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# Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration

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**Objectives:** The growing incidence of infections caused by Enterobacteriaceae producing ESBLs has led to increased use of carbapenems. Temocillin, which resists most β-lactamases, may be a useful alternative. The aim of this study was to assess the pharmacokinetics and target attainment rates of 6 g of temocillin daily divided into three administrations every 8 h (three times daily) or administered by continuous infusion in critically ill patients.

**Patients and methods:** This was a prospective, two-centre, randomized, controlled study in patients with intra-abdominal or lower respiratory tract infections caused by Enterobacteriaceae.

**Results:** Thirty-two patients were included and analysed for clinical efficacy, and pharmacokinetics were measured in 29 of them. Four patients undergoing continuous veno-venous haemofiltration (CVVH) were analysed separately. Mean, median and range of percentages of the dosing interval during which the free drug concentration remained >16 mg/L were 76.4, 98 and 18.7–98.9 in patients treated three times daily and 98.9, 89.7 and 36.4–99.9 in patients with continuous infusion, respectively. Clinical cure rates were 79% and 93% in each of these groups, respectively (not significant). Patients with CVVH received a daily dose of 750 mg given by continuous infusion and had a mean free drug concentration of only 13.8 ± 1.9 mg/L. No adverse event attributable to temocillin was observed.

**Conclusions:** Temocillin (6 g daily) given by continuous infusion allows a larger proportion of critically ill patients to have free drug serum concentrations covering infections caused by Enterobacteriaceae with an MIC of 16 mg/L compared with administration three times daily. Clinical efficacy compared with carbapenems in documented severe infections needs to be further studied.

**Keywords:** target attainment rate, free concentration, continuous veno-venous haemofiltration, tolerance, Monte Carlo simulations, ESBLs

## Introduction

Temocillin (6-α-methoxy-ticarcillin) is a penicillin with activity against most Enterobacteriaceae, while non-fermenters, Gram-positive aerobes and strict anaerobes are not included in its spectrum.[1] The methoxy group attached to the C6 position of the penam nucleus confers stability against a wide variety of β-lactamases,[2] including most ESBLs,[3] AmpCs[4] and even some carbapenemases.[5] *In vitro* studies demonstrated susceptibility rates of up to ~80% and 90% for ESBL-producing strains if using a breakpoint of 8 and 16 mg/L, respectively.[3,6–8] Recently, an observational study in the UK confirmed that temocillin could serve as a potential alternative to carbapenems for treating infections caused by ESBL-/AmpC-producing Enterobacteriaceae.[9] In that study, a 4 g daily dose of temocillin divided into two administrations at a 12 h interval was correlated with higher clinical cure when compared with a lower dosage. However, the pharmacokinetic analysis and Monte Carlo simulations presented

in an earlier study suggested that a higher daily dose might be required to fully cover the wild-type distribution of susceptible Enterobacteriaceae.[10] Moreover, a 4 g daily dose divided into two administrations at a 12 h interval may not be sufficient in critically ill patients where alteration of critical parameters, such as drug volume of distribution (*V*), CL and protein binding, as well as end-organ dysfunctions, may markedly alter antibiotic disposition and potentially reduce the efficacy of anti-infective treatments and adversely affect patient outcome.[11] In addition, suboptimal dosing may lead to emergence of antibiotic resistance.[12]

Since killing of susceptible bacteria by β-lactams is dependent upon the time during which the free drug concentration remains above their MIC,[13] continuous infusion yielding stable serum concentrations above this value has been advocated as an alternative method of dosing β-lactams to increase efficacy,[14] and has been successfully applied for temocillin using a daily dose of 4 g.[10] In the present trial, we aimed at determining the pharmacokinetic parameters of temocillin in critically ill patients using a larger daily dose (6 g) and comparing its administration in three discrete doses of 2 g given at 8 h intervals with the same daily dose administered by continuous infusion. The hypothesis was that the latter regimen would provide longer free-drug serum concentrations supporting a clinical breakpoint of 16 mg/L.

