Dosing regimen of meropenem for adults with severe burns: a population PK study with Monte Carlo simulations

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SYNOPSIS

Objectives: To develop a population model to describe the PK of intravenous meropenem in adult patients with severe burns and investigate potential relationships between dosage regimens and antimicrobial efficacy.

Patients and methods: A dose of 1 g every 8 h was administered to adult patients with total body surface area burns of ≥15%. Doses for subsequent courses were determined using results from the initial course and the patient's clinical condition. Five plasma meropenem concentrations were typically measured over the dosage interval on 1 – 4 occasions. An open two-compartment PK model was fitted to the meropenem concentrations using NONMEM and the effect of covariates on meropenem PK was investigated. Monte Carlo simulations investigated dosage regimens to achieve a target $T_{>MIC}$ for at least 40%, 60% or 80% of the dose interval.

Results: Data comprised 113 meropenem concentration measurements from 20 dosage intervals in 12 patients. The parameters were CL (L/h) = 0.196 L/h/kg x (1-0.023 x (age - 46)) x (1- 0.049 x (albumin-15)), V_1 = 0.273 L/kg x (1 - 0.049 x (albumin-15)), Q = 0.199 L/h/kg and V_2 = 0.309 L/kg x (1 – 0.049 x (albumin-15)). For a target of 80% $T_{>MIC}$, the breakpoint was 8 mg/L for doses of 1 g every 4 h and 2 g every 8 h given over 3 h but only 4 mg/L if given over 5 minutes.

Conclusions: Although 1 g eight-hourly should be effective against *E. coli* and coagulase negative *Staphylococcus,* higher doses, ideally with a longer infusion time, would be more appropriate for empiric therapy, mixed infections and bacteria with MIC values ≥ 4 mg/L.

INTRODUCTION

Severely burned patients present several key challenges in their management, one being infection, which is a major cause of illness and death.[1] The earliest organisms isolated from burn wounds tend to be Gram-positive organisms, such as *Staphylococcus* spp, but in the latter part of the first post-burn week, Gram-negative organisms become dominant, with *Pseudomonas* spp being the most common isolates.[2,3]

Meropenem is a broad-spectrum β-lactam antibiotic commonly used to treat infections in patients with burn injuries. A survey of UK hospitals which treat severely burned adults found that thirteen of the sixteen respondents used meropenem as empiric therapy and / or if susceptible organisms were identified (unpublished data). In most units, the standard adult dose of 1g over 5 minutes every 8 h was used. However, it has been known since the 1970s that the pathophysiological changes which follow a major burn injury may affect the pharmacokinetics (PK) of drugs.[4] These changes are influenced by a number of factors, including the presence of sepsis, the area and depth of the burn, serum protein concentration, age, CL_{CR}, degree of hydration, presence of oedema and time after injury.[5] As a result, several studies have recommended using higher antibiotic doses than are given to patients without burn injuries.[6-9] There is evidence to suggest that meropenem pharmacokinetics are also altered in severely burned patients[5,10,11]and within our own unit, we previously reported the case of a 27 year old man with a total body surface area (TBSA) burn of 52% in whom a dose increase to 1 g over 5 minutes every 4 h was needed to achieve target serum concentrations.[12] No previous population studies have examined intraindividual variability in pharmacokinetic parameters in this patient group.

Since meropenem demonstrates time-dependent killing at clinically relevant concentrations,[13]the most important pharmacodynamic (PD) index to predict antimicrobial

efficacy is the percentage of the dosing interval that the antibiotic concentrations remain above the MIC of the pathogenic organism ($T_{>MIC}$). Many PD studies have selected a $T_{>MIC}$ for at least 40% of the dose interval as the target.[14-19] However, as treatment with meropenem is often empiric, the MIC is not known. Whilst the EUCAST 2013[20] susceptibility breakpoint of 2 mg/L could be selected as the target MIC, a 2009 study of meropenem activity against nosocomial isolates across Europe found 79% of *Pseudomonas aeruginosa* isolates susceptible at a breakpoint of 4 mg/L[21] suggesting this might be a more suitable target. However, such considerations should always be based on local epidemiology, where it is available. In this context, dosage regimens can be optimised through integration of PK-PD targets, derived from both PK data and exposure-response data, with Monte Carlo simulation to predict the probability of attaining a specific PD target at various dosage regimens.[15,22]

The aim of this study was to determine the PK profile of intravenous meropenem given at an initial dose of 1g over 5 minutes every 8 h to adult patients admitted to hospital with severe burns, to develop a population model to describe the PK of meropenem in this patient group, and to use Monte Carlo simulation techniques to investigate potential relationships between dosage regimens and the achievement of PK/PD targets.

PATIENTS AND METHODS

Patients

Adults admitted to a Regional Burns Centre with a major burn (defined as a TBSA burn of at least 15%), receiving meropenem, were eligible for inclusion in the study. Consent was obtained from patients who were deemed fit to give it. For incapacitated adults, assent was obtained from the next of kin, and consent to use the data sought retrospectively from those patients who survived their injury. The study was approved by the Trust Research and Development Committee, the National Ethics Research Committee 3/3/045 and the MHRA (Reference 21310/0001/001-002).

