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Temocillin 6 g Daily in Critically Ill Patients: Continuous Infusion versus Thrice daily Administration

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ABSTRACT

Background: The growing incidence of infections caused by Enterobacteriaceae producing extended spectrum β -lactamases has led to increased use of carbapenems. Temocillin, which resists to most β -lactamases, may stand as a useful alternative.

Aims: To assess the pharmacokinetics and target attainment rates of temocillin 6 g daily divided in 3 administrations every 8 h (thrice daily) or administered by continuous infusion in critically ill patients.

Methods: Prospective, bi-center, randomized, controlled study in patients suffering from intra-abdominal or lower respiratory tract infections caused by Enterobacteriaceae.

Results: Thirty-two patients were included and analyzed for clinical efficacy with pharmacokinetics measured in 29. Four patients undergoing continuous veno-venous hemofiltration (CVVH) were analyzed separately. Mean, median and range percentages of the dosing interval during which the free drug concentration remained above 16 mg/L were 76.4, 98 and 18.7-98.9 in patients treated thrice daily and 98.9, 99.7 and 36.4-99.9 in patients with continuous infusion, respectively. Clinical cure rates were 79% and 93% in each of these groups, respectively (NS). 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 for 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 to thrice daily administration. Clinical efficacy compared with carbapenems in documented severe infections needs to be further studied.

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 -lactamases² including most ESBLs,³ AmpCs,⁴ and even some carbapenemases.⁵ *In vitro* studies demonstrated susceptibility rates of up to approx. 80% and 90% for ESBL-producing strains if using a breakpoint of 8 or 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 ESBL/AmpC-producing Enterobacteriaceae.⁹ In that study, a 4 g daily dose of temocillin divided in 2 administrations at 12 h interval was correlated with higher clinical cure when compared to a lower dosage. However, the pharmacokinetic analysis and the 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 2 administrations at 12 h interval may not be sufficient in critically ill patients where alteration of critical parameters such as drug volume of distribution (V_d), clearance (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 maximized by 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 (PK) parameters of temocillin in critically ill patients using a larger daily dose (6 g) and comparing its administration into 3 discrete doses of 2 g given at 8 h interval to 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, Methods and Materials

Study design, patients, antibiotic treatment and data collection

This was a prospective, bi-center (Cliniques universitaires St-Luc, Brussels, Belgium; St Pierre Hospital, Ottignies, Belgium), randomized, and 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 intensive care unit; (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 to 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: 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); thrice daily: 2 g temocillin (in 50 mL of water for injection) every 8 h injected over a 30 min period. Temocillin dosing regimens were adjusted for creatinine clearance according to **Table 1**. For patients undergoing continuous veno-venous hemofiltration (CVVH), temocillin was administered by continuous infusion and the dose arbitrary set to

750 mg/24h 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 at 0, 0.5, 1, 8, 24, 48, and 72 h after starting the administration of the loading dose. For patients treated with the thrice daily regimen, samples were drawn at 0, 0.5, 1, 2 and 8 h after starting the first administration on first day of therapy. All samples were drawn from 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 were assayed in serum as previously described.¹⁰ In brief, the total antibiotic was extracted by a solid-phase method (OASIS® HLB Extraction Cartridge System, Waters Corp.; typical recovery, 95% to 97%) while the free fraction was separated from serum proteins by ultrafiltration (Centrifree® devices, Merck-Millipore Corp., Billerica, Mass.). 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}

MIC determinations

MIC from the successfully collected isolates were obtained from the automated system used in routine by the clinical microbiology laboratories of the participating centers (Vitek2® and Phoenix® for St Pierre, Ottignies and St Luc, Brussels, respectively).

Population pharmacokinetics and probability of target attainment

Population pharmacokinetic (PK) parameters were estimated by means of Non-Linear Mixed Effect Modeling (NONMEM) using the 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, Texas, USA) and NONMEM® software package (version VI, release 2, ICON Development Solutions, Ellicott City, Maryland, USA). To determine the basic structural PK parameters various 1- and 2-compartment models were tested. Model selection and identification of variability were based on the evaluation of the mean objective function value (MOFV), PK parameter point estimates, and their respective confidence intervals, and goodness-of-fit plots. To detect significant differences between two structural models, the MOFV with a pre-specified 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 times). 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 thrice 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 the 95% percentiles of $\%fT > MIC$ over MIC (for a range of 2 to 256 mg/L).

