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Pharmacokinetics of meropenem in burn patients with infections caused by Gram-negative bacteria: Are we getting close to the right treatment?

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ABSTRACT

Objectives: Infections caused by multidrug-resistant Gram-negative bacteria are associated with high mortality. A relevant concern is the efficacy of antibiotic therapy in burn patients in whom pathophysiological changes strongly influence pharmacokinetic (PK) parameters. This study aimed to describe the PK parameters of meropenem in a population of burn patients.
Methods: Blood samples were collected immediately before and 2 h and 5 h after the start of intravenous drug administration. Plasma meropenem concentrations were determined using an ultra-performance liquid chromatography–photodiode array method.
Results: Seventeen burn patients were enrolled in the study. Thirteen patients (76%) were treated with meropenem for infections by*Pseudomonas aeruginosa* or *Acinetobacter baumannii* isolated from blood or wounds. Mean C_{max}, C_{min}, AUC_{0-24}, half-life, drug clearance and volume of distribution were 28.9 mg/L, 3.7 mg/L, 280.2 mg h/L, 2.0 h, 19.0 L/h and 44.4 L, respectively. Six patients (35%) achieved a $C_{min} \geq 3.3$ mg/L and seven patients (41%) achieved a $C_{max} \geq 28.4$ mg/L, whilst nine patients (53%) achieved an AUC_{0-24} of >226 mg h/L. Given a minimum inhibitory concentration (MIC) of 0.5 mg/L, all patients satisfied the target AUC/MIC of >125, but when the MIC rises to 2 mg/L (the ECOFF), only five patients reached the desired AUC/MIC. Regarding $fT_{>MIC}$ at an MIC of 2 mg/L with a 2-h infusion time, 13 patients (76%) achieved the PK target (>75%).
Conclusion: These data suggest that a combined 2-h infusion with a higher dosage of meropenem, including a loading dose, may be successful to achieve effective PK parameters.

1. Introduction

Despite improvements in the early care of burn patients, infections remain one of the major causes of mortality, responsible for 46–51% of multiorgan failure triggers [1]. In recent years, the emergence of infections caused by multidrug-resistant (MDR) Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, represents a global threat, also in the setting of burn patients [1]. Along with the high mortality rate associated with these infections, an important concern is the efficacy of antibiotic treatment, especially for burn patients in whom pathophysiological changes strongly influence the pharmacokinetic (PK) parameters of many antibiotics [1–5].

Physiological changes in burn patients are time-dependent and a number of factors, such as the area and depth of the burn, presence of sepsis, degree of hydration, serum protein concentrations, age, creatinine clearance and time after injury, may affect pharmacokinetics in burn patients [1–5]. In fact, major changes in fluid volume may increase the volume of distribution of a drug thereby lowering its concentration when a standard dose is given.

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Table 1
Clinical and pharmacokinetic parameters of burn patients treated with meropenem.