## Patients and methods

### *Study design, patients, antibiotic treatment and data collection*

This was a prospective, two-centre (St Luc University Hospital, Brussels, Belgium, and St Pierre Hospital, Ottignies, Belgium), randomized, controlled study. The protocol was approved by the hospital ethics committees. Before enrolment, written consent was obtained from the patient or their nearest relative, and patients were only enrolled once. Patients were eligible if meeting all the following inclusion criteria: (i) hospitalized in an adult ICU; (ii) presenting with clinical signs of an abdominal or a pulmonary infection; and (iii) infected with a pathogen expected to be susceptible to temocillin. Patients were excluded if (i) potentially infected by a pathogen resistant to temocillin; (ii) having a known allergy to any penicillin, including temocillin; (iii) pregnant or lactating (women); or (iv) having participated in another investigational drug study within 4 weeks.

All patients were categorized using APACHE II and SOFA scores. Patients received temocillin according to the following schemes: (i) continuous infusion: loading dose (2 g) administered over 30 min in 50 mL of water for injection followed by infusion (6 g in 48 mL of water for injection infused at a rate of 2 mL/h); (ii) three times daily: 2 g of temocillin (in 50 mL of water for injection) every 8 h injected over a 30 min period. Temocillin dosing regimens were adjusted for $CL_{CR}$ according to Table 1. For patients undergoing continuous veno-venous haemofiltration (CVVH), temocillin was administered by continuous infusion and the dose arbitrarily set to 750 mg/24 h after administration of a loading dose of 750 mg. Temocillin was given as monotherapy for documented infections caused by susceptible pathogens. Additional antibiotics were given according to the microbiological data obtained from samples collected from the infected site.

### *Sample collection and analysis*

For patients treated by continuous infusion, samples were drawn 0, 0.5, 1, 8, 24, 48 and 72 h after starting the administration of the loading dose. For patients treated with the three times daily regimen, samples were drawn 0, 0.5, 1, 2 and 8 h after starting the first administration on the first day of therapy. All samples were drawn with an arterial catheter or from an infusion-free upper extremity. Serum (obtained by centrifugation after blood clotting) was frozen at −80°C until analysis. Total and free temocillin concentrations were determined in serum as previously described.[10] In brief, total antibiotic was extracted by a solid-phase method (OASIS® HLB Extraction Cartridge System, Waters Corp.; typical recovery 95%–97%) while the free fraction was separated from serum proteins by ultrafiltration (Centrifree® device, Merck-Millipore Corp., Billerica, MA). Temocillin was then assayed by HPLC coupled with UV detection using ticarcillin as internal standard and with detection and quantification of both epimers of the two drugs.[10,15]

**Table 1.** Temocillin dose adjustment for $CL_{CR}$

| $CL_{CR}$ (mL/min) or condition | Daily dose | |
|---|---|---|
| | three times daily[a] | continuous infusion[b] |
| >50 | 3×2 g | 6 g/24 h |
| 50–31 | 3×1 g | 3 g/24 h |
| 30–10 | 1×1.5 g | 1.5 g/24 h |
| <10 | 1×750 mg | 750 mg/24 h |
| CVVH | NA | 750 mg/24 h |

NA, not applicable.
[a]Administration as 30 min infusions at 8 h intervals.
[b]Administration by continuous infusion over 24 h. Each patient received a 2 g loading dose.

### *MIC determinations*

MICs for the successfully collected isolates were determined using the automated system routinely used by the clinical microbiology laboratories of the participating centres (Vitek® 2 and Phoenix® for St Pierre, Ottignies, and St Luc, Brussels, respectively).

### *Population pharmacokinetics and probability of target attainment*

Population pharmacokinetic parameters were estimated by means of nonlinear mixed effect modelling (NONMEM) using data from 11 patients treated by intermittent infusion (2 patients were not included because assay of temocillin was only possible for the free fraction). The model was implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE method with INTERACTION. All fitting procedures were performed with the use of the Compaq Visual FORTRAN standard edition 6.6 (Compaq Computer Cooperation, Euston, TX, USA) and the NONMEM® software package (version VI, release 2, ICON Development Solutions, Ellicott City, MD, USA). To determine the basic structural pharmacokinetic parameters, various one- and two-compartment models were tested. Model selection and identification of variability were based on the evaluation of the mean objective function value (MOFV), pharmacokinetic parameter point estimates and their respective CIs, and goodness-of-fit plots. To detect significant differences between two structural models, the MOFV with a prespecified level of significance of $P<0.001$ was used (corresponding to a difference in MOFV of at least 10.8 points). To detect systematic deviations in the model fits, the goodness-of-fit plots were inspected visually. An exponential distribution model was used to account for inter-individual variability. Possible correlation between inter-individual variability coefficients on parameters was estimated and if present accounted for in the stochastic model (NONMEM Omega block option). The precision of the final population model for the entire population was established using the bootstrap option (1000 replications). The percentage of time during which the free drug