Source of products

Temocillin and ticarcillin were obtained as NEGABAN® (Eumedica s.a., Brussels, Belgium) and as 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), and with Fisher 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 3 groups; those given temocillin the daily dose of temocillin (6 g) divided in 3 administrations at 8 h interval (thrice 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 Sequential Organ Failure Assessment score (SOFA)¹⁹ which was significantly higher in patients treated with CVVH (16 versus 7 and 8.5 in the thrice 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.

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) species with temocillin MICs varying from < 2 mg/L to 16 mg/L. Four of the isolates were ESBL-producing strains (*E. coli*, *K. 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 9 other patients. The overall mean treatment duration was 6 days (range, 2 to 22), with no significant difference between groups (6, 7 and 5 days in the thrice daily, continuous infusion, and CVVH groups, respectively). The overall clinical cure rate was 84% [27/32] and, if broken down by groups, 79% (11/14), 93% [13/14] and 75% [3/4] in the thrice daily, continuous infusion, and CVVH groups, respectively (differences are not significant). According to the site of infection, clinical cure rate was 94% [16/17] in intraabdominal 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 1 *Serratia marcescens* (lower respiratory tract infection, MIC = 16 mg/L), 1 *Morganella morganii* (intraabdominal infection, MIC = 4 mg/L), 1 *E. cloacae* (lower respiratory tract infection, MIC ≤ 2 mg/L) and 2 *K. pneumoniae* (both in lower respiratory tract infections, MIC = 8 mg/L and one of unknown MIC but ESBL producer). Clinical cure rate was 75% [3/4] in infections caused by ESBL-producing organisms.

In 3 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*; methicillin-resistant *Staphylococcus aureus* + *Hafnia alvei*; methicillin-susceptible *S. aureus* + multi-resistant *E. coli* [this patient was previously infected by *P. mirabilis*]). In patients treated in the intensive care unit, the overall mortality rate was 31% [10/32]. No

death was related to the primary infection treated with temocillin. Globally, mortality rates were 36% [5/14], 21% [3/14], and 50% [2/4] in the thrice 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 6 were deemed not attributable and 1 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 thrice daily, continuous infusion and CVVH groups, respectively). In the 3 remaining patients, temocillin levels could not be determined due to the presence of other medications and/or metabolites interfering with the UV detection under the conditions of assay. Total and free temocillin serum concentrations from patients in the thrice daily and continuous infusion groups are shown in **Figure 1**. In the thrice daily group and for total temocillin levels, the mean AUC_{24h} 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 mg/L 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 of 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 percentages of dosing interval during which the free drug concentration remains above 16 mg/L were 76.4, 98.0 and 18.7-98.9 in the thrice daily group 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 from 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 time point, resulting in a mean total and free C_{ss} of 80 mg/L and 14 mg/L, respectively. The mean, median and range percentages of dosing interval during which the free drug concentration remained above 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 thrice daily. Inter-individual variability of pharmacokinetic parameters was explained by variations in clearance (CL) and in first distribution volume (V1) for which coefficients of variation [CV]) were 36% and 58%, respectively.

Individual and population predicted values were well correlated (data not shown) with observed concentrations. CL was estimated at 3.69 L/h (standard error [SE] = 0.456), V1 at 14.0 L (SE = 2.51), V2 (2nd distribution volume) at 21.7 L (SE = 4.52) and Q (intercompartmental clearance) at 8.45 L/h (SE = 1.06). A Monte-Carlo simulation for target attainment (%fT>MIC) for the thrice 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 (PK/PD) data of a high daily dose of temocillin (6 g/24 h) in critically-ill patients receiving the drug either as 2 g every 8 h (thrice daily) or by continuous infusion. From our study population, we were able to show that temocillin 6 g daily given thrice daily enables reaching better PK/PD targets when compared to previous published data using 4 g daily divided into 2 administrations given at 12 h interval (twice daily).¹⁰ Moreover, our Monte Carlo simulation showed that, for the average patients, a %fT>MIC of 50 will be reached for a MIC of 32 mg/L and a %fT>MIC up to 80 will be reached for a MIC of 16 mg/L for a daily dosage of 6g of temocillin given thrice daily, which is about twice the MIC value for which a similar %fT>MIC is obtained when using a daily dosage of 4 g given twice daily.¹⁰ Using the lowest 95% confidence interval of the Monte Carlo simulation, a susceptibility breakpoint of 8 mg/L had been proposed for this 4 g daily dose given twice daily. It was expected that using a 6 g daily dose given thrice daily, 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 CV's for the drug V_d [58%] and CL [36%]). This is most likely due to the inclusion of more severely ill patients in the present study compared to those included in the study using the 4 g daily dose with twice daily schedule. This illustrates the difficult task in antibiotic prescribing for critically ill patients for whom several factors alter the drug concentrations such as (i) sepsis (in

