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ORIGINAL ARTICLE

Daptomycin Plasma and CSF Levels in Patients with Healthcare-Associated Meningitis

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Abstract

Background: There are currently few data concerning the cerebrospinal fluid (CSF) penetration of daptomycin in patients with healthcare-associated meningitis. This study aims (1) to better characterize the pharmacokinetics of daptomycin in humans during a 7-day intravenous (IV) therapy course, and (2) to study the penetration of daptomycin in the CSF after IV infusion at the dose of 10 mg/kg.

Results: In this prospective observational study, we enrolled nine patients with an implanted external ventricular drainage and a diagnosis of a healthcare-associated meningitis. Daptomycin was administered at 10 mg/kg for a maximum of 7 days. The pharmacokinetic of daptomycin was studied using a two-compartment population/pharmacokinetic (POP/PK) model and by means of a nonlinear mixed effects modeling approach. A large inter-individual variability in plasma area under the curve (Range: 574.7–1366.3 h mg/L), paralleled by high-peak plasma concentration (C_{max}) (all values > 60 mg/L), was noted. The inter-individual variability of CSF-AUC although significant (range: 1.17–6.81 h mg/L) was narrower than previously reported and with a late occurrence of CSF-C_{max} (range: 6.04–9.54 h). The terminal half-life between plasma and CSF was similar. t_{max} values in CSF did not show a high inter-individual variability, and the fluctuations of predicted CSF concentrations were minimal. The mean value for daptomycin penetration obtained from our model was 0.45%.

Conclusions: Our POP/PK model was able to describe the pharmacokinetics of daptomycin in both plasma and CSF, showing that daptomycin (up to 7 days at 10 mg/kg) has minimal penetration into central nervous system. Furthermore, the observed variability of AUC, t_{max} and predicted concentration in CSF was lower than what previously reported in the literature. Based on the present findings, it is unlikely that daptomycin could reach CSF concentrations high enough to have clinical efficacy; this should be tested in future studies.

Keywords: Daptomycin, Ventriculitis, Meningitis, Pharmacokinetics, Healthcare-associated meningitis, Ventriculitis

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Background

Healthcare-associated meningitis is a serious complication of different neurosurgical procedures associated with significant morbidity and mortality [1–3]. The incidence of these complications varies according to predisposing conditions and risk factors: 1.5% following craniotomy [4], 4–17% after internal ventricular catheter insertion [5] and 8% following external ventricular drainage (EVD) insertion [6]. Furthermore, up to 1.4% of head trauma and 5% of external lumbar catheter placement may be associated with central nervous system (CNS) infections.

Gram-positive (G^+) cocci, especially methicillin-resistant *Staphylococcus aureus* (MRSA) and epidermidis (MRSE), are the most common pathogens involved [7]. Their treatment is challenging because of antibiotics resistance and the difficulty to achieve a therapeutic dose of antibiotics in the CNS. At present, treatment options are represented by vancomycin and linezolid. The penetration of vancomycin within the cerebrospinal fluid (CSF) is poor even in the presence of meningeal inflammation [8]. To overcome this pharmacokinetic drawback, direct instillation of antimicrobial agents into the ventricles could be necessary. Although this approach has never been standardized and never approved by Food and Drugs Administration, intrathecal vancomycin is occasionally necessary in patients with resistant nosocomial EVD-related ventriculitis, as suggested by the guidelines from the Infectious Disease Society [9]. Other agents such as fosfomycin [10] and linezolid [11–14] have been employed in the treatment of nosocomial staphylococcal ventriculitis and meningitis.

More recently, daptomycin has been approved to treat susceptible G^+ infections of soft tissue and skin infections, right heart endocarditis and bacteremia [15–17]. There are few publications on the pharmacokinetics (PK) of daptomycin at dosage as high as 10 mg/kg [18], and there are few case reports published on CNS infection treatment with intravenous (IV) daptomycin [19–22] or by intraventricular administration [23]. The pharmacokinetics of CSF penetration of daptomycin, which has been studied in animals, ranges from 4 to 7% [18], whereas only one clinical study evaluated daptomycin distribution within the CSF after a single IV bolus at the dose level of 10 mg/kg [24].