Pt. ID	Age (years)	Sex	BMI	Degree of burn	% TBSA	RBS	CCI	Reconstructive operations (*n*)	MELD score	CL_{Cr} (mL/min)	CRRT	MV	Septic shock	Possible drug–drug interactions	In-hospital mortality	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{ss} (mg h/L)	AUC_{0-24} (mg h/L)	$t_{1/2}$ (h)	CL_{ss} (L/h)	V_d (L)	Dose
1	71	M	29	2	50	143	5	Y (1)	8	86	N	Y	N	None	N	14.3	2.4	91.3	182.6	3.8	10.9	60.3	1 g b. i.d.
2	40	M	22	2	40	97	0	Y (3)	9	247	N	N	N	None	N	11.3	0.0	25.7	77.1	0.4	38.9	25.0	1 g t. i.d.
3	25	M	22	2	50	92	0	Y (5)	12	252	N	Y	N	None	N	17.1	3.1	61.7	185.1	2.4	32.4	112.9	2 g t. i.d.
4	43	M	29	2	55	115	0	Y (5)	15	64	Y	Y	Y	Norepinephrine	N	16.9	3.3	45.3	181.2	1.9	35.6	70.2	1 g q. i.d.
5	25	M	23	2	50	92	0	Y (4)	10	277	N	N	N	None	N	29.2	0.7	78.1	234.3	1.1	25.6	41.3	2 g t. i.d.
6	71	F	22	1	10	81	3	N	9	58	N	N	N	None	N	25.1	1.7	78.9	236.7	1.5	12.6	28.3	1 g t. i.d.
7	81	M	27	2	40	138	4	Y (5)	10	211	N	N	Y	Furosemide and norepinephrine	N	31.1	0.8	81.2	243.6	1.1	24.6	41.0	2 g t. i.d.
8	50	M	24	2	35	102	1	Y (1)	9	167	N	N	N	None	N	15.1	1.1	50.0	150	1.5	19.9	45.8	1 g t. i.d.
9	72	M	25	2	15	87	3	Y (1)	9	85	N	N	N	None	N	35.6	0.0	75.8	227.4	0.3	13.1	7.5	1 g t. i.d.
10	67	M	25	2	30	114	2	Y (6)	9	169	N	Y	N	None	N	20.8	3.6	67.5	202.5	2.3	14.8	50.5	1 g t. i.d.
11	52	F	37	2	50	119	5	Y (4)	9	98	N	Y	N	Furosemide and norepinephrine	Y	26.0	8.4	121.7	365.1	3.7	8.2	43.8	1 g t. i.d.
12	75	M	17	2	5	80	4	Y (2)	7	64	N	Y	N	None	N	36.5	6.7	158.3	474.9	2.4	6.3	22.4	1 g t. i.d.
13	48	F	19	2	18	66	0	Y (2)	8	82	N	N	N	None	N	74.7	0.0	151.0	453	0.3	6.6	10.4	1 g t. i.d.
14	40	F	23	2	35	75	0	Y (1)	11	150	N	N	N	Furosemide	N	16.0	0.6	36.0	108	1.2	27.7	20.1	1 g t. i.d.
15	70	M	27	2	35	122	5	Y (1)	9	76	N	Y	Y	Furosemide and norepinephrine	Y	50.2	21.4	262.1	786.3	4.8	7.6	53.6	1 g t. i.d.
16	64	M	27	2	45	127	2	Y (2)	20	31.7	N	Y	N	Furosemide	N	52.0	6.9	230.1	460.2	3.3	6.7	33.2	1 g b. i.d.
17	80	M	30	1	10	107	7	Y (1)	8	157	N	Y	N	Furosemide	N	19.9	2.5	64.9	194.7	1.9	30.8	88.2	2 g t. i.d.

Pt., patient; M, male; F, female; BMI, body mass index; TBSA, total body surface area; RBS, revised Baux score; CCI, Charlson comorbidity index; Y, yes; N, no; MELD, Model for End-Stage Liver Disease; CL_{Cr}, creatinine clearance; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; C_{max}, peak serum concentration; C_{min}, trough serum concentration; AUC_{ss}, area under the concentration–time curve at steady-state; AUC_{0-24}, area under the concentration–time curve from 0–24 h; $t_{1/2}$, half-life; CL_{ss}, drug clearance at steady-state; V_d, volume of distribution; b.i.d., twice daily; t.i.d., three times a day; q.i.d., four times a day.

In addition, augmented renal blood flow in burn patients owing to the increase in cardiac output may result in higher drug clearance and a shorter elimination half-life [6,7].

Altered PK parameters may be responsible for toxic effects as well as resulting in suboptimal antibiotic concentrations below those required to be effective against MDR pathogens [2,4].

Subtherapeutic antibiotic concentrations may lead to antimicrobial resistance, which threatens the management of bacterial infections in critically ill patients. Moreover, escalating antimicrobial resistance has substantially increased overall healthcare costs as a result of prolonged hospitalisation associated with treatment failures and the need for implementation of broader infection