which the large amounts of fluids needed during the infectious episode alters V_d 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),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 of actual antibiotic concentrations indicates that therapeutic drug monitoring in this group of patients would be well deserved.

When compared to the thrice daily administration, continuous infusion of the same daily dose clearly offers a higher probability of reaching the desired PK/PD targets. This study also shows that actual serum levels when temocillin is given by continuous infusion are less influenced by patients' pharmacokinetics variability when compared to its thrice daily administration, 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 while enabling covering MICs to a higher range,²² it may, actually, not 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 for higher pharmacokinetic variability and to monitor drug levels on a regular basis.²³ Our data actually show that patients undergoing CVVH

are particularly at risk of receiving suboptimal dose, even if temocillin is given by continuous infusion. As stated before, the regimen used in our CVVH population was set arbitrarily and our data actually confirm the need of at least doubling this dose in order to reach the necessary PK/PD target. A recent study using meropenem concluded that satisfactory PK parameters in patients undergoing CVVH could only be obtained if administering a dose of 500 mg every 6 h using a prolonged infusion of 3 h.²⁴ This dose is 2 times higher than the recommended dose for most severe infections, a ratio significantly superior to the one we used in the present study (approx. 1/5 of the registered dose of 4 g/24 h).

High clinical cure rates were obtained using a 6 g daily dose and a trend towards superiority was even observed for patient in the continuous infusion vs. the thrice daily group. Our study was not designed to assess the clinical efficacy of temocillin, but the results are nevertheless worth of being taken into account, giving that (i) all our patients were hospitalized in intensive care units 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) 50% of the strains had an MIC \geq 8 mg/L and (v) ESBL-producing strains were also included. It is important to highlight the fact that using temocillin for treatment of intraabdominal infections in intensive care units patients has not been reported before. Thus, the high clinical cure 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 daily of temocillin in more than 170 patients (P.F. Laterre, unpublished

data). The present study remains, however, limited by its rather small sample size, which did not allow providing robust data on the clinical efficacy of temocillin administered by continuous infusion compared with its thrice daily administration. Also, no final dosing recommendation can be given for patients undergoing renal replacement therapy.

In conclusion, temocillin 6 g daily given thrice daily is well tolerated and, according to the pharmacokinetic data, is adequate to reach in average patients the necessary free drug concentration meeting the a average %fT>MIC value of 80 for an MIC of 16 mg/L, corresponding to a correct coverage for most isolates of Enterobacteriaceae, since the MIC of temocillin against 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 toxicities or administration issues.

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P.F.L., S.C. and P.M.T. designed the study. P.M.F., X.W, 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 to the writing of the manuscript and approved its final version.

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Table 1. Temocillin dose adjustment for creatinine clearance

Creatinine clearance (mL/min) or Condition	Daily dose	
	thrice daily ^a	Continuous infusion ^b
> 50	3 x 2 g	6 g / 24h
50 – 30	3 x 1 g	3 g / 24h
30 - 10	1 x 1.5 g	1.5 g / 24h
< 10	1 x 750 mg	750 mg / 24h
CVVH ^c	NA	750 mg / 24h

^a administrations as a 30 min infusion at 8 h intervals

^b administration by continuous infusion over 24h. Each patient received a 2 g loading dose

