0.73. Basic goodness-of-fit plots for total plasma, unbound plasma, and total ELF concentrations are displayed in Fig. S2 to S4 in the supplemental material. They indicate adequate fitting performances of the model to the data. Visual predictive checks are presented on Fig. 2 and show an acceptable agreement between the predicted and observed data over the dosing interval for both free and total plasma and ELF total concentrations.

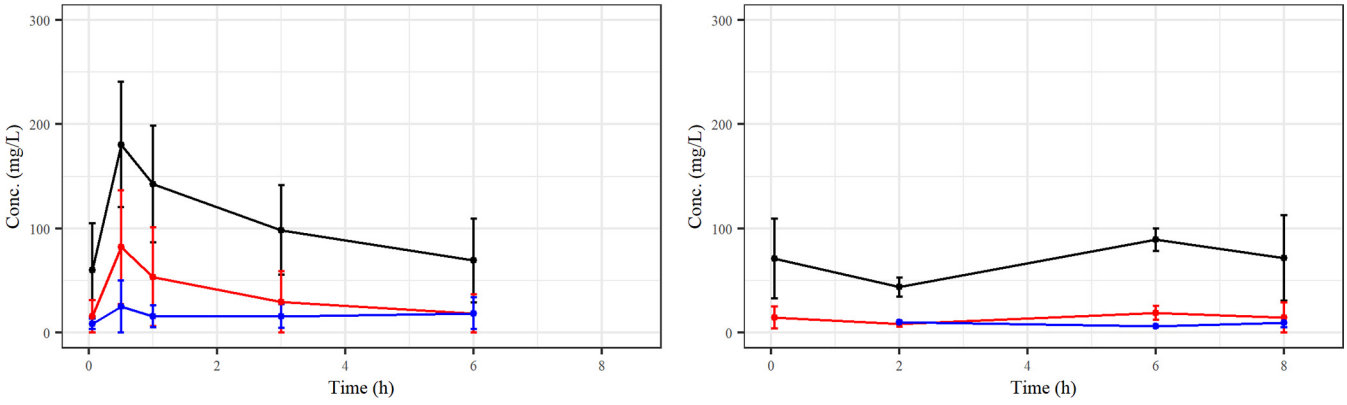

FIG 1 Mean (± standard deviation [SD]) observed free (red) and total (black) concentrations of temocillin in plasma and total concentration of temocillin in ELF (blue), after intermittent infusion, 2 g every 8 h over 0.5 h (n = 23) (left), and continuous infusion, 6 g over 24 h (n = 9) (right).

