



Pharmacokinetics of Daptomycin in Critically Ill Pediatric Patients

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ABSTRACT The pharmacokinetics of daptomycin (10 mg/kg once daily) was studied in 4 critically ill pediatric patients aged 8 to 14 yrs. The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of plasma concentrations on day 1 ranged between 123.8 to 663.9 $\mu\text{g} \cdot \text{h/ml}$, with lower values observed in septic and burn patients; clearance ranged from 15.1 to 80.7 ml/h/kg. Higher-than-recommended doses of daptomycin may be needed in septic children to ensure optimal drug exposure. Interpatient variability may suggest a role for therapeutic drug monitoring.

KEYWORDS burn, children, critically ill, daptomycin, pharmacokinetics, sepsis

Daptomycin is a lipopeptide agent active against Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. It has been approved for adult patients with complicated skin and soft tissue infections (cSSTI) and right-sided endocarditis (RIE) due to *S. aureus*, as well as *S. aureus* bacteremia when associated with RIE or cSSTI. It has also been approved for treatment of pediatric (1 to 17 yrs old) patients with cSSTI by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (1).

Most of the pediatric pharmacokinetic studies of daptomycin published to date have focused on single-dose pharmacokinetics (2–4). In a recently published randomized controlled trial evaluating the safety and efficacy of daptomycin for complicated skin and skin structure infections in children, multiple-dose pharmacokinetic analysis was performed in 6 patients (12 to 17 yrs old) receiving 5 mg/kg, 2 patients 7 to 11 yrs old receiving 7 mg/kg, 7 patients (2 to 6 yrs old) receiving 9 mg/kg, and 30 patients (12 to 23 months old) receiving 10 mg/kg of daptomycin once daily (QD) (5). The pediatric dosages approved by the FDA and EMA are 5, 7, 9, and 10 mg/kg QD, respectively, for patients aged 12 to 17, 7 to 11, 2 to 6, and 1 to <2 yrs old. For pediatric patients with cSSTI associated with *S. aureus* bacteremia, the doses approved by EMA are higher, i.e., 7, 9, and 12 mg/kg QD for patients aged 12 to 17, 7 to 11, and 1 to 6 yrs old, respectively.

Little is known, however, regarding pharmacokinetics of daptomycin in critically ill children. Daptomycin is primarily eliminated by the kidneys; several factors may affect the clearance and volume of distribution of renally excreted antibiotics in critically ill patients, potentially resulting in suboptimal concentrations and treatment failure. In sepsis, for example, high cardiac output and low systemic vascular resistance may increase renal perfusion and therefore clearance. In addition, fluid extravasation, together with aggressive fluid resuscitation and other physiologic derangements, may lead to a significant augmentation of the volume of distribution (6). Limited studies in

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adults have already demonstrated altered pharmacokinetics of daptomycin in critically ill patients, resulting in lower drug exposure (7, 8).

Herein, we studied multiple-dose pharmacokinetics of daptomycin administered as salvage therapy in pediatric critically ill patients.

Patients who met the following criteria were eligible for the study: 1 to 16 yrs old, hospitalized in 2 pediatric intensive care units (PICU; Heraklion University Hospital, Heraklion, Crete, and Hippokraton General Hospital, Thessaloniki, Greece) from June 2014 to December 2016, treated with daptomycin for (proven or probable) infections caused by Gram-positive organisms not responding or intolerant to other antimicrobial agents, and with normal serum creatinine for age. The decisions to initiate/discontinue daptomycin treatment, as well as the dosage administered for each patient, were at the discretion of the treating physicians and infectious disease consultants, with no involvement of the study team.

Daptomycin (Cubicin, distributed by Novartis, Greece) was administered as a 30-min infusion dissolved in 50 ml of normal saline. Blood samples (0.5 ml) were collected immediately before and 30, 60, 90, 120, 240, and 360 min after the end of the 1st and 5th dose. Following centrifugation of the samples, plasma was collected and immediately stored at -80°C until assayed. Determination of daptomycin levels in plasma was performed using Ultra Performance liquid chromatography with UV detection at 220 nm (9).

Daptomycin pharmacokinetics were studied separately for the 1st and 5th day of administration, in order to investigate possible changes in parameters associated with alterations in patients' physiologic status. An individual pharmacokinetic model was built with Phoenix WinNonlin software (version 7.0; Certara, Princeton, NJ) and both one- and two-compartment structural models were fitted to daptomycin concentrations over time. Subsequent model selection was based on the Akaike information criterion (AIC). Various parameters were then determined for both the 1st and 5th days of daptomycin treatment, including clearance, volume of distribution, maximum plasma concentration (C_{max}), and areas under the concentration-time curve from time zero to infinity ($\text{AUC}_{0-\infty}$) for day 1 and from time zero to 24 h (AUC_{0-24}) for day 5.

The demographic and clinical characteristics of patients enrolled in the study were also recorded, including age, sex, body weight, body surface area, vital signs, reason for PICU admission, comorbidities, type of infection for which daptomycin was administered, coadministration of other medications (including antimicrobial agents), results of daily obtained full blood count and biochemical tests (including kidney and liver function and creatine phosphokinase levels), signs and symptoms that were likely associated with daptomycin administration, and outcome. In case serum creatinine levels were abnormal by the time of administration of the 5th dose of daptomycin, the corresponding drug concentrations were not included in the analysis.

Furthermore, based on daily vital signs and full blood count results, we determined whether the patients included in the study fulfilled the revised pediatric sepsis definition criteria (10) prior to the administration of the 1st and 5th doses of daptomycin. According to the above-referenced consensus statement, sepsis is defined as systemic inflammatory response syndrome (SIRS) in the presence of infection, and age-specific, SIRS-defining, values for heart rate, respiratory rate, and leukocyte count are provided (10). In addition, the Pediatric Risk of Mortality score was calculated for all patients, in order to quantify severity of illness (11).