^c continuous veno-venous hemofiltration

^d NA: not applicable

Table 2. Patients' characteristics and treatment parameters

	Group		
	Thrice daily ^a	continuous infusion ^b	CVVH ^c
Recruitment			
Patients enrolled (no.)	14	14	4
PK population (no.)	13	12	4
Demography			
M/F (ratio)	6/8	11/3	0/4
Age (years) ^d	65 ± 15	68 ± 11	60 ± 16
Weight (kg) ^d	68 ± 12	71 ± 15	58 ± 7
Body mass index (kg/m ²) ^d	24 ± 4	24 ± 5	23 ± 2
Creatinine clearance (mL/min) ^d	82 ± 48	56 ± 34	NA
Severity score on admission			
APACHE II ^{e,f}	16	17	20.5
SOFA ^{e,g}	7	8.5	16 ^h
Infection types ⁱ			
LRTI (positive blood culture; no.)	6	4 (1)	1
IAI (positive blood culture; no.)	6 (2)	8 (3)	3 (2)
UTI (positive blood culture; no.)	1 (1)	1	0
BSI from unknown origin (no.)	1	1	0
Treatment parameters and outcomes			
Treatment durations (days) ^d	6 ± 2	7 ± 5	5 ± 3
Dosage adjustment for creatinine clearance			
50 – 30 mL/min (no.)	3	1	0
30 – 10 mL/min (no.)	2	4	0
Clinical cure (% (ratio))	79 (11/14)	93 (13/14)	75 (3/4)
Overall ICU mortality (% (ratio))	36 (5/14)	14 (2/14)	50 (2/4)

^a administration of the daily dose divided into 3 30-min infusions at 8 h intervals

^b administration of the daily dose by continuous infusion over 24h. Each patient received a 2 g loading dose

^c patients under continuous veno-venous hemofiltration and receiving a loading dose of 750 mg followed by a continuous infusion of 750 mg/24h

^d mean ± SD

^e median

^f Acute Physiology and Chronic Health Evaluation II score²⁵
^g Sequential Organ Failure Assessment score¹⁹

^h Significantly different from the 2 other groups ($P=0.0007$)

ⁱ LRTI: lower respiratory tract infection; IAI: intraabdominal infection; UTI: urinary tract infection; BSI: blood stream infection