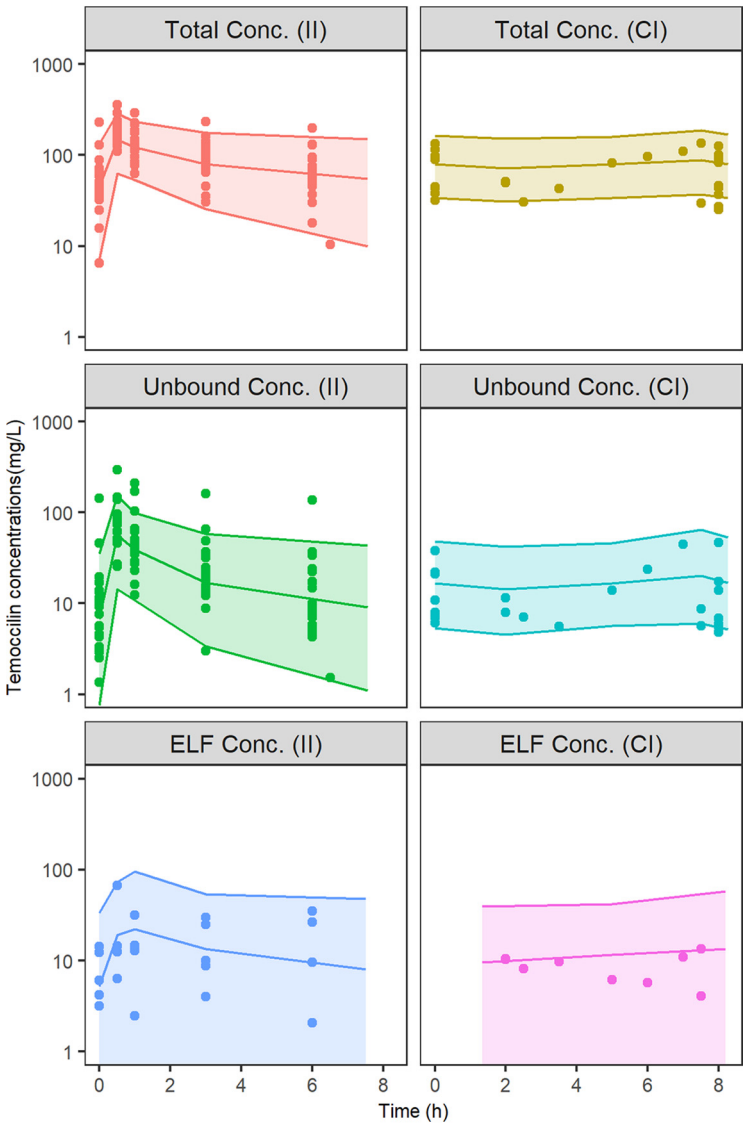

FIG 2 Visual predictive checks (simulations of the data set) of total and free plasma and total ELF concentrations after intermittent infusions (II) and continuous infusions (CI). Solid lines, medians and 90% prediction intervals; filled circles, observed concentrations.

PK/PD analysis. The probability of target attainment (PTA) was computed for two PK/PD targets (50% T $>$ MIC for II and 100% T $>$ MIC for both modes of infusion) against a range of MICs in plasma (free concentrations) and ELF (total concentrations) (Fig. 3). The same targets were considered after dichotomization of creatinine clearance between $\geq$60 mL/min/1.73 m^2 and $<$60 mL/min/1.73 m^2, respectively, as shown in Fig. S5 in the supplemental material, as well as in the case of ARC, as shown in Fig. S6 in the supplemental material. Furthermore, PTA was performed for 60 $\leq$ creatinine clearance (Cl_{CR}) $<$ 90 mL/min/1.73 m^2 and 90 $\leq$ Cl_{CR} $<$ 120 mL/min/1.73 m^2 as shown in Fig. S7 in the supplemental material. The corresponding PK/PD breakpoints are determined using a probability of success of 90% and are summarized in Table 2.

DISCUSSION

To the best of our knowledge, this is the first report of temocillin PK in the ELF of critically ill patients with pneumonia. Ratios of AUCs show that penetration ratio is higher than previously published for most other β-lactams, except cefepime, for both modes of infusion (14–18). As illustrated in Table 2, CI offers better PK/PD indexes than II in all scenarios considered: for the less stringent PD targets (50% T $>$ 1$\times$ MIC in II