concentration remained above the MIC (%$fT_{>MIC}$)[16] was determined from the parameter estimates using MICLAB version 2.36 (Medimatics, Maastricht, the Netherlands) for the three times daily group and from the raw data of each patient for the continuous infusion group. Monte Carlo simulation of 10000 subjects was performed with the same program using a log-normal distribution of parameters. The results were used to calculate the median and 95th percentiles of %$fT_{>MIC}$ (for a range of 2–256 mg/L).

### Source of products

Temocillin and ticarcillin were obtained as Negaban® (Eumedica s.a., Brussels, Belgium) and Timentin® (GlaxoSmithKline Belgium, Rixensart, Belgium), respectively. All other drugs were procured as described previously.[17,18] Products for chromatography were of HPLC grade and obtained from Sigma-Aldrich Corp. (St Louis, MO, USA) or E. Merck AG (Darmstadt, Germany).

### Statistical analyses

Patient data were analysed with Student's *t*-test for parametric data (GraphPad InStat® version 3.10 for Windows, GraphPad Software, San Diego, CA, USA) and Fisher's exact test for non-parametric data (JMP 5.1, SAS Institute Inc., Cary, NC, USA).

## Results

### Patient characteristics

Thirty-two patients were enrolled in the study. They were divided into three groups: those given the daily dose of temocillin (6 g) divided into three administrations at 8 h intervals (three times daily; $n=14$); those given temocillin by continuous infusion ($n=14$); and those treated with CVVH and receiving temocillin by continuous infusion ($n=4$). Demographic data and treatment-related parameters are presented in Table 2. Patients' characteristics were similar between groups except for the median SOFA score,[19] which was significantly higher in patients treated with CVVH (16 versus 7 and 8.5 in the three times daily and continuous infusion groups, respectively; $P=0.0007$). Most patients were treated for lower respiratory tract infections ($n=11$) or intra-abdominal infections ($n=17$) and only two for urinary tract infections ($n=2$). Eleven patients (34%) had concurrent bacteraemia.

**Table 2.** Patients' characteristics and treatment parameters

| | Group | | |
|---|---|---|---|
| | three times daily[a] | continuous infusion[b] | CVVH[c] |
| Recruitment | | | |
| patients enrolled, *n* | 14 | 14 | 4 |
| pharmacokinetic population, *n* | 13 | 12 | 4 |
| Demography | | | |
| male/female, *n*/*n* | 6/8 | 11/3 | 0/4 |
| age (years), mean ± SD | 65 ± 15 | 68 ± 11 | 60 ± 16 |
| weight (kg), mean ± SD | 68 ± 12 | 71 ± 15 | 58 ± 7 |
| BMI (kg/m$^2$), mean ± SD | 24 ± 4 | 24 ± 5 | 23 ± 2 |
| $CL_{CR}$ (mL/min), mean ± SD | 82 ± 48 | 56 ± 34 | NA |
| severity score on admission | | | |
| APACHE II,[25] median | 16 | 17 | 20.5 |
| SOFA,[19] median | 7 | 8.5 | 16[d] |
| Infection type | | | |
| LRTI (positive blood culture), *n* | 6 | 4 (1) | 1 |
| IAI (positive blood culture), *n* | 6 (2) | 8 (3) | 3 (2) |
| UTI (positive blood culture), *n* | 1 (1) | 1 | 0 |
| BSI of unknown origin, *n* | 1 | 1 | 0 |
| Treatment parameters and outcomes | | | |
| treatment duration (days), mean ± SD | 6 ± 2 | 7 ± 5 | 5 ± 3 |
| dosage adjustment for $CL_{CR}$ | | | |
| 50–31 mL/min, *n* | 3 | 1 | 0 |
| 30–10 mL/min, *n* | 2 | 4 | 0 |
| clinical cure, % (*n*/*n*) | 79 (11/14) | 93 (13/14) | 75 (3/4) |
| overall ICU mortality, % (*n*/*n*) | 36 (5/14) | 14 (2/14) | 50 (2/4) |

LRTI, lower respiratory tract infection; IAI, intra-abdominal infection; UTI, urinary tract infection; BSI, bloodstream infection; NA, not applicable.
[a]The daily dose was divided into three 30 min infusions at 8 h intervals.
[b]The daily dose was administered by continuous infusion over 24 h. Each patient received a 2 g loading dose.
[c]Patients received a loading dose of 750 mg followed by continuous infusion of 750 mg/24 h.
[d]Significantly different from the two other groups ($P=0.0007$).