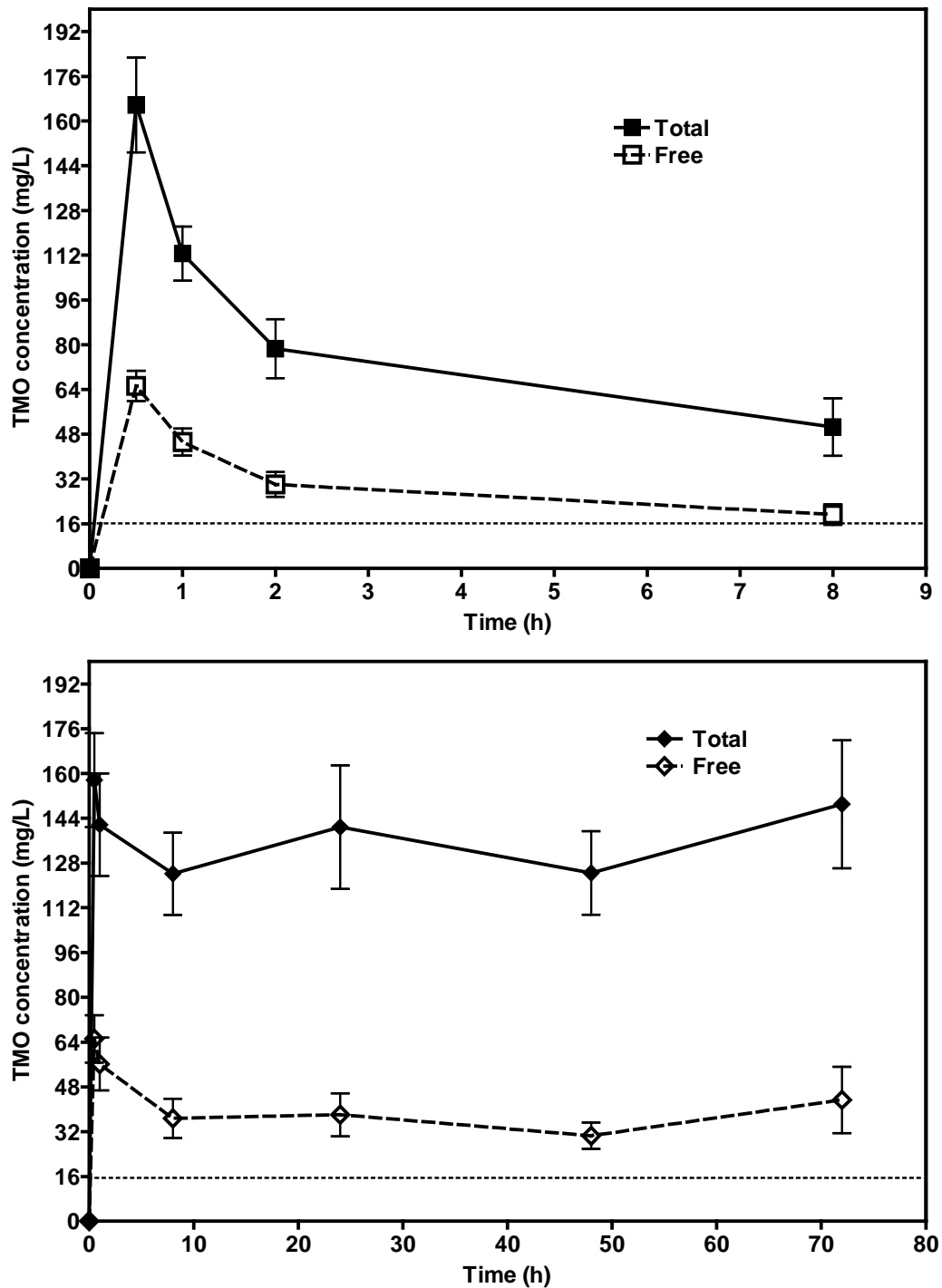
NA: not applicable,

Table 3. Available isolates and MIC data

Isolates	no. of isolates in group			no. of isolates with an MIC (mg/L) of			
	Thrice daily	Continuous infusion	CVVH	≤ 2	4	8	16
<i>E. coli</i>	4	6	3 (1 ^a)		4	6	1
<i>K. pneumoniae</i>	5 (1 ^a)	1	0	1	1	3	
<i>K. oxytoca</i>	0	1	0	1			
<i>E. cloacae</i>	2	2 (1 ^a)	0	2	1		
<i>E. aerogenes</i>	0	1 (1 ^a)	0				1
<i>P. mirabilis</i>	1	0	0		1		
<i>M. morganii</i>	0	0	1		1		
<i>S. marcescens</i>	1	1	0				2
Gram positive bacterium	1	0	0				
Total	14	12	4	4	8	9	4