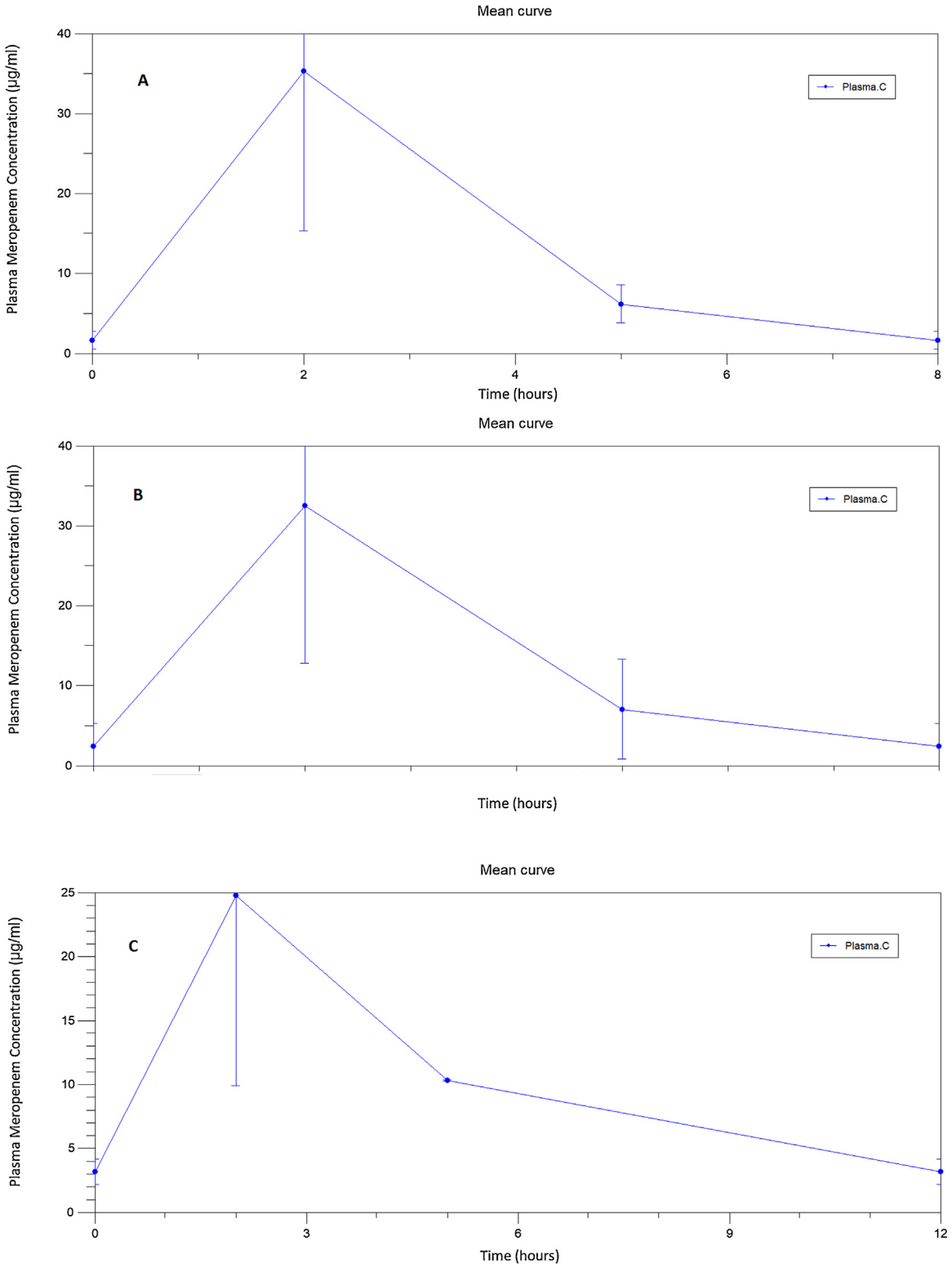

Fig. 1. Mean drug concentration–time curves corresponding to dosages of (A) 2 g q8h, (B) 1 g q8h and (C) 1 g q12 h. Bars indicate the confidence intervals for the mean value. q8h, every 8 h; q12 h, every 12 h.

Table 2
Simulated pharmacokinetic/pharmacodynamic data for different hypothetical minimum inhibitory concentrations (MICs).