Patient demographics (gender, age, weight and height), burn details (TBSA burn, full and partial thickness burn surface area and percentage burn remaining at time of diagnosis of infection), routine clinical data (e.g. serum creatinine and serum albumin) and antibiotic prescribing information were collected for each patient. In addition, the following data were recorded: post-burn day when blood samples were taken; length of stay in the Intensive Therapy Unit (ITU); Abbreviated Burn Severity Index (ABSI) Score[23] and patient outcome.

Study protocol

Initial courses of meropenem commenced at a standard dose of 1 g over 5 minutes every 8 h, as per Trust antimicrobial guidelines. After at least 24 h of therapy, blood samples were taken at the following times: predose; 30 minutes, 1, 2 and 4 h post dose; and immediately before the next dose. Blood samples (3 mL) were collected using serum gel tubes, centrifuged at 4,500 rpm, then the resulting serum was separated into plain 2 mL plastic tubes, stored and transported at 4^0C for analysis within 24 hours, in line with previous published stability data.[24] Samples were analysed by HPLC at the National Antimicrobial Reference Laboratory (approved

by Clinical Pathology Accreditation Ltd (UK)) using a previously reported method.[25] This has a lower limit of detection of 0.3 mg/L and a limit of quantification of 1 mg/L, where the intra and inter assay coefficient of variation (CV)% were both less than 10%. The results were reported within 24 hours and the dosage regimen was then modified if necessary and when the length of course allowed to maintain concentrations above 4 mg/L for at least 40% of the dose interval. If a patient required a second or third course of meropenem, the decision of what starting dose to use was influenced by results from the initial course and the patient's clinical condition. Serum concentrations were measured and doses amended as described for initial courses.

Pharmacokinetic analysis

A population PK modelling approach was applied to the data using NONMEM Version 7.2.[26] (ICON Development Solutions, Ellicott City, MD, USA) with first order conditional estimation and interaction (FOCEI). Post-processing of the NONMEM results was performed with R 2.1.4.0[27] and diagnostic plots were performed with Xpose version 4 programmed in R 2.1.4.0.[28]

Based on a graphical exploratory analysis, an open, two-compartment model with zero order input and linear elimination and linear distribution from the central to peripheral compartment was selected to describe the meropenem plasma concentrations after intravenous administration. This model was parameterized in terms of CL, central volume of distribution (V_1), intercompartmental clearance (Q) and volume of distribution of the peripheral compartment (V_2). Observed C_{max} was defined as the measured serum concentration at 30 minutes in each patient. Individual parameter estimates were obtained from the Empirical Bayes Estimates (EBEs) and were used to calculate half-lives; $AUC_{0\text{-}24}$was calculated from the total daily dose and individual estimates of CL.

Log-normal distributions were assumed for between-subject variability (BSV) and between occasion variability (BOV) in the PK parameters; an "occasion" was defined as a set of

concentration-time data collected over one day. A proportional model was used to describe the residual error. The shrinkage of the EBE of the BSV were calculated as previously suggested.[29]

Once the base model had been identified and, in the absence of significant shrinkage, EBE of the BSV were used to identify potential relationships between individual PK estimates and the clinical covariates gender, age, weight (using linear and allometric relationships), serum creatinine concentration, measured CL_{CR}, serum albumin, percentage of TBSA burn, percentage of full and partial thickness burn surface area, percentage burn remaining at time of diagnosis of infection and post-burn day. These covariates were first examined using scatter plots then added to and removed from the population model in a stepwise manner.[30]

Improvements in the fit obtained with each model were assessed in several ways. First, the NONMEM generated objective function value (OFV) was used to perform the likelihood ratio test. A decrease in OFV of ≥10.83 was required to reach statistical significance ($p = 0.001$) for the addition of one fixed effect in a hierarchical model. In addition, improvement in the fit was assessed by reductions in the BSV, BOV, residual variability and standard errors of the parameter estimates. Diagnostic plots and shrinkage were also examined.[29]

The final population model was evaluated in three ways: a non-parametric bootstrap sampling procedure with 1,000 samples was conducted using PsN toolkit[31] and a prediction-corrected visual predictive check (pcVPC) was based on 1,000 simulations.[32] Finally, normalised prediction distribution errors (NPDE) obtained from 10,000 simulations were computed using the software developed by Brendel *et al*.[33]

Pharmacodynamic simulations

The final PK model was used for simulations that were undertaken to explore the role of the dosage regimen on the probability of target attainment (PTA). The final parameters of the