**Table 3.** Available isolates and MIC data

| Isolates | No. of isolates in group | | | No. of isolates with an MIC (mg/L) of | | | |
|---|---|---|---|---|---|---|---|
| | three times daily | continuous infusion | CVVH | ≤2 | 4 | 8 | 16 |
| *E. coli* | 4 | 6 | 3 (1[a]) | | 4 | 6 | 1 |
| *K. pneumoniae* | 5 (1[a]) | 1 | 0 | 1 | 1 | 3 | |
| *Klebsiella oxytoca* | 0 | 1 | 0 | 1 | | | |
| *E. cloacae* | 2 | 2 (1[a]) | 0 | 2 | 1 | | |
| *E. aerogenes* | 0 | 1 (1[a]) | 0 | | | | 1 |
| *P. mirabilis* | 1 | 0 | 0 | | 1 | | |
| *M. morganii* | 0 | 0 | 1 | | 1 | | |
| *S. marcescens* | 1 | 1 | 0 | | | | 2 |
| Gram-positive bacterium | 1 | 0 | 0 | | | | |
| Total | 14 | 12 | 4 | 4 | 8 | 9 | 4 |

[a]ESBL positive.

### *Microbiological data*

Table 3 shows the identification of the isolates successfully collected with their corresponding MICs. Bacteria mainly belonged to *Escherichia coli* ($n=13$), *Klebsiella* spp. ($n=7$) or *Enterobacter* spp. ($n=5$), with temocillin MICs varying from <2 to 16 mg/L. Four of the isolates were ESBL-producing strains (*E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Enterobacter aerogenes*).

### *Treatment parameters and outcomes*

Temocillin was used as monotherapy in 23 patients and combined with an anti-staphylococcal agent in the other 9 patients. The overall mean treatment duration was 6 days (range 2–22), with no significant difference between groups (6, 7 and 5 days in the three times daily, continuous infusion and CVVH groups, respectively). The overall clinical cure rate was 84% (27/32); in the three times daily, continuous infusion and CVVH groups it was 79% (11/14), 93% (13/14) and 75% (3/4), respectively (differences are not significant). According to the site of infection, the clinical cure rate was 94% (16/17) in intra-abdominal infections, 64% (7/11) in lower respiratory tract infections and 100% in both urinary tract infections (2/2) and bacteraemia (2/2). Isolates from patients who failed were one *Serratia marcescens* (lower respiratory tract infection, MIC=16 mg/L), one *Morganella morganii* (intra-abdominal infection, MIC=4 mg/L), one *E. cloacae* (lower respiratory tract infection, MIC ≤2 mg/L) and two *K. pneumoniae* (both in lower respiratory tract infections, MIC=8 mg/L and one of unknown MIC but an ESBL producer). The clinical cure rate was 75% (3/4) in infections caused by ESBL-producing organisms.

In three patients treated with temocillin and cured, bacterial superinfection was reported. The corresponding isolates reported were not in the spectrum of temocillin [*Pseudomonas aeruginosa*+*Enterococcus faecium*; MRSA+*Hafnia alvei*; MSSA+multiresistant *E. coli* (this patient was previously infected by *Proteus mirabilis*)]. In patients treated in the ICU, the overall mortality rate was 31% (10/32). No death was related to the primary infection treated with temocillin. Overall, mortality rates were 36% (5/14), 21% (3/14) and 50% (2/4) in the three times daily, continuous infusion and CVVH groups, respectively (differences are not statistically significant). No death was related to the primary infection treated with temocillin.

### *Adverse events*

No visible drug incompatibility or neurotoxicity signs were reported during the study. Seven adverse events were recorded, among which six were deemed not attributable and one possibly related to temocillin. One patient (from the continuous infusion group), who had been previously treated with cefuroxime and metronidazole, developed a severe pseudomembranous colitis while under temocillin treatment.