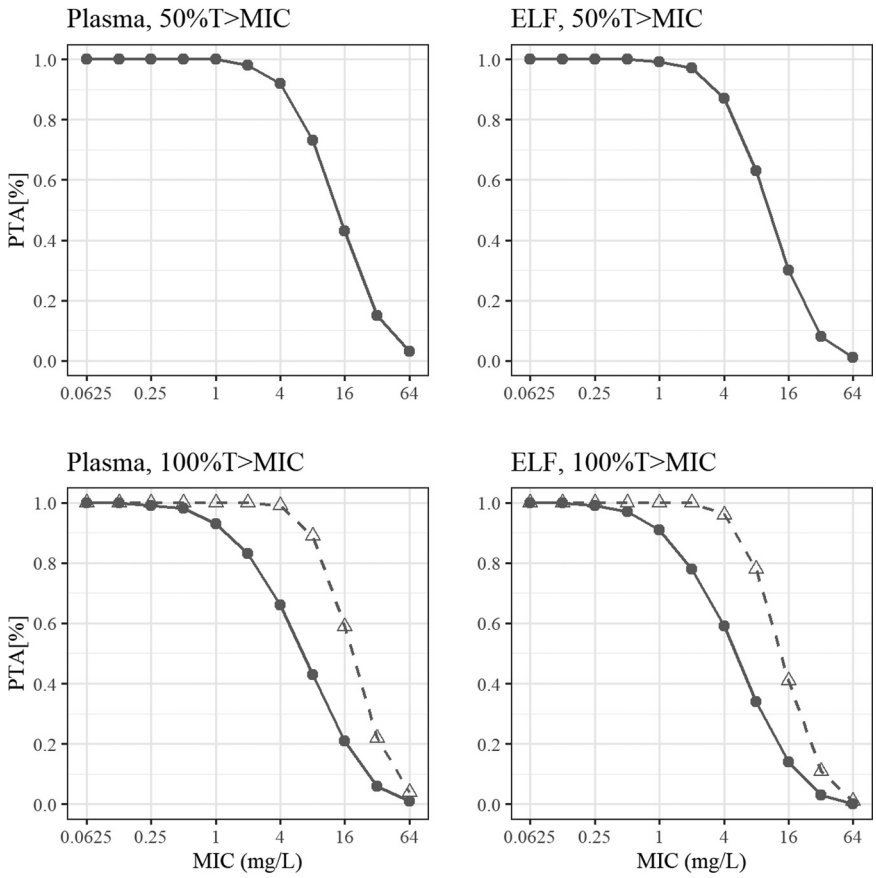

FIG 3 Probability of target attainment (obtained with the Monte Carlo simulations, n_{sim} = 32,000) for free plasma concentrations (left) and total ELF concentrations (right) for different dosing regimens and PK/PD targets (50% or 100% of time above the MIC). Continuous lines with filled circles, II (2 g/8 h over 0.5 h infusion); broken line with open triangles, CI (6 g/24 h).

and 100% T $>$ 1$\times$ MIC in CI), the breakpoints in plasma and ELF were found to be 4 mg/L and 2 mg/L in II, respectively, versus 4 mg/L in CI. For the most stringent PD target (100% T $>$ 4$\times$ MIC for both II and CI), the breakpoints in plasma and ELF were 0.25 mg/L in the II versus 1 mg/L in the CI, respectively. Nonetheless, these values remain well below the only available to date BSAC breakpoints ($\leq$8 mg/L) that recommend the usage of temocillin in systemic infections and, moreover, below the mean MIC of 9.94 mg/L (based on Etest) of the pathogens isolated in this cohort of patients. At best, an MIC of 8 mg/L was achieved for the less stringent PD targets in ELF for both II and CI in patients with moderate renal impairment (30 to 60 mL/min/1.73 m^2). However, as already pointed out, as many as 33.3% of the pathogens in this cohort had an MIC $>$ 8 mg/L to temocillin by Etest, thereby precluding its usage even in the less stringent scenario.

The renal function was found to be a clinically relevant covariate on the drug clearance in the population pharmacokinetics (popPK) analysis, which is consistent with temocillin's renal elimination (19). This is also in line with PK/PD findings for other renally excreted beta-lactams (20–22). The incidence of ARC in our study is also in line with current reports in critically ill patients (23).