Pt. ID	AUC_{0-24}/MIC			$T_{>MIC}$ (% over 6, 8 or 12 h)[a]					
	MIC =0.5 mg/L	MIC =1 mg/L	MIC =2 mg/L	MIC =0.5 mg/L	MIC =1 mg/L	MIC =2 mg/L (ECOFF susceptible)	MIC =8 mg/L (ECOFF resistant)	MIC =12 mg/L (6 × ECOFF MIC)
1	365	183	91	100	100	100	43	25
2	154	77	39	47	42	37	27	0
3	370	185	93	100	100	100	58	40
4	362	181	91	100	100	100	68	49
5	469	234	117	100	92	78	51	43
6	473	237	118	100	100	93	56	45
7	487	244	122	100	93	79	52	44
8	300	150	75	100	100	80	42	31
9	455	227	114	48	44	41	33	31
10	405	203	101	100	100	100	65	48
11	730	365	183	100	100	100	100	77
12	950	475	237	100	100	100	91	73
13	906	453	227	52	48	45	37	35
14	216	108	54	100	85	70	40	31
15	1573	786	393	100	100	100	100	100
16	920	460	230	100	100	100	91	75
17	389	195	97	100	100	100	56	42

Pt., patient; AUC_{0-24}, area under the concentration–time curve from 0–24 h; $T_{>MIC}$, time that the drug concentration remains above the MIC; ECOFF, epidemiological cut-off.
[a] 100% indicates a coverage ≥100% of the dosing interval.

control interventions aimed at reducing the spread of antibiotic-resistant pathogens [1–5].

Therefore, PK studies are necessary to produce accurate recommendations that can be used as an additional tool in the management of infections [8].

So far, few data are available regarding the pharmacokinetic/pharmacodynamic (PK/PD) meropenem target for efficacy, especially in burn patients. Data from intensive care unit patients described an area under the concentration–time curve from 0–24 h (AUC_{0-24}), trough serum concentration (C_{min}) and peak serum concentration (C_{max}) of 226 mg h/L, 3.3 mg/L and 28.4 mg/L respectively, as PK/PD targets [3,6,9–14].

Moreover, published data have described an AUC_{0-24}/MIC (minimum inhibitory concentration) ratio and $\%fT_{>MIC}$ (percentage of time that the drug concentration remains above the MIC) of 125 and 75%, respectively, as the most significant parameters to evaluate the therapeutic efficacy of meropenem [3,6,9–14].

The aim of this prospective study was to describe the PK/PD parameters of meropenem in burn patients treated with a 2-h infusion.

2. Materials and methods

All patients admitted to the Burn Center of CTO Hospital, Città della Salute e della Scienza (Turin, Italy) from January 2016 to April 2018 and treated with meropenem as empirical or targeted therapy were prospectively enrolled in the study. Meropenem was administered as a 2-h intravenous (i.v.) infusion at a dosage of 1 g every 8 h (q8h) up to 2 g q8h according to the clinical characteristics of the patient.

The study was approved by the local Ethical Committee of AOU Città della Salute e della Scienza, and written informed consent was obtained from patients before sampling. The study was performed in accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki.

2.1. Patient characteristics

Information regarding demographic and clinical characteristics was collected for each patient, including days of hospitalisation, length of stay in the unit and specific burn index.

Sepsis and septic shock were classified according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [15]. Mortality was evaluated at discharge.

Microbiological data were also collected when available. In case of targeted therapy, for each patient the micro-organism, site of infection and MIC were reported.

2.2. Blood sampling and meropenem assay

Plasma meropenem concentrations were determined at steady-state ≥48 h after the beginning of therapy. The C_{min} corresponds to concentration before administration and the C_{max} is defined as the concentration at the end of the infusion. The AUC_{0-24} of meropenem was calculated with blood sample collection by multiplying the AUC values corresponding to each daily dose (e.g. $AUC_{0-8} \times 3$) [10,13].

Blood samples were collected before the infusion, at the end of the infusion (2 h) and 5 h after i.v. drug administration. Blood samples were collected in lithium heparin tubes (7 mL) and plasma was obtained by centrifugation at 2800 × *g* for 10 min at 4 °C (ALC PK 130R refrigerated centrifuge; DJB Labcare Ltd., Newport Pagnell, UK).

Each sample was stored at −20 °C until analysis (<3 weeks). Stability tests performed during method validation reported drug stability (<5% degradation) within 1 month (data not shown).