### *Pharmacokinetic data*

Pharmacokinetic data were available in 29 patients (13, 12 and 4 in the three times daily, continuous infusion and CVVH groups, respectively). In the three remaining patients, temocillin levels could not be determined due to the presence of other medications and/or metabolites interfering with UV detection under the conditions of the assay. Total and free temocillin serum concentrations from patients in the three times daily and continuous infusion groups are shown in Figure 1. In the three times daily group and for total temocillin levels, the mean $AUC_{24}$ was 1764 mg·h/L, the mean $C_{max}$ 170 mg/L and the mean $C_{min}$ 51 mg/L, corresponding to mean $C_{max}$ and $C_{min}$ of free temocillin of 65 and 19 mg/L, respectively. In the continuous infusion group, total temocillin concentrations stabilized after 8 h (the first peak being due to the administration of a loading dose of 2 g) to a mean steady-state concentration ($C_{ss}$) of 135 mg/L, corresponding to 37 mg/L free temocillin. The mean protein binding in 37 samples from 11 patients was 59% (SD 16%, range 19%–85%; one outlier of −6% was excluded). There was no relation between protein binding and concentration of temocillin over the concentration range measured (11.5–95.8 mg/L).

The mean, median and range of percentages of dosing interval during which the free drug concentration remained >16 mg/L were 76.4, 98.0 and 18.7–98.9 in the three times daily group