Two previous PK studies have been undertaken with temocillin in critically ill patients; however, they were not focused on severe pneumonia (4, 5). With the same dose given by CI, Laterre et al. (5) reported higher average concentrations of free temocillin in plasma (mean, 37 mg/L; n = 11) than that observed in our study (13.7 $\pm$ 11.8 mg/L). This difference can probably be explained by differences in the distribution of the creatinine clearance, 56 $\pm$ 34 mL/min/1.73 m^2 in the study by Laterre et al. (5) versus 119.2 $\pm$ 33.2 mL/

TABLE 2 PK/PD breakpoints in plasma (free concentrations) and ELF (total concentrations) for specific PD targets according to different modes of administration using a probability of success of 90%[a]

	Mode of administration			
	II		CI	
PD target	Plasma	ELF	Plasma	ELF
50% T > 1× MIC	4	2	NA	NA
Cl_{CR} < 60 mL/min/1.73 m²	8	8	NA	NA
60 ≤ Cl_{CR} < 90 mL/min/1.73 m²	8	4	NA	NA
90 ≤ Cl_{CR} < 120 mL/min/1.73 m²	4	4	NA	NA
Cl_{CR} ≥ 60 mL/min/1.73 m²	4	2	NA	NA
Cl_{CR} > 120 mL/min/1.73 m²[b]	2	2	NA	NA
50% T > 4× MIC	1	0.5	NA	NA
Cl_{CR} < 60 mL/min/1.73 m²	2	2	NA	NA
60 ≤ Cl_{CR} < 90 mL/min/1.73 m²	2	1	NA	NA
90 ≤ Cl_{CR} < 120 mL/min/1.73 m²	1	1	NA	NA
Cl_{CR} ≥ 60 mL/min/1.73 m²	1	0.5	NA	NA
Cl_{CR} > 120 mL/min/1.73 m²	0.5	0.5	NA	NA
100% T > 1× MIC	1	1	4	4
Cl_{CR} < 60 mL/min/1.73 m²	4	4	8	8
60 ≤ Cl_{CR} < 90 mL/min/1.73 m²	2	2	8	8
90 ≤ Cl_{CR} < 120 mL/min/1.73 m²	2	1	8	4
Cl_{CR} ≥ 60 mL/min/1.73 m²	1	0.5	4	4
Cl_{CR} > 120 mL/min/1.73 m²	0.5	0.5	4	4
100% T > 4× MIC	0.25	0.25	1	1
Cl_{CR} < 60 mL/min/1.73 m²	1	1	4	2
60 ≤ Cl_{CR} < 90 mL/min/1.73 m²	0.5	0.5	2	2
90 ≤ Cl_{CR}<120 mL/min/1.73 m²	0.5	0.25	2	1
Cl_{CR} ≥ 60 mL/min/1.73 m²	0.25	0.125	1	1
Cl_{CR} > 120 mL/min/1.73 m²	0.125	0.125	1	0.5

[a]NA, not applicable; II, intermittent infusion; CI, continuous infusion; Cl_{Cr}, creatinine clearance.
[b]These patients are included in the group of patients with Cl_{CR} ≥ 60 mL/min.

min/1.73 m² in the present study. Moreover, in the De Jongh et al. (4) study, temocillin was given at a lower dose of 4 g/day via CI in 6 patients who displayed a higher mean free plasma concentration of 21.5 mg/L and a higher plasma breakpoint of 16 mg/L in parallel with a lower CL_{CR} (102 ± 18 mL/min/1.73 m²) than in our study, thereby also possibly explaining the discrepancies observed with our results.

This study's limitations include its single-center design, the fact that it was not designed to test clinical efficacy of temocillin, and a relatively low number of patients, some of which were severely ill with late-stage ARC (23). Furthermore, the choice of microbiological diagnostic techniques such as Vitek 2 and Etest, which was anterior to EUCAST guidelines, might have underestimated or overestimated sensitivity to temocillin in comparison to disk diffusion and broth microdilution tests, which are now recommended (24). Moreover, this study included mainly normal weight patients; therefore, no conclusions may be drawn as to PTA of temocillin in obese (BMI > 30) critically ill patients (25). Finally, MIC distributions of various ESBL-producing organisms are largely unknown at this stage, making it difficult to generate recommendations for temocillin usage solely based on PTA analysis.