159 population PK model were used to generate individual total drug concentration profiles for each
160 of the 1,000 simulated patients using NONMEM. The clinical characteristics of the simulated
161 patients mirrored those of the original patient group. Simulations were performed for four steady
162 state dosage regimens given by bolus injection over 5 minutes: 1 g every 8 h; 2 g every 8 h; 1 g
163 every 6 h; 1 g every 4 h. In addition, three 3 hour infusion regimens: 1 g every 8 h; 2 g every 8 h
164 and 1 g every 6 h and steady state concentrations arising from three continuous infusions: 3, 4
165 and 6 g over 24 h were simulated. For evaluation of these dosage regimens, MIC values were
166 chosen across the range 0.125-128 mg/L. In each patient, the time that the drug concentration
167 remained above the MIC was calculated as the cumulative percentage of the dosage period.[34]
168 For each MIC and dosing regimen, PTA was defined as the probability of 1000 simulated
169 patients achieving the target $T_{>MIC}$ for at least 40%, 60% or 80% of the dose interval. For each
170 meropenem regimen, the highest MIC at which the PTA was ≥ 90% was defined as the PK-PD
171 susceptible breakpoint.

172 A second analysis was conducted using MIC distributions of *Escherichia coli*, coagulase
173 negative *Staphylococcus, P. aeruginosa* and *Enterococcus faecalis* derived from the EUCAST
174 database.[20] These MIC distributions were extracted from 8005 strains of *E. coli*, 143 strains of
175 coagulase negative *Staphylococcus,* 57505 strains of *P. aeruginosa* and 12369 strains of *E.*
176 *faecalis*. The cumulative fraction of response (CFR) was used to estimate the overall response
177 of pathogens to meropenem for each of the ten dosage regimens, subdivided according to CL.
178 This estimate accounts for the variability of drug exposure in the population and the variability in
179 the MIC combined with the distributions of MICs for the pathogens. For each MIC, the fraction of
180 simulated patients who met the PD target was multiplied by the fraction of the distribution of
181 microorganisms for each MIC. The CFR was calculated as the sum of fraction products over all
182 MICs.

183

RESULTS

Patient Demographics

Twelve patients (7 male) were recruited to the study with a mean age at the time of the first course of 46 years (range 27 to 73).The median percentage of TBSA burn was 41% (range 20 to 80) and the median ABSI Score was 10 (range 5 to 12). Most burns (n = 10) resulted from flame injuries; inhalation injury was present in 7 cases. All patients were mechanically ventilated, spending a median of 40.5 days in intensive care (range 19 to 119 days). Five did not survive their injury. The following pathogenic bacteria were isolated: coagulase negative *Staphylococcus* in 9 patients; *P. aeruginosa* in 4 patients, mixed coliforms and *Enterococcus* spp in 4 patients, *E. coli*, *Stenotrophomonas maltophilia* and *Enterobacter cloacae* in 3 patients. Other microorganisms found were *E. faecalis*, *Bacillus cereus*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Haemophilus influenzae*, *Klebsiella* spp and *Proteus mirabilis.*

In general, renal function was not impaired at the time of recruitment into the study and none of the patients required renal replacement therapy. The median (range) of serum creatinine was 41 μmol/L (22 to 112) and of measured CL_{CR} was 136.5 ml/min (60 to 217). Measured CL_{CR} was only available for 8 of the 12 patients.

Serum Concentration-Time Profiles

A total of 113 plasma meropenem concentration measurements were available, with a median of 9 (range 4-24) measurements per patient. One high trough concentration that was inconsistent with all other data from the same patient was removed from the analysis. Overall, there were 20 sets of measurements (occasions); 7 patients had one occasion, 3 patients had two occasions, 1 patient had three occasions and 1 patient had four occasions. Individual concentration-time profiles are presented in Figure 1.

Patients initially received a standard intravenous infusion of meropenem over 5 minutes at doses of 1 g every 8 h for 3-5 consecutive days. In seven patients, sub-optimal serum concentrations were reported, which required an increase in the frequency of administration in three patients to 1 g every 6 h, in one patient to 2 g every 8 h and to 1 g every 4 h in one patient. Observed C_{max} ranged from 9.2 to 79.2 mg/L with a mean (SD) of 28.4 (16.1) mg/L while the pre-dose trough ranged from 0.3 to 19.2 mg/L with a mean (SD) of 2.8 ±4.2 mg/L.

Pharmacokinetic Analysis

An open two compartment disposition model with zero order input and linear elimination and distribution adequately described the time course of plasma concentration following meropenem administration.

All parameters were linearly related to body weight. Scatterplots of individual estimates of the parameters against the measured and derived clinical and demographic data identified additional potential relationships between CL and age, measured CL_{CR}, serum albumin, TBSA burn, full thickness burn surface area and percentage burn remaining at time of diagnosis of infection. Relationships were identified between V_1 and V_2 and serum albumin; only the inclusion of age on CL and serum albumin on CL, V_1 and V_2 achieved statistically significant reductions in the OFV when included individually in the population model. A further improvement in the fit was achieved by including BOV in CL in the model. The final population model reduced the OFV from 385.5 (base model) to 276.0 and had the following structure:

CL = 0.196 L/h/kg x (1-0.023 x (age - 46)) x (1- 0.049 x (albumin-15))

V_1 = 0.273 L/kg x (1 - 0.049 x (albumin-15))