Therefore, the aims of this study were (1) to better characterize the pharmacokinetics of daptomycin in humans during a 7-day IV therapy course, and (2) to study the penetration of daptomycin in the CSF after IV infusion at the dose level of 10 mg/kg.

Methods

Study Design and Population

This prospective, observational pharmacokinetics study was conducted in a neuro-intensive care unit at Spedali Civili University Brescia Hospital, from 2010 to 2012, and in accordance with the Declaration of Helsinki. Ethical approval was obtained (registration number 1723) along with written informed consent for each patient. Ethical approval was also obtained by the Pisa Hospital to use in the present paper the Pisa dataset. The last dataset included patients who required daptomycin at different dose levels (i.e., 6–10 mg/kg), but who did not suffer from organ or systemic failures, or pathological conditions that could influence the pharmacokinetics of daptomycin (as well as burn injuries, obesity, etc.).

Inclusion criteria was: ≥ 18 years old with an indwelling external CSF access device and the presence of ventriculostomy-related meningitis diagnosed according to the Center for Diseases Control (CDC) criteria [25] by an infectious disease specialist, or a systemic infection requiring the use of daptomycin.

Exclusion criteria were: (1) patients with conditions known or suspected to alter drug's pharmacokinetics (i.e., burned or cystic fibrosis patients), and (2) patients with one of the following: impaired renal function (defined as creatinine clearance < 30 mL/min), pregnancy, obesity, hepatic failure (Child Class C), documented hypersensitivity to daptomycin or significantly elevated creatine phosphokinase (CPK) levels at baseline (> 250 U/L).

Study Procedures

Daptomycin was administered as a single daily dose at 10 mg/kg based on total body weight, over a 40-min IV infusion, for a maximum of 7 days. Daptomycin was associated with vancomycin plus an anti-pseudomonal β-lactam (cefepime in all our patients) as per CDC guidelines [25]. Blood samples (4 mL) were collected just before the start of the infusion (t_0) (minimum plasma concentration, C_{min}) and 1 h after the end of the infusion that presumably was the time (time to peak, t_{max}) at which daptomycin could achieve the highest concentrations in tissues (C_{max}). CSF samples (1 mL) were collected using the indwelling EVD from the more proximal port, simultaneously with t_{max} blood sample (CSF-C_{max}). After centrifugation (5 min at 4000 rpm), aliquots were stored at -80 °C (maximum 4 weeks) and within 45 min after sample collection. For each patient, serum creatinine and body weight were also collected.

Possible adverse events were recorded as diarrhea, headache, dizziness, rash, abnormal liver function tests, elevated CPK, hypotension and dyspnea. Moreover, we did record also severe adverse events: Anaphylaxis/

hypersensitivity reactions, myopathy and rhabdomyolysis (CPK was monitored every 2 days), eosinophilic pneumonia (any patient developed dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates), clostridium difficile-associated diarrhea as reported by food and drugs administration [26].

Concerning the CSF collection, all EVDs were connected to a backer system (Medtronic®) with a continuous and sealed CSF drainage. To avoid CSF dilution, no flushing was performed before the CSF collection. If EVD was blocked by any hematic cloth, hence requiring flushing, samples were not collected on that day.

Bioanalytical Methodology

Plasma and CSF levels were assayed by a validated Liquid chromatography–mass spectrometry method based on what described by Baietto et al. [27, 28]. Briefly, extraction of daptomycin from plasma and CSF was performed in a PTFE microfuge tube by the addition of 200 µL of parent sample followed by 40 µL of internal standard working solution and then 200 µL of acetonitrile. The tube was vortexed for 10 s and then centrifuged at 12,000 rpm for 10 min at 4 °C. One hundred microliters of the supernatant were transferred in a vial and diluted with 400 µL of water mixed with TFA (trifluoracetic acid) solution (98:2, v:v), and then transferred to autosampler vials and injected [28]. Limit of quantitation for plasma and CSF daptomycin level was 1.56 mg/L. Concentrations below the limit of quantitation (BLQ) were considered equal to the limit of quantitation [29]. CSF penetration was determined using the formula: AUC-CSF/AUC-plasma × 100%.