In conclusion, penetration ratios that were estimated by MC simulations at 73% were higher than previously demonstrated for other β-lactams, except cefepime. However, the current BSAC breakpoint of 8 mg/L was achieved for II and CI only in patients with creatinine clearance of <60 mL/min/1.73 m² and with the least stringent PD target both in plasma and ELF. While it has not been demonstrated that efficacy of a β-lactam in severe pneumonia is entirely dependent on its ELF concentration levels, our results suggest that temocillin should not be recommended in severe nosocomial

pneumonia without further clinical data in accordance with recent EUCAST clinical breakpoints.

MATERIALS AND METHODS

Study design and participants. This was a single-center, prospective, randomized study that was conducted in six intensive care units (ICUs), with a total of 53 medical and surgical beds, at the Centre Hospitalier Universitaire du Sart-Tilman, Liège, Belgium, between March 2016 and February 2017. The study was approved by the local ethics committee (EudraCT number 2015-004591-30), and informed consent was obtained from relatives because all patients were ventilated at the time of inclusion.

Eligible patients had to meet the following inclusion criteria: age $>$ 18; diagnosis of ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia (HAP) requiring mechanical ventilation with a documented pathogen showing temocillin Vitek 2 *in vitro* sensitivity of $\leq$8 mg/L; and creatinine clearance based on 24-h urine output collection and measurement $\geq$30 mL/min/1.73 m^2.

The enrolled patients were prospectively randomized in a 2.5:1 ratio to either the intermittent infusion group (II; 2 g over 0.5 h every 8 h) or the continuous infusion group (CI; 6 g over 24 h after a loading dose of 2 g over 0.5 h). The *a priori* defined ratio was chosen to study the temocillin concentration at five time points, using only one ELF sample per patient. No power size calculation was deemed necessary for this descriptive study.

Data collection, study drug, and sampling. Demographic and clinical data were prospectively collected including age, sex, weight, admission diagnosis, duration of ICU stay before temocillin treatment, clinical pulmonary infectious score (CPIS), simplified acute physiology score (SAPS) 3, sequential organ failure assessment (SOFA), and acute physiology and chronic health evaluation (APACHE) scores, presence of septic shock, and in-hospital and ICU mortality.

Temocillin (Négaban; Eumedica, Belgium) was dissolved in 50 mL of NaCl 0.9% saline solution and injected into a central venous catheter via a volumetric pump with an infusion dead space of less than 2 mL. Stability of the infusion has been published elsewhere (26).

All serum and mini-bronchoalveolar lavage (mini-BAL) samples were obtained within 15 min either side of the expected time of sampling after at least 24 h of infusion in the CI group and at least 3 doses in the II group. Serum samples (10 mL) were collected from indwelling arterial catheters at three predetermined time points for each patient in the CI group: i.e., 8am, time of the mini-BAL, and 4 pm. In the II group, blood samples were obtained at predose and 0.5, 1, 3, and 6 h after the start of temocillin infusion.

Mini-BAL samples (one per patient, evenly at the blood sampling times) were collected through a standardized mini-BAL procedure as follows: 2 $\times$ 40 mL of sterile 0.9% saline solution using a non-bronchoscopy catheter (Bal-Cath system; Kimberly Clark, Zaventem, Belgium).

Analytical methods. Blood and mini-BAL samples were immediately centrifuged at 3,000 rpm for 10 min and 10,900 rpm for 5 min, respectively; the supernatant was immediately separated and kept at $-$20°C until analysis, except for the BAL microbiological culture. For determination of total temocillin, 200 μl of BAL were spiked with ticarcillin (internal standard) and cleaned up by liquid-liquid extraction prior to chromatographic analysis. For determination of free temocillin concentration, 500 μL of serum or BAL was beforehand filtered by centrifugation using an Amikon 10-kDa ultrafiltration device (Millipore). Then, 300 μL of this ultrafiltered serum (or 200 μL of ultrafiltered BAL) were spiked with ticarcillin and were cleaned up by liquid-liquid extraction. The ultrafiltered serum/BAL was directly analyzed without extraction.