Q = 0.199 L/h/kg

229 V_2 = 0.309 L/kg x (1 – 0.049 x (albumin-15))

230 The population model identified a typical whole body clearance estimate of 0.196 L/h/kg in a
231 patient with the mean age of 46 years and the mean albumin concentration of 15 g/L. Inclusion
232 of weight, age and albumin reduced BSV in CL and Q from 47.2% and 94.4%, respectively, to
233 negligible values. The shrinkage of BSV in V_2 was estimated at 27.6%. BOV for V_1, V_2 and Q
234 were negligible and fixed to 0; BOV for CL was 28.8%. The population model predicted a wide
235 range of CL estimates (0.082 to 0.352 L/h/kg), which mainly reflected the age range of the
236 patients. Individual parameter estimates for each patient on each occasion are listed in Table 1.
237 The mean CL was 18.4 L/h and ranged from 5.3 to 36.0 L/h; mean estimates of distribution and
238 elimination half-lives were 0.4 h (range 0.3 to 0.6 h) and 2.9 h (range 1.3 to 9.7 h), respectively.
239 $AUC_{0\text{-}24}$ ranged from 83 to 563 mg·h/L (mean 226 mg·h/L).

240 The final population model parameters and non-parametric bootstrap estimates are presented in
241 Table 2. From 1,000 replicates analysed during the bootstrap analysis, 11% failed to minimize
242 successfully and were excluded. The population estimates of the final model were similar to the
243 mean of the non-parametric bootstrap replicates that minimized successfully and were
244 contained within the 95% confidence intervals. The precision of the NONMEM parameter
245 estimates was also acceptable except for BSV in V_2, which had a standard error >80% and had
246 to be fixed to the estimated value. Likewise, histograms of distributions of the individual random
247 effects on parameters were centred around the population typical value (data not shown) and
248 the pcVPC presented in Figure 2 demonstrates consistency between the model predictions and
249 the raw data. Finally, the NPDE check confirmed a normal distribution around each individual
250 observation within the predictions of the model.

251 **Pharmacodynamic analysis**

The percentages of simulated patients who achieved 40%, 60% or 80% of $T_{>MIC}$ at each MIC value with six of the meropenem dosage regimens are presented in Figure 3. For targets of 40% and 60% $T_{>MIC}$, the PK-PD breakpoint was 8 mg/L for a dose of 1 g every 8 h if given over 3 h but only 4 mg/L if administered over 5 minutes. For a target of 80% $T_{>MIC}$ the PK-PD breakpoint was 8 mg/L for all infusions and doses of 1 g 4 hourly and 2 g over 3 h every 8 h but reduced to 4 mg/L if the 8 hourly dose was given over 5 minutes. Table 3 shows that when the results were integrated with the MIC distribution for each organism and split according to CL estimates, the cumulative fraction of response (CFR) for the all targets were ≥99% with all the dosage regimens for *E. coli* and coagulase negative *Staphylococcus.* For *E. faecalis* and *P. aeruginosa,* the CFRs were >89% for all the continuous infusions, except for doses of 3 and 4 g daily in patients whose CL was > 20 L/h. Continuous infusions consistently achieved better results than 3 hour infusions and 3 hour infusions were better than bolus administration. The lowest CFR results were obtained with a dose of 1 g every 8 h over 5 minutes, which was only acceptable for patients whose CL estimates were < 10 L/h.

DISCUSSION

This study determined the population PK of meropenem following intravenous doses of 1-2 g given every 4-8 h to a group of twelve adults with severe burns. The influence of patient covariates on PK parameters and PK-PD relationships were investigated with the aim of proposing a suitable dose regimen for this population.

The 2-compartment structural model was in line with other studies of meropenem PK.[10,19] Whilst considerable inter-patient variability was observed in the meropenem PK values, the mean clearance and volume of distribution estimates were around 20-40% higher than those reported in other patient groups.[19,25,35,36] Physiological changes and excessive hydration in patients with major burns can adversely affect the PK of antibiotics and increase both CL and volume of

distribution. Even greater increases in V would be expected in patients with large burns due the increased extracellular fluid volume and hydration required to compensate for the loss of intravascular fluid accompanying hypoalbuminaemia.[4]

A recent study of Korean patients with burn injuries[10] explored the relationship between meropenem dose and the likelihood of achieving serum concentrations above the MIC of *P. aeruginosa* for >40% of the dosing interval. Although they reported higher clearance and distribution volumes than seen in non-burn patients, their estimates were lower than observed in our study. These findings may reflect differences in the characteristics of the patients since serum albumin concentrations were markedly lower (15 compared with 27 g/L) and body weight higher (83 compared with 66 kg) in our study.