Pharmacokinetic Analysis

The pharmacokinetic of daptomycin was studied using a two-compartment population/pharmacokinetic (POP/PK) model and by means of a nonlinear mixed effects modeling approach (NONMEM 7.3®).

The plasma/serum and the CSF were represented by compartment 1 and compartment 2, with the quantity of drug in the two compartments denoted as A_1 (elimination rate k_1) and A_2 (elimination rate, k_2), respectively. The distribution rate of the drug from the plasma compartment to the CSF compartment was denoted as k_{12} (Fig. 1). Since there was no transit of drug from CSF to plasma (i.e., $k_{21}=0$), the plasma compartment could be considered independent from the CSF compartment.

In order to overcome the limited size of the CSF database, the pharmacokinetic study was performed in two steps. A one-compartment model was first used to estimate the plasma clearance (CL_1) and the plasma volume (V_1). Then, the two-compartment model was used to estimate the CSF clearance (CL_2), and volume (V_2) and the distribution rate k_{12}.

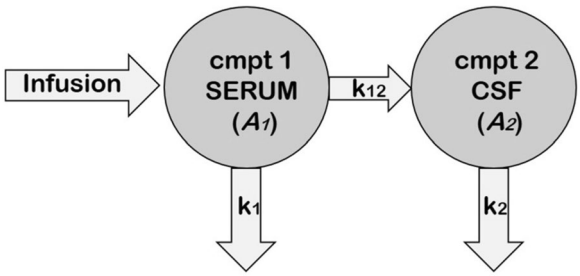

Fig. 1 Schematic representation of the final two-compartment model developed in the present study. Cmpt 1, compartment 1 (plasma/serum compartment); cmpt2, compartment 2 (CSF compartment); A1, quantity of daptomycin in compartment 1 with k_1 denoting its elimination rate; A2, quantity of daptomycin in compartment 2 with k_2 denoting its elimination rate. k_{12} denotes distribution rate of daptomycin between serum and CSF

The study was performed utilizing two sets of data provided by the Pisa and Brescia Hospitals. The pharmacokinetic model for the plasma compartment was developed using the Pisa Hospital database. This database included measures for multiple occasions of 54 patients including only plasma concentrations. This one-compartment model (CMP1-Pi) represented an extension of the model previously published by Di Paolo et al. [30] obtained using a proportional plus additive residual error model. The obtained final parameterizations of clearance and volume are:

$$\mathrm{CL}_1 = \theta_1(\mathrm{CRCL}/80)^{\theta 3}e^{\eta 1}$$
$$V_1 = \theta_2 * WT$$

where CRCL is the creatinine clearance (CRCL) calculated using the Cockcroft–Gault formula. The results are briefly summarized in supplementary material Tables 1 and 2.

To compute the plasma clearance and volume for Brescia database (CMP1-Br), we used a proportional model (rather than proportional plus additive error model), and this was due to the limited size of the database. Such a choice allowed us to stabilize the convergence process.

In the second step, given the single CSF measurement for each drug administration, it was decided to compute the CSF compartment with a limited number of parameters, i.e., clearance, volume and distribution rate, parametrized as:

$$\mathrm{CL}_2 = \theta_4 e^{\eta 2};\ V_2 = \theta_5;\ K_{12} = \theta_6$$

An inter-individual variability for V_2 and/or for k_{12} could not be included in the model due again to the very limited size of the data available. Because for the

two-compartment model, we used a non-standard system of ordinary differential equations, the NONMEM subroutine called "ADVAN = 6" was utilized and the tolerance value was set to 1e−5. This new model was referred to as CMP12_Br.