Meropenem quantification was performed by an ultra-performance liquid chromatography–photodiode array (UPLC-PDA) method, validated following US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines. Briefly, 200 μL of plasma was added to 50 μL of internal standard (thymidine) and underwent protein precipitation with 400 μL of acetonitrile:methanol (50:50 v:v) and then was diluted 1:10 with pure water before injection on a ACQUITY UPLC HSS T3 column (2.1 × 150 mm, 1.8 μm) (Waters Corp., Milford, MA, USA). Chromatographic separation was achieved in a gradient run of 10 mM KH_2PO_4 (pH 3.2) and acetonitrile for 13 min at 40 °C with a flow of 0.4 mL/min.

Accuracy as well as intraday and interday precision were all within the limits imposed by the FDA and EMA guidelines (deviations from nominal concentration and coefficients of variation both <15%). Calibration curves were linear in the range of 0.585–15 mg/L, with $R^2 > 0.996$ for each analytical session. Samples with plasma concentrations >15 mg/L were diluted in order to fit the linearity range, demonstrating good dilution integrity after serial dilutions.

All PK parameters were calculated by means of a non-compartmental model using Kinetica software (Thermo Fisher Scientific, Waltham, MA, USA) and are summarised in Table 1 and represented graphically in Fig. 1.

Simulated data for meropenem PK parameters calculated with MICs corresponding to 0.5, 1 and 2 mg/L [susceptible by epidemiological cut-off value (ECOFF)], 8 mg/L (resistant by ECOFF) and 12 mg/L (6 × ECOFF MIC) were calculated by considering a log-linear elimination kinetic in accordance with the experimentally determined half-life ($t_{1/2}$) (Table 2).

Differences between different drug dosages (1 g vs. 2 g three times a day) in terms of AUC or C_{min} were through a non-parametric Mann–Whitney test using IBM SPSS Statistics v.24.0 (IBM Corp., Armonk, NY, USA). Statistical comparisons for patients treated with 1 g every 12 h or 1 g every 6 h were not performed considering the small sample size (two and one patients, respectively).

3. Results

Seventeen patients were enrolled in the study. All patients were aged >25 years and had severe injuries [second- or third-degree thermal injuries ranging from 5–55% of their total body surface area (TBSA)] (Table 1).

The majority of patients were male (13/17; 76%), with a mean ± standard deviation (S.D.) age of 57 ± 18.3 years, a mean ± S.D. TBSA of 34 ± 16.4%, a mean ± S.D. body mass index (BMI) of 25.2 ± 4.7, a mean serum creatinine concentration of 0.85 mg/dL and a mean creatinine clearance of 134 mL/min. The mean total protein serum concentration was 5.8 g/dL (Table 1).

Most patients were receiving mechanical ventilation (9/17; 53%) and had an indwelling central arterial line (14/17; 82%) at the time of infection (Table 1).

Thirteen patients (76%) were treated with meropenem as targeted therapy for infections caused by MDR *P. aeruginosa* or *A. baumannii* isolated from blood or wounds. According to the Sepsis-3 criteria [15], 12 patients (71%) had sepsis and 3 (18%) had septic shock. There were no deaths at 14 days from hospital admission, whilst mortality at discharge was 12% (2/17) with a mean revised Baux score [16,17] of 103. The main meropenem PK parameters are reported in Table 1 and the AUC values are presented in Fig. 1. The mean C_{max}, C_{min}, AUC_{0-24}, $t_{1/2}$, drug clearance and volume of distribution (V_d) were 28.9 mg/L, 3.7 mg/L, 280.2 mg h/L, 2.0 h, 19.0 L/h and 44.4 L, respectively.

Six patients (35%) achieved a $C_{min} \geq 3.3$ mg/L and seven patients (41%) achieved a $C_{max} > 28.4$ mg/L, whilst nine patients (53%) achieved an AUC_{0-24} of >226 mg h/L. No statistically significant differences in PK parameters were observed between different dosing regimens (*P*-values of 0.787 for AUC, 0.324 for C_{max} and 0.510 for C_{min}).

Simulated data for meropenem PK parameters calculated with MICs corresponding to 0.5, 1, 2 (ECOFF), 8 and 12 mg/L (6 × ECODD MIC) are reported in Table 2.