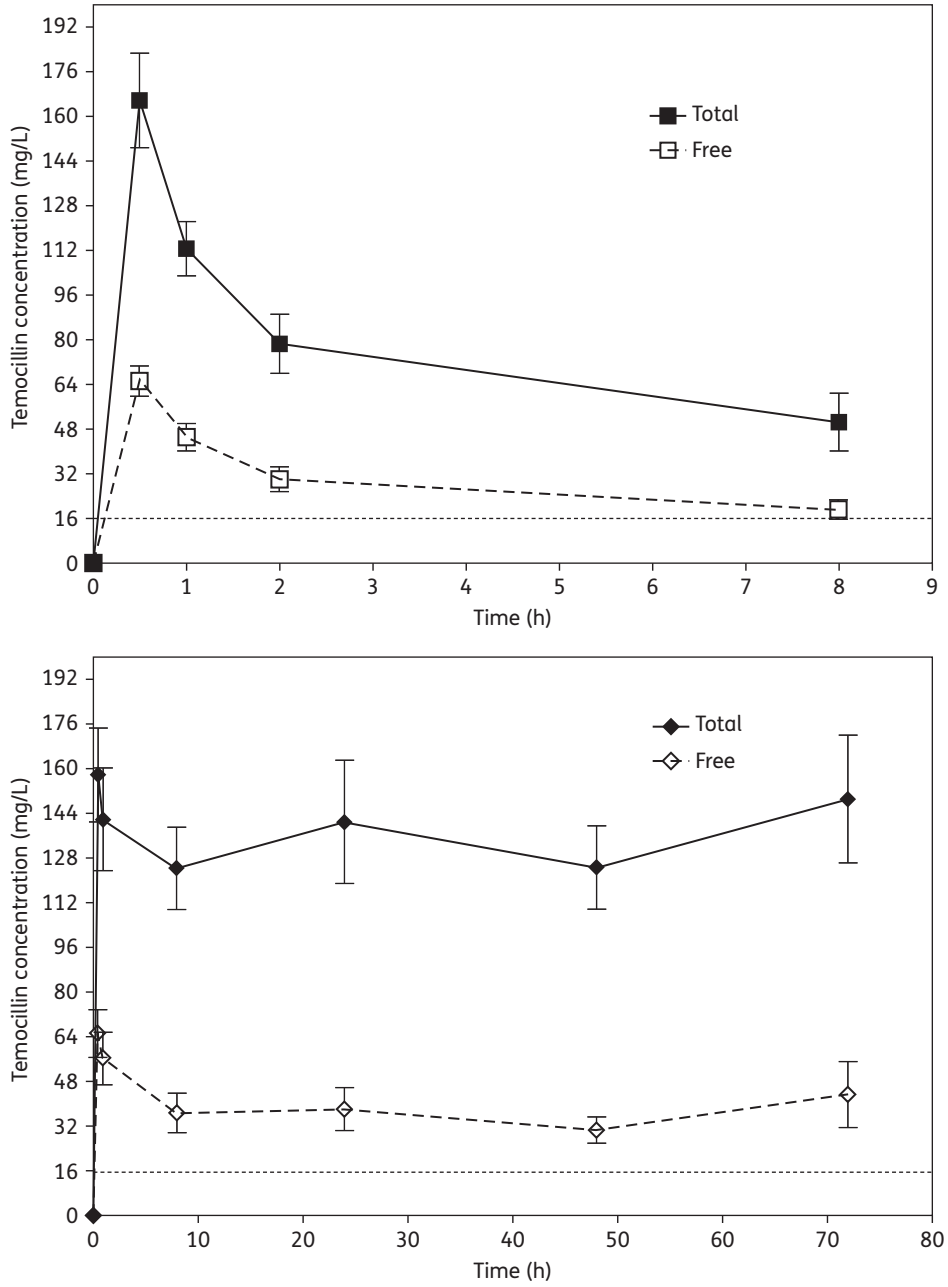


**Figure 1.** Total and free temocillin serum concentrations. Upper panel: patients ($n=13$) in the three times daily group (daily dose of 6 g divided into three administrations at 8 h intervals). Lower panel: patients ($n=11$) in the continuous infusion group (2 g loading dose followed by a 6 g/24 h continuous infusion). All values are means ± SEM. The horizontal broken line is drawn at a serum concentration value of 16 mg/L (potential susceptibility breakpoint).

and 88.9, 99.7 and 36.4–99.9 in the continuous infusion group, respectively. As shown in Figure 2, the mean pharmacokinetic profile in patients undergoing CVVH was different from that in the continuous infusion group. Concentrations stabilized after 8 h but a significant drop in temocillin levels had already occurred at that timepoint, resulting in a mean total and free $C_{ss}$ of 80 and 14 mg/L, respectively. The mean, median and range of percentages of dosing interval during which the free drug concentration remained >16 mg/L were 37.2, 33.0 and 9.2–73.7, respectively.

### *Population pharmacokinetic modelling and probability of target attainment*

A two-compartment model with a proportional error model best described the data of the patients treated three times daily. Inter-individual variability of pharmacokinetic parameters was explained by variations in CL and in first distribution volume (*V*1), for which coefficients of variation (CVs) were 36% and 58%, respectively. Individual and population predicted values were well correlated (data not shown) with observed concentrations.

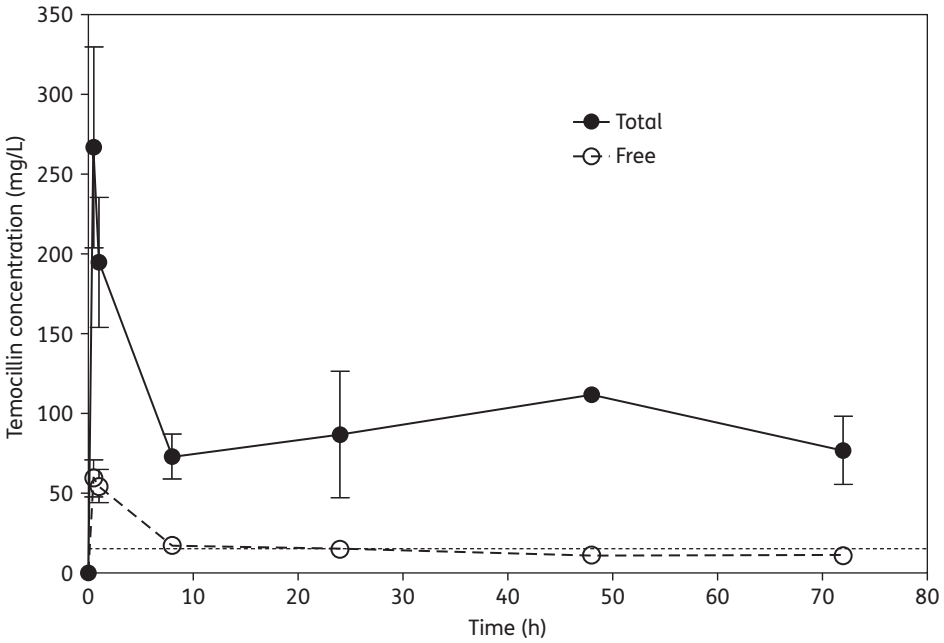


**Figure 2.** Total and free temocillin serum concentrations in patients ($n=4$) undergoing CVVH (750 mg loading dose followed by 750 mg/24 h by continuous infusion). All values are means ± SEM. The horizontal broken line is drawn at a serum concentration value of 16 mg/L (potential susceptibility breakpoint).