As suggested by Kullar et al. [24], the obtained pharmacokinetics quantities have been used to estimate the daptomycin penetration in CSF using both the area under the curve (AUC) ratio and the peak concentration ratio for the two compartments.

As a side note for Brescia database, because patient 7 had no measurement of CSF concentration, we used his/her data for the estimation of the first compartment parameters only. Finally, for two patients the last and last two measures, respectively, have been excluded from the database because the reported value was ten times or higher than the values reported previously from the same patients (measures considered as outlier). Such a large difference denoted a departure from the steady-state conditions assumed for the development of the model.

Statistical Analyses and Software

We expressed continuous variables as mean (standard deviation, SD) for normal distributed variables or median (interquartile range, IQR) for the non-normal distributed variables. Qualitative variables were expressed as frequency and percentage.

Pharmacokinetic analyses have been performed using NONMEM 7.3®. Bootstrap analyses and visual predictive checks (VPC) have been generated with the "bootstrap" and "vpc" tools of the PsN-Toolkit Ref. 29. Goodness-of-fit plots have been generated through the combination of the Xpose package and the R software (release 3.3.3). Finally, concentration plots have been obtained using MATLAB 2016b®.

Results

We enrolled nine neurosurgical patients (4 male, 5 female) for a total of 87 CSF and 99 plasma samples, with a mean ± SD of 5.56 ± 1.67 study/days per patient. Table 1 shows individual patients' baseline and clinical characteristics. The underlying diseases were intracerebral hemorrhage ($n = 2$), subarachnoid hemorrhage ($n = 3$), cerebral malignancy ($n = 2$) and traumatic brain injury ($n = 1$). Two patients died (patient 3 and 8). In supplementary materials Table 3, we reported the available CSF parameters collected along with the CSF microbiological results.

Median daptomycin dosage was 650 mg (IQR, 150 mg). Daptomycin at 10 mg/kg was well tolerated with no adverse events (severe and nonsevere) noted during the 7-day drug course.

Pharmacokinetic Model Building

Concerning the pharmacokinetics, the results of run CMP1-Br model (basic model) and CMP12-Br model (the final model) are summarized in supplementary materials Table 1. The obtained values confirm that the final model developed for the plasma compartment of daptomycin using the Pisa database fits very well the Brescia database. We report in Fig. 2 the goodness-of-fit plots for model CMP12-Br and in Fig. 3 the visual predictive check for models CMP1-Br and CMP12-Br. Bootstrap results are shown in supplementary materials Table 2, while diagnostic plots confirm that the estimates of the pharmacokinetics quantities are reliable. In supplementary materials Figs. 1 and 2, the concentration C_1 and C_2 of daptomycin in compartments 1 (plasma) and 2 (CSF) is plotted for each patient. It can be observed that the variation of concentration in compartment 2 is relatively small compared to compartment 1. Since the

Table 1 Patient demographics and clinical characteristics

Patient ID	Sex	Age	Days of study	Weight (kg)	Cr	CLCR	Dose (mg)	Diagnosis
1	M	66	5	80	0.86	95	800	Neurinoma
2	M	52	7	65	0.4	148	650	IVH + IPH
3*	F	18	5	45	0.32	91	450	Hydrocephalus
4	F	30	7	80	0.32	197	800	IPH
5	M	59	7	60	0.65	108	600	SAH
6	F	75	6	70	0.44	114	700	SAH
7	M	19	3	85	0.86	174	850	TBI
8*	F	38	7	48	0.53	44	500	Astrocytoma
9	F	41	3	60	0.99	27	600	SAH
Mean ± SD		44.22 ± 20.23	5.56 ± 1.67	56.89 ± 14.17	0.59 ± 0.25	110.88 ± 55.85	661 ± 138.69	

CLCR (mL/min) clearance of creatinine calculated using cockcroft–Gault formula, *Cr* creatinine (mg/dL), *IPH* intraparenchymal hemorrhage, *IVH* intraventricular hematoma, *SAH* subarachnoid hemorrhage, *SD* standard deviation and *TBI* traumatic brain injury