^a ESBL-positive

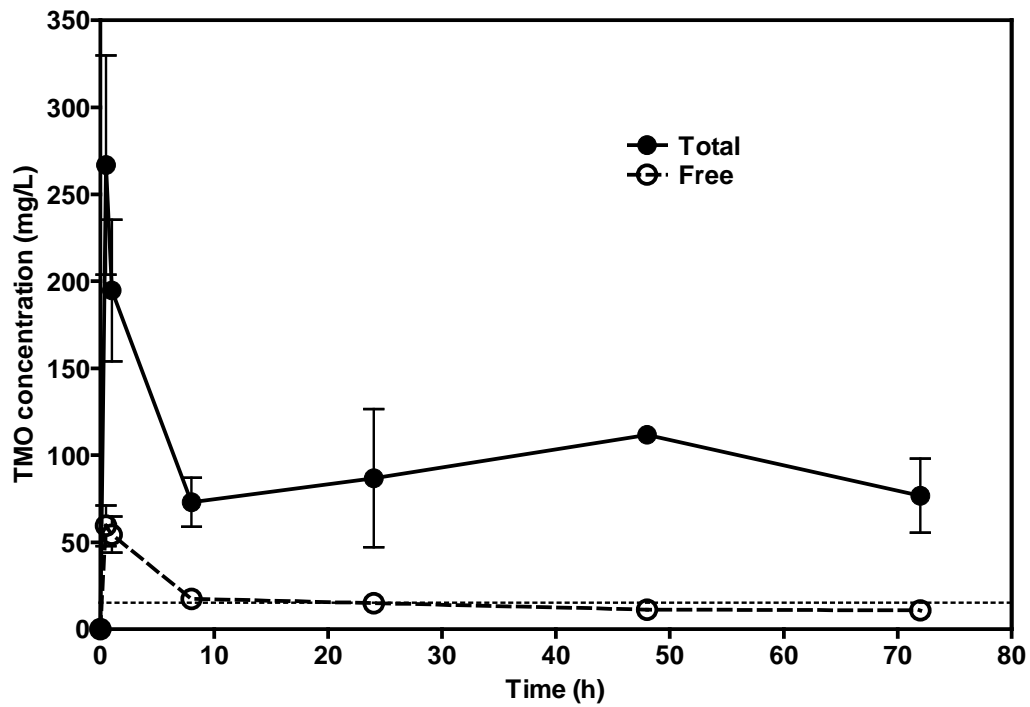
Figure 1



Caption to Figure 1. Total (plain lines) and free (dashed lines) temocillin serum concentrations. Upper panel: patients (n=13) from thrice daily group (daily dose of 6 g divided in 3 administrations at 8 h interval). Lower panel: patients (n=11) from continuous infusion group (2 g loading dose followed by a 6 g/24h continuous

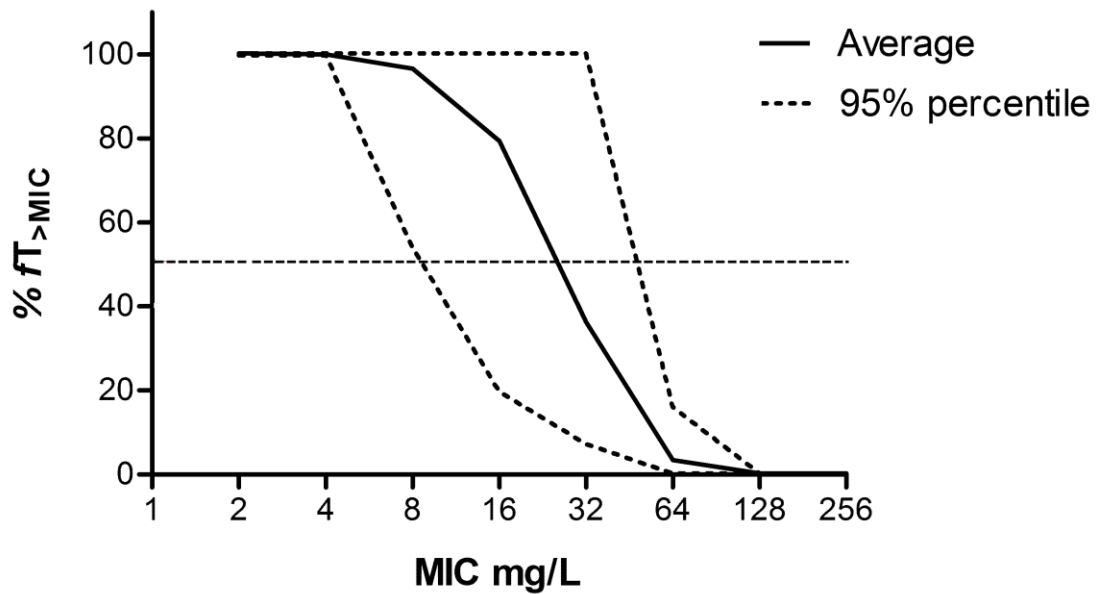
infusion). All values are means \pm SEM. The horizontal dotted line is drawn at a serum concentration value of 16 mg/L (potential susceptibility breakpoint).

Figure 2



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

1 Figure 3



2

3 Caption to **Figure 3**. Probabilities of target attainment of temocillin (as obtained with
 4 the Monte Carlo simulation; solid line, mean value; thick dotted lines, 95% confidence
 5 interval) for a discontinuous administration of a 6 g daily dose divided in 3
 6 administrations at 8 h interval (thrice daily). The abscissa shows the MIC range used
 7 for the simulations and the ordinate the fraction of time (as a percentage) during
 8 which free serum levels remain above the corresponding MIC. The thin horizontal
 9 dotted line indicates the 50% $fT > MIC$ limit achieving a bacteriostatic effect and
 10 survival for penicillins in animal models with Gram-negative bacteria.²⁶