The final population model related all parameters linearly to body weight, which is consistent with the findings of early population PK analyses.[16,35] The identification of age and serum albumin as factors influencing the PK of meropenem, with age having the greater effect, also correspond well with previous findings.[18,35] Meropenem is primarily renally cleared[36] and the effect of age probably reflects an age-related change in renal function. Although renal function has been included as a covariate in other population studies,[5,19] it could not be properly investigated in this study. The small number of patients and lack of renal impairment were contributing factors but an additional issue was that due to technical difficulties in collecting urine, measured CL_{CR} values were only available for 14 of the 20 occasions in 8 of the 12 patients. Using an equation to estimate CL_{CR}, such as the Cockcroft-Gault equation,[37] was unsatisfactory because there was a very poor correlation between estimated and measured CL_{CR} values. Similar findings were previously reported by Conil et al,[38] who concluded that formulae based on serum creatinine are imprecise in assessing renal function in burn patients and should be abandoned in favour of direct measurement based on a 24 h urine collection. Serum albumin was found to influence *CL*, V_1 and V_2. Hypoalbuminaemia is a consequence of

301 the hypermetabolic phase because of leakage to the extravascular fluid and decreased hepatic
302 production[4] and is consistent with higher estimates of these parameters.

303 Although a weak correlation between meropenem CL and TBSA burn was identified with the
304 base model, in contrast with the findings of Doh *et al*,[10] attempts to estimate the effect of TBSA
305 on the parameters failed, probably because there were insufficient data to support a relationship
306 in the population model due to the relatively small number of patients.

307 This study identified an influence of weight, age and albumin concentration on the
308 pharmacokinetics of meropenem. However, with such a small data set, there is limited power to
309 conduct a comprehensive covariate analysis and the clinical impact of these covariates cannot
310 be clearly defined. When these factors were included in the model, between subject variability
311 in CL could no longer be identified. This might be interpreted as indicating that all variability
312 between individuals was explained by these covariates. However, between occasion variability
313 remained high and a more likely explanation is that meropenem pharmacokinetics change so
314 much within a patient who has a burn injury that it cannot be separated from pharmacokinetic
315 variability between patients. The results presented in Table 1 for patient 6 support this
316 suggestion. Clearance estimates ranged from 14 to 36 L/h despite minimal changes in age,
317 weight or albumin concentration between occasions.

318 Based on the developed model, the Monte Carlo simulations determined the PK-PD breakpoints
319 for a range of meropenem regimens and MIC values. It was noticeable that of the five patients
320 who did not survive their injury, three had serum concentrations above 4 mg/L for more than
321 40% of the dose interval at their starting dose of 1 g every 8 h. Although these poor outcomes
322 may have reflected other aspects of the patient's condition, it may also suggest that a target of
323 40% of the dose interval above 4 mg/L was insufficient. In their study of meropenem in febrile
324 neutropenic patients, Ariano *et al* calculated the mean $T_{>MIC}$ to be 83% for clinical responders

compared with 59% for non responders[39]. This is in line with another clinical study of beta-lactams which showed a significantly greater outcome when $T_{>MIC}$ was at least 80%. [40] In the present study, a regimen of 1 g over 5 minutes every 8 h would be sufficient to achieve 80% $T_{>MIC}$ against highly susceptible bacteria, such *E. coli* and coagulase negative *Staphylococcus.* However, for infections due to *E. faecalis* or less susceptible strains of *P. aeruginosa,* a dose of 1 g over 5 minutes every 4 h may be necessary to achieve 80% $T_{>MIC}$. Given the low toxicity risk of high dose meropenem[41] in patients without renal impairment, and the possible consequences of sub-therapeutic dosing, a dose of 1g every 4 h should be considered in patients with infections caused by these organisms and also for empiric treatment. A better approach may be to administer meropenem by infusion, either over 3 hours[42] or by continuous infusion.[43] However, although a continuous infusion would improve the $T_{>MIC,}$ there may be practical limitations due stability issues with meropenem.[44] Additionally, with continuous infusion there is always the risk of T>MIC of 0%, if a patient has an unusually high meropenem clearance. For infections caused by a known organism with a known MIC, the regimen could be tailored according to the pharmacokinetic data presented in this study.

In summary, the PK of intravenous meropenem in adults with severe burns is influenced by age, body weight and serum albumin but there is wide between and within patient variability in CL and V_2. Although a dose of 1 g eight-hourly should be effective against *E. coli* and coagulase negative *Staphylococcus, a* higher dose of 1 g over 5 minutes every 4 h or 2 g over 3 h every 8 h would be more appropriate for empiric therapy, mixed infections and bacteria with MIC values of 4 mg/L and above.