*Refer to patients died

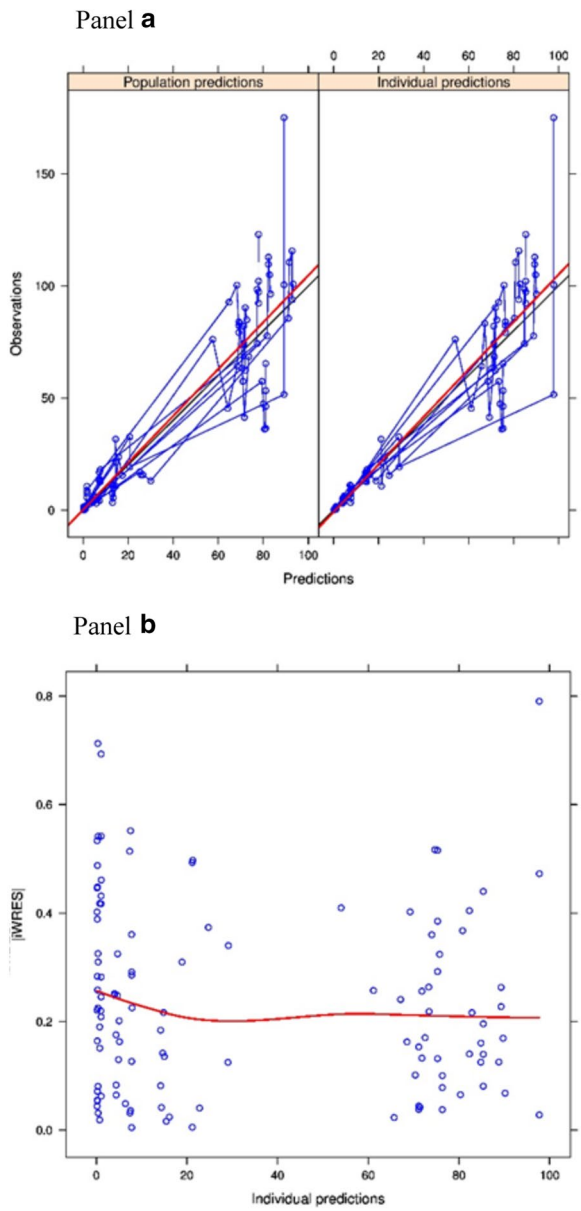

Fig. 2 Goodness-of-fit plots for model CMP12-Br. Population (left) and individual (right) prediction values (Panel A) and individual-weighted residuals (Panel B) plotted against observations (OBS) and individual prediction (IPRED), respectively. Symbols, individual values; red line, LOWESS line (Color figure online)

concentration in compartment 2 undergoes "moderate changes," having a single data point for each occasion can be considered acceptable, though not optimal.

Table 2 reports values of the principal pharmacokinetic parameters estimated from the POP/PK model. A large inter-individual variability in systemic exposure was evident (AUC range: 574.7 up to 1366.3 h mg/L), paralleled by C_{max} (values always higher than the limit of 60 mg/L). The mean value for daptomycin penetration obtained from our POP/PK model was about 0.45%.

It is worth noting that the reduced penetration of daptomycin into CSF is witnessed by the late occurrence of C_{max}, ranging from 6.04 up to 9.54 h after the start of infusion (Table 2), despite the terminal half-life in plasma and CSF were similar (8.51 ± 2.71 h and 7.77 ± 3.74 h, respectively). Finally, t_{max} values in CSF did not show a high inter-individual variability, and the fluctuations of predicted CSF concentrations were minimal (supplementary materials Fig. 2).

Discussion

To the best of our knowledge, this study presents the first investigation and description of the penetration of daptomycin in the CNS by a POP/PK approach in human during a 7-day course therapy. Although the limited number of CSF samples available, the developed POP/PK model is reliable enough to fit plasma and CSF drug concentrations. The most intriguing finding is related to the low penetration rate of daptomycin in CSF and the low inter-individual variability of predicted CSF concentrations.