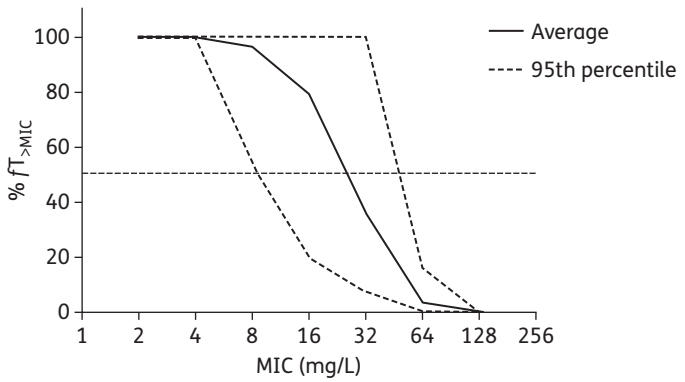


**Figure 3.** Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation) for discontinuous administration of a 6 g daily dose divided into three administrations at 8 h intervals (three times daily). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal broken line indicates the 50% $fT_{>MIC}$ limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria.[26]

CL was estimated at 3.69 L/h (SEM=0.456), *V*1 at 14.0 L (SEM=2.51), second distribution volume (*V*2) at 21.7 L (SEM=4.52) and Q (intercompartmental CL) at 8.45 L/h (SEM=1.06). A Monte Carlo simulation for target attainment (%$fT_{>MIC}$) for the three times daily group was performed. The results presented in Figure 3 show that a target of %$fT_{>MIC}$ of 80 was reached for the mean population for an MIC of 16 mg/L and a target of around 40 was reached for the mean population for an MIC of 32 mg/L. The 95% percentile indicates a %$fT_{>MIC}$ of 50% at MIC values slightly above 8 mg/L.

## Discussion

This study is the first to provide detailed pharmacokinetic/pharmacodynamic data for a high daily dose of temocillin (6 g/24 h) in critically ill patients receiving the drug either as 2 g every 8 h (three times daily) or by continuous infusion. In our study population, we were able to show that 6 g of temocillin daily given three times daily makes it possible to reach better pharmacokinetic/pharmacodynamic targets when compared with previously published data using 4 g daily divided into two administrations given at a 12 h interval (twice daily).[10] Moreover, our Monte Carlo simulation showed that, for the average patient, a %$fT_{>MIC}$ of 40 will be reached for an MIC of 32 mg/L and a %$fT_{>MIC}$ up to 80 will be reached for an MIC of 16 mg/L for a daily dosage of 6 g of temocillin given in three daily administrations, which is about twice the MIC value for which a similar %$fT_{>MIC}$ is obtained when using a daily dosage of 4 g given in two daily administrations.[10] Using the lowest 95% CI of the Monte Carlo simulation, a susceptibility breakpoint of 8 mg/L had been proposed for this 4 g daily dose given in two daily administrations. It was expected that, using a 6 g daily dose given in three daily administrations, this breakpoint could be increased to 16 mg/L. In fact it appears now to be lower and only slightly above 8 mg/L, due to the high variability in pharmacokinetics in our cohort [higher CVs for the drug *V* (58%) and CL (36%)]. This is most likely due to the inclusion of more severely ill patients in the present study compared with those included in the study using the 4 g daily dose with a twice daily schedule. This illustrates the difficult task of antibiotic prescribing for critically ill patients, in whom several factors alter drug concentrations, such as (i) sepsis (in which the large amount of fluids needed during the infectious episode alters *V* and the elimination rates of antibiotics, making standard regimens derived from

patients with less severe infections or healthy volunteers inapplicable);[20] (ii) the increased cardiac output (which can result in increased renal blood flow and glomerular hyperfiltration, leading to increased antibiotic CL and potentially subtherapeutic drug concentrations); and[11] (iii) obesity (which may have a significant impact on the distribution of antibiotics, resulting in inappropriate drug concentrations when standard regimens are administered).[21] The wide variations in actual antibiotic concentrations indicate that therapeutic drug monitoring in this group of patients would be well justified.