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476 Table 1 Individual estimates of PK parameters on each sampling occasion

Patient number	Occ	Daily dose (mg)	Age (years)	Weight (kg)	Albumin (g/L)	AUC_{0-24} (mg.h/L)	CL (L/h)	V_1 (L)	V_2 (L)	Q (L/h)	D$t_{1/2}$ (h)	E$t_{1/2}$ (h)
1	1	3000	27	68	15	146	20.5	18.6	20.4	13.5	0.32	2.0
2	1	3000	38	53	13	164	18.2	15.9	12.2	10.5	0.31	1.6
2	2	6000	38	65	10	443	13.5	22.1	17.0	12.9	0.41	2.5
2	3	4000	38	65	9	231	17.4	23.0	17.6	12.9	0.40	2.2
3	1	3000	62	114	15	208	14.4	31.1	29.8	22.6	0.40	3.4
4	1	3000	73	87	13	336	8.9	26.1	30.7	17.3	0.48	5.2
5	1	3000	45	93	12	111	26.9	29.1	37.2	18.5	0.39	2.7
6	1	3000	35	102	15	83	36.0	27.8	39.3	20.3	0.31	2.3
6	2	3000	35	100	15	99	30.3	27.3	38.6	19.9	0.33	2.5
6	3	4000	35	100	17	203	19.7	24.6	34.8	19.9	0.36	2.9
6	4	4000	35	100	16	285	14.0	25.9	36.7	19.9	0.41	4.0
7	1	3000	37	65	24	229	13.1	9.9	9.4	12.9	0.20	1.3
8	1	3000	27	74	15	118	25.3	20.2	20.5	14.7	0.30	1.8
8	2	6000	27	74	15	238	25.2	20.2	20.5	14.7	0.30	1.8
9	1	3000	40	65	14	176	17.1	18.6	16.1	12.9	0.34	1.9
9	2	4000	40	75	18	297	13.5	17.4	15.1	14.9	0.30	2.1
10	1	3000	59	99	16	220	13.6	25.7	25.1	19.7	0.37	3.1
10	2	3000	59	70	15	221	13.6	19.1	18.7	13.9	0.36	2.5
11	1	3000	70	86	10	563	5.3	29.2	38.0	17.1	0.61	9.7
12	1	3000	39	103	18	141	21.3	23.9	23.0	20.4	0.30	2.0
Mean		**3500**	**46**	**82.9**	**14.8**	**226**	**18.4**	**22.8**	**25.0**	**16.5**	**0.4**	**2.9**
SD		**950**	**16**	**17.5**	**3.3**	**118**	**7.4**	**5.3**	**9.8**	**3.5**	**0.1**	**1.8**

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Abbreviations Occ, sampling occasions; CL, clearance; V_1, volume of the central compartment; V_2, volume of the peripheral compartment; Q, intercompartmental clearance; $AUC_{0\text{-}24}$, daily area under the concentration-time curve;D$t_{1/2}$, distribution half-life; E$t_{1/2}$, elimination half-life

481 Table 2 Parameter estimates and bootstrap analysis of the final population PK model for meropenem in patients with burn injuries

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Pharmacokinetic Parameter	Central Tendency (SE)	Non-Parametric Bootstrap	
		Mean (SE)	95% Confidence Interval
CL(L/h/kg)	0.196 (0.013)	0.201 (0.016)	0.169 - 0.223
V_1 (L/kg)	0.273 (0.026)	0.291 (0.035)	0.216 – 0.330
V_2 (L/kg)	0.309 (0.032)	0.316 (0.048)	0.229 – 0.388
Q (L/h/kg)	0.199 (0.035)	0.186 (0.036)	0.139 – 0.259
CL_AGE	0.023 (0.001)	0.023 (0.003)	0.018 – 0.028
CL,V_1,V_2_ALB	0.049 (0.012)	0.049 (0.017)	0.021 – 0.078
BSV V_2	0.079 (0.046)	0.079 FIX	0.079 FIX
BOV CL	0.083 (0.026)	0.080 (0.037)	0.023 – 0.144
Residual variability	0.044 (0.012)	0.043 (0.014)	0.021 – 0.066

483 Abbreviations: SE (standard error, expressed as variance); CL, clearance; V_1, volume of the central compartment; V_2, volume of the peripheral
484 compartment; BSV, between-subject variability; BOV, between occasion variabili

Table 3.Cumulative fraction of predicted response to achieve targets of 40%, 60% and 80% $T_{>MIC}$ for 10meropenem dosage regimens against strains of *E.coli*, coagulase negative *Staphylococcus*, *E. faecalis* and *P. aeruginosa*.