All pretreated samples were analyzed using a validated method on ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) (Acquity Waters-Quattro Premier Waters) equipped with a solvent quaternary pump, an injector, an Acquity HSS T3 column (100 $\times$ 2.1 mm; 1,8 μm) thermostatized at 40°C, and MassLynx computer software (Waters Corporation).

Measure of urea and determination of ELF concentrations. The concentrations of urea in the serum and ELF were determined as described by Rennard et al. (27) with the urea nitrogen/1900 kit (Roche Professional Diagnostics, Mannheim, Germany). The concentration of temocillin in ELF was thereafter determined using urea as an endogenous marker according to the following formula (27, 28).

$$\mathrm{TEM_{ELF}} = \frac{\mathrm{TEM_{BAL}} \times \mathrm{urea_{PLA}}}{\mathrm{urea_{BAL}}}$$

where calculated $\mathrm{TEM_{ELF}}$ is the concentration of temocillin in ELF, $\mathrm{TEM_{BAL}}$ is the concentration of temocillin in the mini-BAL fluid, $\mathrm{urea_{PLA}}$ is the concentration of urea in serum (collected concomitantly with bronchoscopy), and $\mathrm{urea_{BAL}}$ is the concentration of urea in the mini-BAL fluid.

MIC determinations. MICs were first determined using the automated system Vitek 2 (bioMérieux) and subsequently by Etest (bioMérieux).

PK analysis. A population PK model was developed. A nonlinear mixed effects modeling approach was performed with NONMEM version 7.4.0 (double precision; Icon Development Solutions, Ellicott City, MD, USA) and PsN-toolkit version 4.6.0 (29). The first-order conditional estimation method with interaction was used. One- and two-compartment structural models were fitted to free (Cu) and total (Ct) serum and total ELF (Celf) concentrations. The estimated pharmacokinetic parameters reflect the unbound concentrations of temocillin. The relationship between bound and unbound concentrations of temocillin was described by an E_{max}-type model of parameters Cb_{max}, the maximal concentration of temocillin that can be bound and BC_{50}, the concentration of unbound temocillin for which half of Cb_{max} is reached. The

passage of unbound temocillin from plasma to ELF was modeled with an entry clearance into ELF (Q_{in}) and an exit clearance from ELF (Q_{out}). At steady state, the AUC ratio (R_{AUC}) between Cu and Celf corresponds to the Q_{out}/Q_{in} ratio. The interindividual variability in the PK parameters was estimated with the use of exponential models. The correlation between individual values of plasma clearance and central volume of distribution was estimated. Additive, proportional, and mixed error models were investigated to describe the residual variability. Weight, body surface area, and creatinine clearance were tested as covariates on volumes of distribution and/or clearance parameters. Power functions were used for this purpose. A decrease in objective function of >3.84 was used to consider a covariate as statistically significant with a 5% type I error. The correlation between unbound and total temocillin concentration measurements from the same sample was tested using the L2 function in NONMEM. Precision of the estimations was evaluated by using the sampling importance resampling (SIR) procedure, implemented with PsN (30). An internal validation of the model was performed by visual inspection of goodness-of-fit (GOF) plots, based on model predictions and residuals, and visual predictive checks (VPCs).

Monte Carlo simulations. (i) PK/PD analysis. Steady-state concentrations of temocillin in serum and ELF were generated for 32,000 virtual subjects by Monte Carlo simulations, with the same demographic characteristics as the 32 patients included in the study, for each of the two dosing scenarios. Subsequently, the %T > MIC were calculated as well as the probabilities of target attainment (PTA) for different PD targets based on Cu for plasma. The BSAC defined breakpoints for systemic infections caused by *Enterobacterales* were used (11).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 2.3 MB.