Given an MIC of 0.5 mg/L, all patients satisfied the target AUC/MIC of >125, but when the MIC rose to 2 mg/L (ECOFF), only five patients reached the desired AUC/MIC. Regarding $fT_{>MIC}$ at an MIC of 2 mg/L with a prolonged infusion time of 2 h, 13 patients (76%) achieved the pharmacokinetic target (>75%).

4. Discussion

Severe infections are the main cause of death among burn victims, mainly due to loss of the natural skin barrier against pathogenic micro-organisms. Moreover, coagulated proteins and other microbial nutrients in the lesion as well as local avascularisation lead to bacterial colonisation and facilitate access to the systemic circulation [3].

Antibiotic therapies are usually difficult to manage in this setting, since patients with major burns experience pathological changes that have been shown to influence the pharmacokinetics of antibiotics. Subsequently, it has been demonstrated that conventional doses of some antibiotics given to patients with major burns may result in subtherapeutic serum concentrations with unsuccessful microbiological and clinical cure [1–4].

Moreover, the increasing incidence of infections caused by MDR Gram-negative infections in this setting poses a great challenge for clinicians aiming to provide maximally effective therapy.

Here we report the main PK/PD findings of a 2-h infusion of meropenem in burn patients aimed at identifying the best treatment option in this setting. The patients included in this study had a mean revised Baux score of 103, indicating that in this group the expected mortality ranges from 30–55% depending on age, burn extension and concomitant inhalation injury; noticeably, observed mortality at hospital discharge was 12%.

The results showed wide PK variability among patients, as already highlighted in previous studies on similar populations of critical patients owing to the peculiar pathophysiological conditions [6,18]. Deepening this issue, in terms of dosage or timing, dosing regimens were adjusted on the basis of patient characteristics (i.e. renal insufficiency, dialysis, renal replacement therapy, fluid overload, degree of burns), leading to satisfactory PK coverage throughout 24 h. This was further confirmed by the absence of significant differences in terms of drug concentrations between different dosing regimens (Fig. 1).

The mean C_{min} and C_{max} values were found to be similar to those reported in the literature in 65% and 59% of patients, respectively [3,6,9–14]. Of note, for TBSA ≥ 50%, only two patients had a $C_{min} \geq 3.3$ mg/L and only one patient had a $C_{max} > 28.4$ mg/L, suggesting that the percentage TBSA might strongly affect the V_d and other physiological parameters, although in the current study no statistically significant correlation was found, possibly due to the small number of patients enrolled.

Despite the 2-h i.v. infusion, patients in this study had lower AUC_{0-24} compared with data from the literature, and only nine patients (53%) achieved the target of >226 mg h/L [3,6,9–14]. Moreover, an AUC/MIC of 125 was achieved in all patients except one when the MIC was 0.5 mg/L or 1 mg/L, whereas the proportion of patients reaching this PK/PD target decreased progressively at higher MICs.

Considering the targeted $fT_{>MIC}$ (75%), the vast majority of patients (76%) achieved a satisfactory $fT_{>MIC}$ when an MIC of 2 mg/L was considered.

This proposal is also supported by a recently published population PK analysis in septic shock patients where prolonged or continuous infusion and increased dosages of meropenem appeared to enhance therapeutic effectiveness, particularly in patients with augmented renal clearance [14]. Moreover, prolonged infusion of meropenem appears to be associated with a higher clinical improvement rate and a lower mortality in severe infection [19]. According to data from a different setting of critically ill patients, the current data support the idea that burn patients may also benefit from prolonged infusion of a high dosage of meropenem (2 g q8h), possibly with a loading dose, regardless of augmented renal clearance [14,19,20].

Moreover, according to the need for better personalised therapy, a more active approach with routine use of therapeutic drug monitoring appears to be effective to reduce toxicity and to improve efficacy, especially in burn patients.

Funding

None.

Competing interests

None declared.

Ethical approval

This study was approved by the local Ethical Committee of AOU Città della Salute e della Scienza (Turin, Italy) [PROT. No. 0063741]. Written informed consent was obtained from patients before sampling. The study was performed in accordance with International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki.

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