			Cumulative Fraction of Predicted Response (%)											
			E. coli			***coagulase negative Staphylococcus***			***E.faecalis***			***P.aeruginosa***		
	Dose / interval	*Clearance*	**40%** $T_{>MIC}$	**60%** $T_{>MIC}$	**80%** $T_{>MIC}$	**40%** $T_{>MIC}$	**60%** $T_{>MIC}$	**80%** $T_{>MIC}$	**40%** $T_{>MIC}$	**60%** $T_{>MIC}$	**80%** $T_{>MIC}$	**40%** $T_{>MIC}$	**60%** $T_{>MIC}$	**80%** $T_{>MIC}$
Over 5 minutes	**1g/ 8h**	CL <10 L/h	100	100	100	100	100	99	93	89	84	95	93	92
		10<CL<20 L/h	100	100	100	99	99	99	74	60	47	88	84	81
		CL>20 L/h	100	100	100	99	98	98	50	28	18	83	77	72
	2 g/ 8h	CL <10 L/h	100	100	100	100	100	100	98	96	93	99	97	96
		10<CL<20 L/h	100	100	100	100	99	99	92	84	72	94	91	88
		CL>20 L/h	100	100	100	99	99	99	79	58	42	89	84	80
	1 g/ 6h	CL <10 L/h	100	100	100	100	100	100	96	93	90	98	96	94
		10<CL<20 L/h	100	100	100	99	99	99	88	72	64	91	87	86
		CL>20 L/h	100	100	100	99	99	98	70	48	32	87	82	77
	1 g/ 4 h	CL <10 L/h	100	100	100	100	100	100	98	97	97	99	99	98
		10<CL<20 L/h	100	100	100	100	100	99	93	91	85	95	94	91
		CL>20 L/h	100	100	100	99	99	99	85	77	70	91	89	85
Over 3 hours	**1 g/ 8 h**	CL <10 L/h	100	100	100	100	100	99	95	92	88	96	95	93
		10<CL<20 L/h	100	100	100	99	99	99	88	73	57	91	88	84
		CL>20 L/h	100	100	100	99	99	98	71	52	30	87	83	78
	2 g/ 8 h	CL <10 L/h	100	100	100	100	100	100	98	97	96	99	98	97
		10<CL<20 L/h	100	100	100	100	100	99	96	92	83	98	94	90
		CL>20 L/h	100	100	100	100	99	99	91	78	69	93	89	85
	1 g/ 6 h	CL <10 L/h	100	100	100	100	100	100	97	96	95	98	97	97
		10<CL<20 L/h	100	100	100	100	99	98	92	87	80	94	91	89
		CL>20 L/h	100	100	100	99	99	99	86	74	70	91	87	86
Over 24 hours	**3 g/ 24 h**	CL <10 L/h	100	100	100	100	100	100	95	95	94	97	97	96
		10<CL<20 L/h	100	100	100	100	100	100	89	89	89	92	92	92
		CL>20 L/h	100	100	100	99	99	99	76	75	74	88	88	87
	4 g/ 24 h	CL <10 L/h	100	100	100	100	100	100	97	97	97	99	99	98
		10<CL<20 L/h	100	100	100	100	100	100	94	90	89	96	92	92
		CL>20 L/h	100	100	100	99	99	99	86	83	81	91	90	89
	6 g/ 24 h	CL <10 L/h	100	100	100	100	100	100	99	99	98	99	99	99
		10<CL<20 L/h	100	100	100	100	100	100	97	96	94	98	96	95
		CL>20 L/h	100	100	100	99	99	99	92	89	88	94	91	91

Figure 1: Serum concentration-time profiles of meropenem from 12 patients (20 occasions) with burn injury. Key: open circles 1 g every 8 h, open triangles, 1 g every 6 h, closed triangles 1 g every 4 h, closed squares 2 g every 8 h