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N.L. and F.F. designed the study. N.L. obtained the funds, C.V. obtained the data. N.M., J.D., V.M., R.D., and N.G. did the analyses. N.L., F.F., C.V., and N.G. interpreted the data. N.L. and N.G. wrote the manuscript, which was reviewed by S.M.

REFERENCES

1. Livermore DM, Hope R, Fagan EJ, Warner M, Woodford N, Potz N. 2006. Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England. J Antimicrob Chemother 57:1012–1014. https://doi.org/10.1093/jac/dkl043.
2. Gupta ND, Smith RE, Balakrishnan I. 2009. Clinical efficacy of temocillin. J Antimicrob Chemother 64:431–433. https://doi.org/10.1093/jac/dkp208.
3. Balakrishnan I, Awad-El-Kariem FM, Aali A, Kumari P, Mulla R, Tan B, Brudney D, Ladenheim D, Ghazy A, Khan I, Virgincar N, Iyer S, Carryn S, Van de Velde S. 2011. Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae. J Antimicrob Chemother 66:2628–2631. https://doi.org/10.1093/jac/dkr317.
4. De Jongh R, Hens R, Basma V, Mouton JW, Tulkens PM, Carryn S. 2008. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. J Antimicrob Chemother 61:382–388. https://doi.org/10.1093/jac/dkm467.
5. Laterre P-F, Wittebole X, Van de Velde S, Muller AE, Mouton JW, Carryn S, Tulkens PM, Dugernier T. 2015. Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. J Antimicrob Chemother 70:891–898. https://doi.org/10.1093/jac/dku465.
6. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J. 2007. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 30:11–18. https://doi.org/10.1016/j.ijantimicag.2007.02.002.
7. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. 2018. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis 18:108–120. https://doi.org/10.1016/S1473-3099(17)30615-1.
8. Lee YR, Miller PD, Alzghari SK, Blanco DD, Hager JD, Kuntz KS. 2018. Continuous infusion versus intermittent bolus of beta-lactams in critically ill patients with respiratory infections: a systematic review and meta-analysis. Eur J Drug Metab Pharmacokinet 43:155–170. https://doi.org/10.1007/s13318-017-0439-5.
9. Alexandre K, Fantin B. 2018. Pharmacokinetics and pharmacodynamics of temocillin. Clin Pharmacokinet 57:287–296. https://doi.org/10.1007/s40262-017-0584-7.
10. Craig WA. 2003. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 17:479–501. https://doi.org/10.1016/S0891-5520(03)00065-5.
11. Andrews JM, Jevons G, Walker R, Ashby J, Fraise AP. 2007. Temocillin susceptibility by BSAC methodology. J Antimicrob Chemother 60:185–187. https://doi.org/10.1093/jac/dkm179.
12. European Committee on Antimicrobial Susceptibility Testing. 2021. Temocillin: rationale for the clinical breakpoints, version 1.0. https://www.eucast.org/publications_and_documents/consultations/#c18518.
13. Udy AA, Roberts JA, Boots RJ, et al. 2010. Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49:1–16.
14. Boselli E, Breilh D, Saux MC, Gordien JB, Allaouchiche B. 2006. Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia. Intensive Care Med 32:2059–2062. https://doi.org/10.1007/s00134-006-0401-5.
15. Frippiat F, Musuamba FT, Seidel L, Albert A, Denooz R, Charlier C, Van Bambeke F, Wallemacq P, Descy J, Lambermont B, Layios N, Damas P, Moutschen M. 2015. Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study. J Antimicrob Chemother 70:207–216. https://doi.org/10.1093/jac/dku354.
16. Rodvold KA, George JM, Yoo L. 2011. Penetration of anti-infective agents into pulmonary epithelial lining fluid: focus on antibacterial agents. Clin Pharmacokinet 50:637–664. https://doi.org/10.2165/11594090-000000000-00000.
17. Boselli E, Breilh D, Duflo F, Saux M-C, Debon R, Chassard D, Allaouchiche B. 2003. Steady-state plasma and intrapulmonary concentrations of cefepime administered in continuous infusion in critically ill patients with