It is well known that in the absence of an intense meningeal inflammation, as in the case of EVD-related meningitis, the penetration of antibacterial drugs into CNS is very limited [31] with the exception of meropenem that has the best penetration in the CNS. In our patients, the final POP/PK model suggests a very limited penetration of daptomycin within the CNS compartment (only 0.45% of plasma concentrations). This value is slightly lower than the only other one available in the literature, i.e., 0.8% reported by Kullar and colleagues [24]. It is worth noting that our model seems to be more accurate. Indeed, the coefficient of variation for our estimate is 48.13%, against the value of 87.5% reported by Kullar's study. Similar observation can be made regarding the C_{max} values in plasma and CSF. Moreover, the inter-individual variability in our patients is nearly halved with respect to the former study by Kullar and coworkers. The possible explanation of that striking difference could be the larger population of patients available to set up the plasma PK model, on which the CSF modeling was based.

In addition, all patients in the present study have received a standardized combination of daptomycin and vancomycin plus an antibiotic against the G-cocchi (notably reducing the meningeal inflammation), where just a few did in the Kullar's protocol. Finally, we have studied the daptomycin CSF penetration over a mean ($\pm$SD) of 5.6 days (± 1.57) course, where Kullar et al. administered a single drug dose.

Even though we found a difference in daptomycin penetration between our patients and the Kullar's population, this difference should be contextualized in