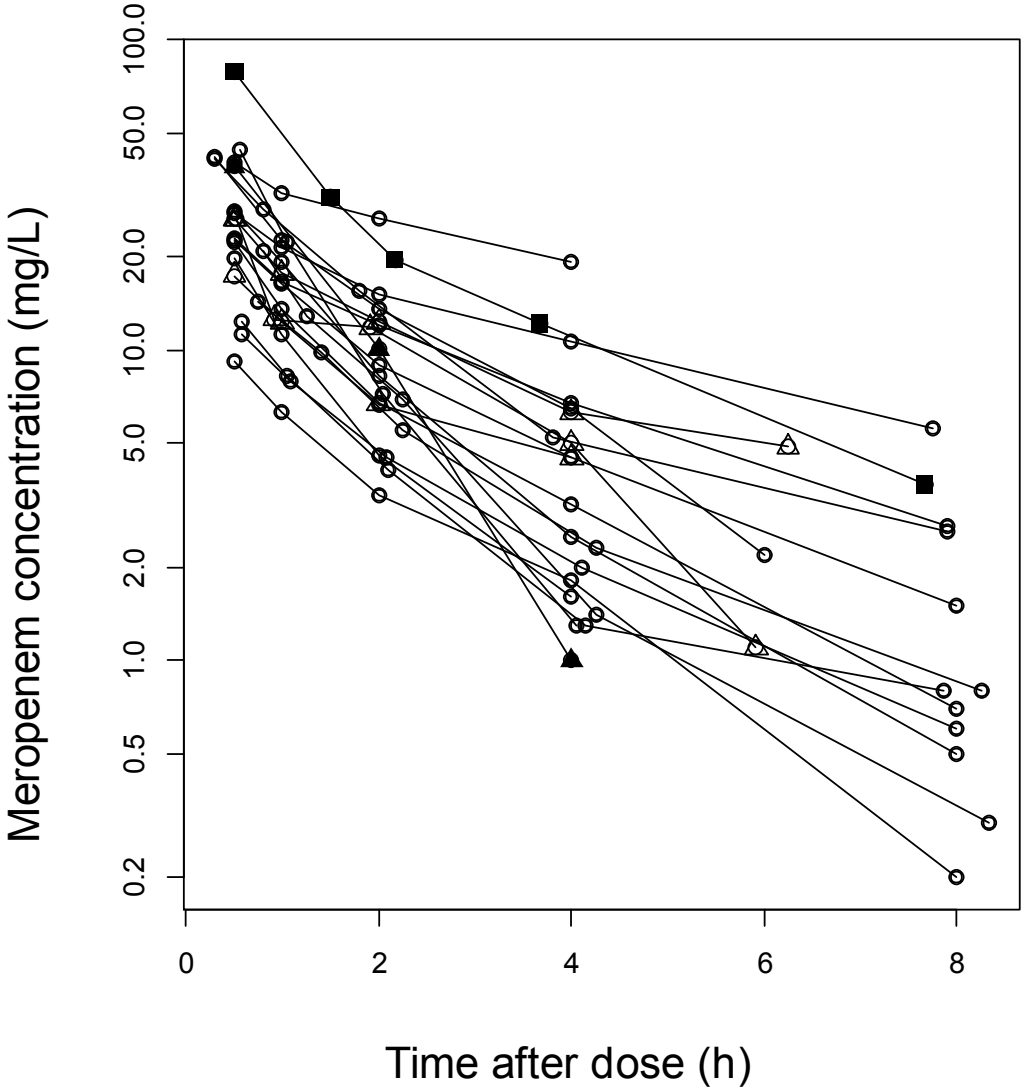

Figure 2.Prediction-corrected visual predictive check of the final model describing the PK of meropenem in patients with severe burn injuries. The solid lines represent the 5th, 50th and 95th percentiles of the plasma meropenem concentrations and the model-based predictions of the percentiles and their 95% confidence intervals.

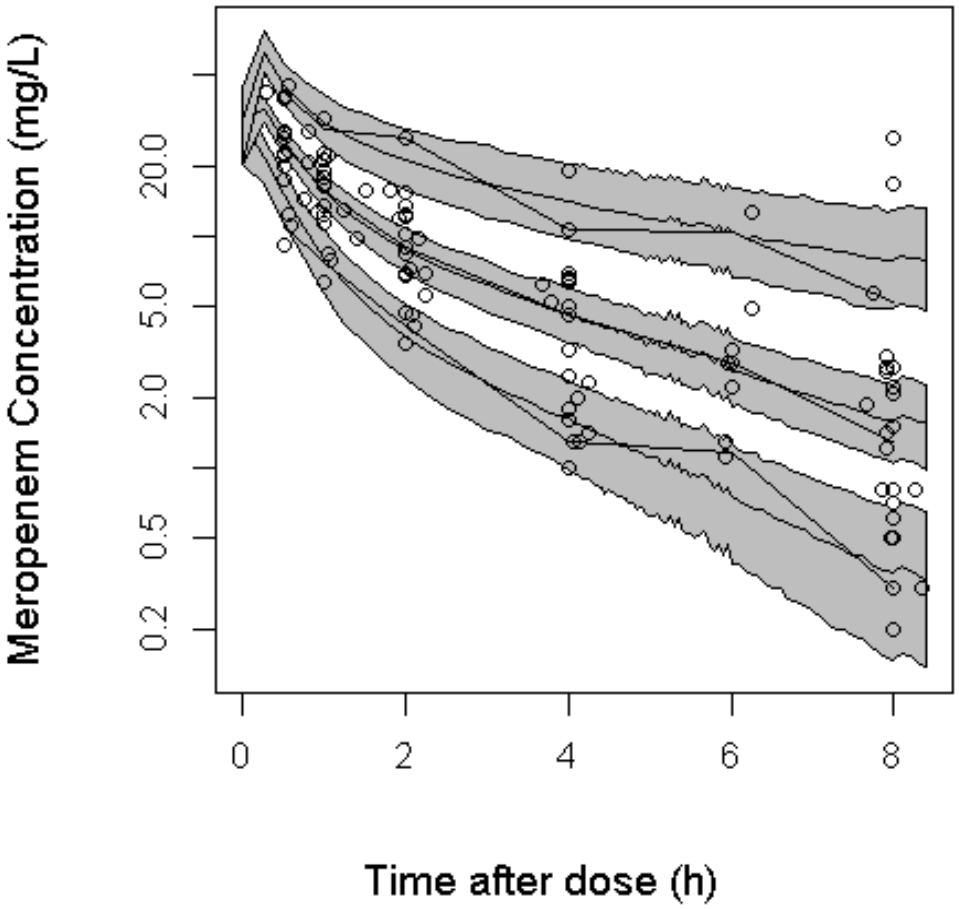

Figure 3.Percentage probabilities of achieving a target 40% (left), 60% (middle) and 80% (right) $T_{>MIC}$ using 6 different meropenem dosage regimens. Key: open circles 1 g every 8 h over 5 min, closed circles 1 g every 8 h over 3 h, open squares 2 g every 8 h over 5 min, closed squares 2 g every 8 h over 3 h, open triangles 3 g over 24 h, closed triangles 6 g over 24 h.