severe nosocomial pneumonia. Crit Care Med 31:2102–2106. https://doi.org/10.1097/01.CCM.0000069734.38738.C8.
18. Heffernan AJ, Sime FB, Lipman J, Dhanani J, Andrews K, Ellwood D, Grimwood K, Roberts JA. 2019. Intrapulmonary pharmacokinetics of antibiotics used to treat nosocomial pneumonia caused by Gram-negative bacilli: a systematic review. Int J Antimicrob Agents 53:234–245. https://doi.org/10.1016/j.ijantimicag.2018.11.011.
19. Overbosch D, van Gulpen C, Mattie H. 1985. Renal clearance of temocillin in volunteers. Drugs 29(Suppl 5):128–134. https://doi.org/10.2165/00003495-198500295-00027.
20. Casu GS, Hites M, Jacobs F, Cotton F, Wolff F, Beumier M, De Backer D, Vincent J-L, Taccone FS. 2013. Can changes in renal function predict variations in beta-lactam concentrations in septic patients? Int J Antimicrob Agents 42:422–428. https://doi.org/10.1016/j.ijantimicag.2013.06.021.
21. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, Depuydt P, Decruyenaere J, Lipman J, Wallis SC, De Waele JJ. 2013. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 17:R84. https://doi.org/10.1186/cc12705.
22. Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, Daali Y, Pugin J, Karmime A, Fathi M, Lew D, Harbarth S. 2015. Augmented renal clearance, low beta-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 45:385–392. https://doi.org/10.1016/j.ijantimicag.2014.12.017.
23. Sime FB, Udy AA, Roberts JA. 2015. Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol 24:1–6. https://doi.org/10.1016/j.coph.2015.06.002.
24. European Committee on Antimicrobial Susceptibility Testing. 2021. Addendum: temocillin breakpoints and AST methods. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Addenda/Addendum_Temocillin_breakpoints_and_AST_2020.pdf.
25. Alobaid A, Hites M, Lipman J, Taccone FS, Roberts JA. 2016. Effects of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents 47:259–268. https://doi.org/10.1016/j.ijantimicag.2016.01.009.
26. Carryn S, Couwenbergh N, Tulkens PM. 2010. Long-term stability of temocillin in elastomeric pumps for outpatient antibiotic therapy in cystic fibrosis patients. J Antimicrob Chemother 65:2045–2046. https://doi.org/10.1093/jac/dkq229.
27. Rennard SI, Basset G, Lecossier D, O'Donnell KM, Pinkston P, Martin PG, Crystal RG. 1986. Estimation of volume of epithelial lining fluid recovered by lavage using urea as marker of dilution. J Appl Physiol (1985) 60:532–538. https://doi.org/10.1152/jappl.1986.60.2.532.
28. Rennard SI, Ghafouri M, Thompson AB, Linder J, Vaughan W, Jones K, Ertl RF, Christensen K, Prince A, Stahl MG. 1990. Fractional processing of sequential bronchoalveolar lavage to separate bronchial and alveolar samples. Am Rev Respir Dis 141:208–217. https://doi.org/10.1164/ajrccm/141.1.208.
29. Lindbom L, Pihlgren P, Jonsson EN, Jonsson N. 2005. PsN-Toolkit–a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 79:241–257. https://doi.org/10.1016/j.cmpb.2005.04.005.
30. Dosne A-G, Bergstrand M, Harling K, Karlsson MO. 2016. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. J Pharmacokinet Pharmacodyn 43:583–596. https://doi.org/10.1007/s10928-016-9487-8.