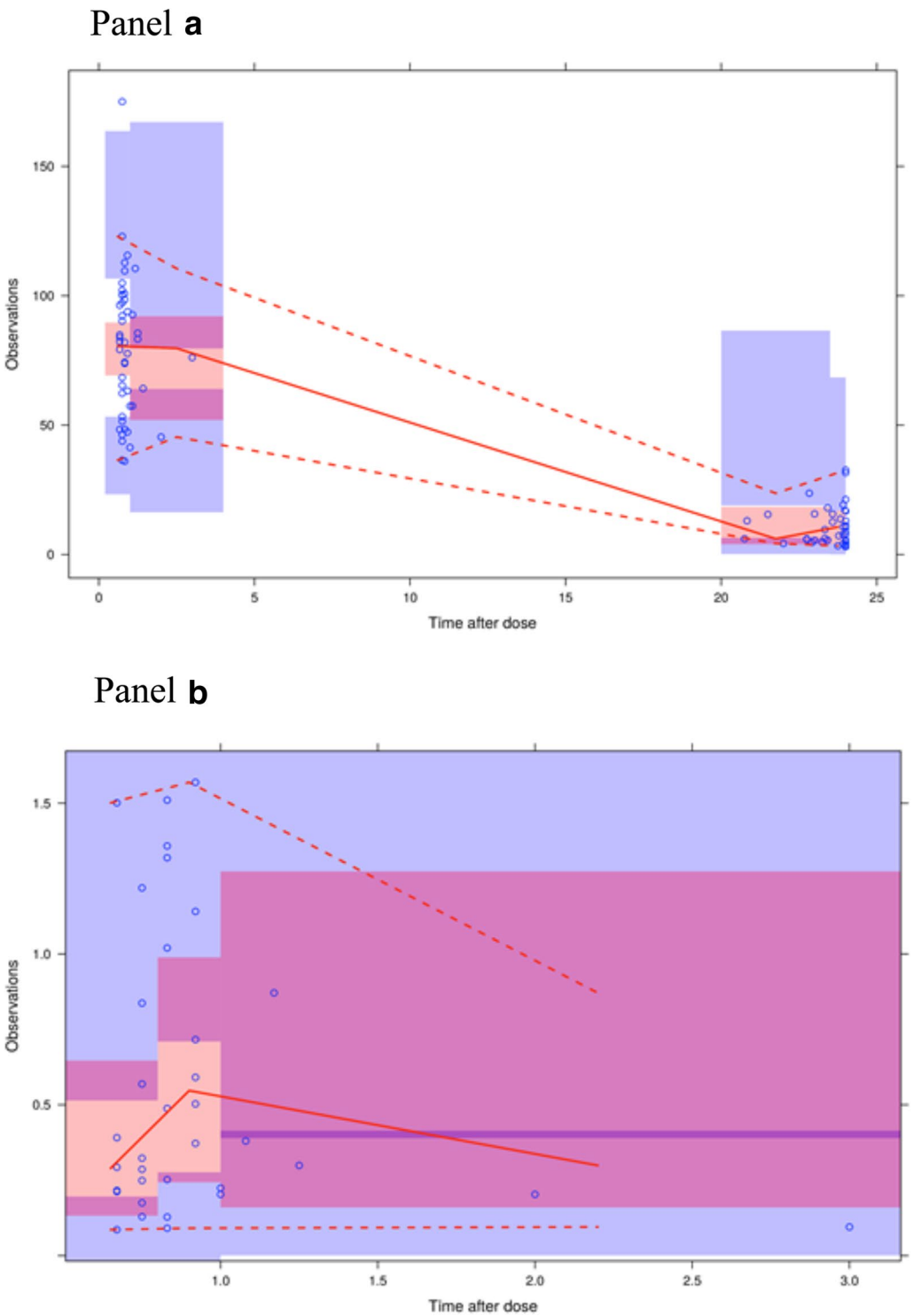

Fig. 3 Visual predictive check plots for model CMP1-Br (panel A.) and CMP12-Br (Panel B.) obtained by resampling 1000 times the original database. Symbols, individual measured values of daptomycin concentrations; red lines, median (continuous line) and 95% confidence intervals (dashed lines) of measured values; box, 95% confidence intervals of median (pale pink) and 95% CI (pale blue) (Color figure online)

Table 2 Main pharmacokinetic parameters of daptomycin in plasma (compartment 1) and CSF (compartment 2)

Patients	PLASMA				CSF				CSF/serum ratio	
	AUC (h x mg/L)	C_{max} (mg/L)	t_{max} (H)	$T_{1/2}$ (h)	AUC (h x mg/L)	C_{max} (mg/L)	t_{max} (h)	$T_{1/2}$ (h)	AUC (%)	C_{max} (%)
1	965.9	83.87	0.67	9.38	4.00	0.19	8.60	7.15	0.41	0.23
2	574.7	72.15	0.67	5.58	1.51	0.09	6.74	4.54	0.26	0.12
3	728.9	76.36	0.67	7.08	2.61	0.14	7.67	6.17	0.35	0.18
4	590.7	72.55	0.67	5.74	1.17	0.08	6.04	3.43	0.20	0.10
5	713.4	75.91	0.67	6.93	2.98	0.15	7.90	7.21	0.42	0.20
6	1148.7	90.21	0.67	11.16	6.27	0.29	9.30	9.41	0.55	0.32
8	962.7	85.92	0.67	8.98	8.73	0.39	9.54	15.64	0.91	0.46
9	1366.3	98.15	0.67	13.27	6.81	0.31	9.30	8.60	0.50	0.32
Mean	881.4	81.89	0.67	8.51	4.26	0.21	8.14	7.77	0.45	0.24
SD	280.4	9.28		2.71	2.73	0.11	1.28	3.74	0.22	0.12

The AUC and C_{max} ratio values are also presented, suggesting a highly limited passage of the drug from plasma to the liquor