When compared with administration three times daily, continuous infusion of the same daily dose clearly offers a higher probability of reaching the desired pharmacokinetic/pharmacodynamic targets. This study also shows that actual serum levels when temocillin is given by continuous infusion are less influenced by patients' pharmacokinetic variability when compared with its administration three times daily, which may have an impact on clinical outcome. An alternative, often proposed, to continuous infusion is to extend the infusion time of β-lactams to 4 h rather than limiting it to 30 min. While this strategy has been successfully applied for carbapenems to meet instability issues when the drug is stored at room temperature, enabling coverage of organisms with a higher range of MICs,[22] it may not actually be necessary for temocillin, which shows a much higher stability than carbapenems even in concentrated solutions.[10] Other strategies would be to identify patients at risk of higher pharmacokinetic variability and to monitor drug levels on a regular basis.[23] Our data show that patients undergoing CVVH are particularly at risk of receiving a suboptimal dose even if temocillin is given by continuous infusion. As stated above, the regimen used in our CVVH population was set arbitrarily and our data confirm the need to at least double this dose in order to reach the necessary pharmacokinetic/pharmacodynamic target. A recent study using meropenem concluded that satisfactory pharmacokinetic parameters in patients undergoing CVVH could only be obtained if a dose of 500 mg was administered every 6 h using a prolonged infusion of 3 h.[24] This dose is 2-fold higher than the recommended dose for most severe infections, a ratio significantly superior to the one we used in the present study (∼one-fifth of the currently approved dose of 4 g/24 h).

High clinical cure rates were obtained using a 6 g daily dose and a trend towards superiority was observed for patients in the continuous infusion versus the three times daily group. Our study was not designed to assess the clinical efficacy of temocillin, but the results are nevertheless worth being taken into account, given that (i) all our patients were hospitalized in ICUs and were severely ill; (ii) most infections were life-threatening; (iii) temocillin was used as a first-line therapy in 25% of our patients; (iv) the MIC for 50% of the strains was ≥8 mg/L; and (v) ESBL-producing strains were also included. It is important to highlight the fact that using temocillin for treatment of intra-abdominal infections in ICU patients has not been reported before. Thus, the high clinical cure rate observed for this indication warrants further investigation. Lastly, the absence of drug incompatibility issues and/or neurotoxicity signs is reassuring. This is in line with our current clinical experience using 6 g of temocillin daily in >170 patients (P.-F. Laterre, unpublished data). The present study remains, however, limited by its rather small sample size, which did not allow us to provide robust data on the clinical efficacy of temocillin administered by continuous infusion compared with administration three times daily. Also, no final dosing recommendation can be given for patients undergoing renal replacement therapy.

In conclusion, 6 g of temocillin daily given in three daily administrations is well tolerated and, according to the pharmacokinetic data, is adequate to reach in average patients the necessary free drug concentration meeting the average $\%fT_{>MIC}$ value of 80 for an MIC of 16 mg/L, corresponding to correct coverage for most isolates of Enterobacteriaceae, since the MIC of temocillin for these bacteria rarely exceeds this value.[3] For patients with high pharmacokinetic variations and/or to cover strains against which temocillin would have higher MICs, continuous infusion may be a useful and practical alternative as it is associated with a higher $\%fT_{>MIC}$ without apparent toxicity or administration issues.

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## Transparency declarations

P.-F. L. has been consultant for Ferring, EISAI and Tigenix. S. V. d. V. is and S. C. was an employee of Eumedica s.a.; S. C. is currently an employee of GSK Biologicals. J. W. M. has been a consultant for and/or received research funding from Angelini, AstraZeneca, Basilea, Janssen-Cilag, Merck & Co, Cubist, Pfizer, Polyphor and Roche. P. M. T. is an unpaid advisor to Eumedica and his laboratory is receiving research funding from Eumedica through a Public Private Partnership grant awarded by the Belgian *Région Wallonne* for the study of pharmacokinetics of temocillin in special populations. All other authors: none to declare.

### *Author contributions*

P.-F. L., S. C. and P. M. T. designed the study. P.-F. L., X. W. and T. D. were in charge of the patients. S. C., S. V. d. V., A. E. M. and J. W. M. performed the sample analysis and a first descriptive analysis of the pharmacokinetic profiles. A. E. M. and J. W. M. developed the pharmacokinetic/pharmacodynamic models, performed the Monte Carlo simulations and calculated the target attainment rates. All authors participated in the writing of the manuscript and approved the final version.

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