AUC area under the curve, *CSF* cerebrospinal fluid, C_{max} highest concentration, t_{max} time to peak

the clinical frame, with special reference to minimal inhibitory concentration (MIC) values of daptomycin, the highest doses of the drug and the administration of dexamethasone. Indeed, daptomycin MIC values for G^+ microorganisms (e.g., *S. aureus*, *S. pneumoniae*) generally range between 0.1 and 1 mg/L. CSF-C_{max} concentration achieved in our patients (0.21 ± 0.11 mg/L), as well as the one found by Kullar et al. (0.461 ± 0.51 mg/L at the same time point,), could be effective only in the case of low MIC, whereas the dose of 10 mg/kg is highly effective in the plasma compartment (being the C_{max} mean value of 81.89 ± 9.28 mg/L). Therefore, the effective treatment could be attained by prescribing daily doses higher than 10 mg/kg. However, although severe adverse events were not observed in the present study, the further increase in drug daily doses could expose the patient to the risk of possible severe toxicity [32]. To the best of our knowledge, there are no studies that have evaluated a higher daptomycin dosage. Moreover, it is worth noting that the present patients did not receive dexamethasone, which is known to affect the distribution of daptomycin into CSF [33].

The low rate of daptomycin CNS penetration in our patients was associated to the high values of CSF t_{max} predicted by the final model (6–9.5 h). This finding was in agreement with the pharmacokinetics of other antimicrobial drugs that have a low rate of distribution within the CNS [29] because of their hydrophilic nature. Moreover, daptomycin distribution is limited to the intercellular space, as suggested by the calculated plasma volume in the present population (0.14 L/kg). This value was similar to the previous reported in studies enrolling patients with severe infections [30, 34], hence higher than value reported by Dvorchik and colleagues [35].

Our study has some obvious limitations associated with the reduced number of enrolled patients and the administration of other antibiotics, which in turn hampers a possible correlation analysis between daptomycin pharmacokinetics and clinical outcomes. However, the treatment of severe CNS infections is often based on drugs other than daptomycin and in some selected cases by the intraventricular administration of drugs, which overcomes the problem of blood–brain barrier permeability. Moreover, the study did not consider CSF protein and plasma level, which may influence drug pharmacokinetics because daptomycin is highly bounded to proteins (from 90 to 93%). Therefore, the decreased level of protein founded in critically ill patients could lead to an increased free fraction of daptomycin that may exert a greater bactericidal effect and be responsible for a higher renal clearance. At the same time, the presence of an external ventricular device leads to a CSF drainage, affecting the drug clearance.

Conclusions

In conclusion, the POP/PK model was able to describe the pharmacokinetics of daptomycin in both plasma and CSF, showing that doses of 10 mg/kg administered for up to 7 days were associated with a minimal penetration into CNS. Furthermore, the observed variability of AUC, t_{max} and predicted concentration in CSF was lower than what previously reported in the literature [24], while the observed variability of plasma quantities was instead comparable. Based on the present findings, it is unlikely that daptomycin could reach concentrations high enough to result in a therapeutic effect for healthcare-associated meningitis. Further studies with larger databases are recommended to confirm the present results and to establish the daptomycin clinical efficacy.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0657-y) contains supplementary material, which is available to authorized users.

Abbreviations
CSF: Cerebrospinal fluid; CNS: Central nervous system; MRSA: Methicillin-resistant *Staphylococcus aureus*; MRSE: Methicillin-resistant *Staphylococcus epidermidis*; G^+: Gram-positive; EVD: External ventricular drainage; POP/PK: Population/pharmacokinetic; AUC: Area under the curve; CDC: Center for diseases control; CPK: Creatine phosphokinase; CRCL: Creatinine clearance; SD: Standard deviation.

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Author contribution
SP and LS contributed to study conception and design. TT, SP and LS acquired the clinical data, AD and TT collected daptomycin CSF and plasma dosage data. All authors helped in interpretation of results. In particular, AP, LG, FC and FC contributed to the POP/PK model elaboration. SP, AD, AP, LG, FC and FC drafted the manuscript. All authors critically revised the manuscript. All the authors approved the manuscript.

Source of support
None.

Compliance with ethical standards

Conflict of interest
All the authors declare that they do not have any Competing Interest.

Ethics approval and consent to participate
This study was approved by the institutional review board (Spedali Civili di Brescia, university of Brescia; IRB1723). Written informed consent was obtained from patients or their legal representatives.

Availability of data and materials
The dataset is available in Github repository, https://github.com/pivadoc/DaptomycinDataset.git.

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