The study was approved by the Hospital Ethics Committee. Written informed consent was obtained from patients' parents or alternative legal representatives.

Four patients (2 female) who received daptomycin at 10 mg/kg QD were studied (Table 1). Of these, patients 1, 2, and 3 constituted a relatively homogeneous group in terms of age (median age, 9.5 yrs; range, 8 to 10 yrs), while patient 4 was an adolescent (14 yrs). Patients 2, 3, and 4 fulfilled sepsis criteria on day 1 of daptomycin treatment; patient 2 also had extended full-thickness burns. Isolated pathogens tested susceptible to daptomycin by the disk diffusion method, and outcome was favorable in all cases. For all subjects, the pharmacokinetic model with the lower AIC value was the one-

TABLE 1 Patient characteristics, medications coadministered, and fulfillment of sepsis definition criteria and PRISM^a score on days 1 and 5

Patient no.	Age (yrs)	Sex	Body wt (kg)	Reason(s) for PICU admission	Type(s) of infection	Organism isolated (origin)	Medications coadministered	Day 1		Day 5	
								Sepsis criteria met?	PRISM score	Sepsis criteria met?	PRISM score
1	10	M	40	Nontraumatic coma, brain edema, bilateral craniectomy, <i>Bartonella quintana</i> CNS ^b infection	Febrile skin and soft-tissue infection complicating craniectomy	<i>Staphylococcus epidermidis</i> (blood, repeatedly)	Phenytoin, levetiracetam, midazolam, esmolol, enoxaparin sodium, ranitidine, methylprednisolone, piperacillin-tazobactam, gentamicin, rifampin, doxycycline	No	2	No	2
2	8	M	26	Extended (25%) full-thickness burn	Breakthrough sepsis on vancomycin	<i>Enterococcus faecium</i> (blood)	Ranitidine, meropenem, gentamicin, fluconazole	Yes	2	Yes	1
3	9.5	F	45	Rupture of appendix, peritonitis, septic shock	Surgical site infection	<i>Enterococcus faecalis</i> (surgical site, peritoneal fluid)	Remifentanyl, propofol, ranitidine, meropenem, amikacin, metronidazole	Yes	7	No	1
4	14	F	45	Acute peritonitis, septic shock	Peritonitis, intra-abdominal abscesses, septic shock		Remifentanyl, propofol, ranitidine, noradrenaline, meropenem, metronidazole, micafungin	Yes	7	Yes	1

^aPRISM, pediatric risk of mortality.

^bCNS, central nervous system.

TABLE 2 Values of pharmacokinetic parameters generated with one-compartment model for critically ill pediatric patients treated with daptomycin (10 mg/kg QD)

Patient no.	Day 1				Day 5			
	Clearance (ml/h/kg)	Volume of distribution (liter/kg)	AUC _{0-∞} (μg · h/ml)	C _{max} (μg/ml)	Clearance (ml/h/kg) ^c	Volume of distribution (liter/kg)	AUC ₀₋₂₄ (μg · h/ml) (ratio) ^c	C _{max} (μg/ml)
1	15.1	0.16	663.9	59.8	9.9 (0.65)	0.28	1,009.9 (1.52)	60.4
2	80.7 ^a	0.26	123.8 ^b	35.4	56.4 (0.69)	0.55	177.3 (1.43)	19.2
3	28.1 ^a	0.28	355.8 ^b	33.9	27.7 (0.98)	0.34	360.1 (1.01)	32.9
4	42.3	0.23	236.5	40.7	15.4 (0.36)	0.26	651.4 (2.75)	49.8

^aRatios of corresponding clearance values to that of patient 1: 5.34 for patient 2 and 1.86 for patient 3.

^bRatios of corresponding AUC_{0-∞} values to that of patient 1: 0.19 for patient 2 and 0.53 for patient 3.

^cIn parentheses, ratio of each day 5 value to the corresponding day 1 value.

compartment model. The resulting values of pharmacokinetic parameters for day 1 and day 5 of daptomycin treatment are presented in Table 2.

Among patients 1, 2, and 3 (similar age), on day 1 of daptomycin administration, those with sepsis (2 and 3) had higher clearance (ratios, 5.34 and 1.86) and lower AUC_{0-∞} values (ratios, 0.19 and 0.53) compared to those of patient 1 (Table 2). Notably, patient 2, a burn patient with sepsis, exhibited the highest clearance and lowest AUC_{0-∞} values. These interpatient differences were also observed in a proportional way on day 5. Between day 1 and day 5 of daptomycin treatment, notable inpatient differences in pharmacokinetic values were observed. In particular, a trend for a decrease in clearance values (corresponding ratios, 0.36 to 0.98) and an increase in AUC (corresponding ratios of AUC₀₋₂₄/AUC_{0-∞}, 1.01 to 2.75) was observed for all 4 patients (Table 2).

The pharmacokinetic/pharmacodynamic (PK/PD) parameters best correlating with daptomycin efficacy *in vivo* are AUC/MIC and C_{max}/MIC ratios. The mean AUC₀₋₂₄/MIC values associated with static, 1-log killing, and 2-log killing effects against *S. aureus* are 438 ± 67, 666 ± 87, and 1,061 ± 296, respectively (1, 8). Daptomycin exhibits linear pharmacokinetics when administered at doses up to 12 mg/kg QD in healthy adults (12). A dose of 4 mg/kg QD results in a mean AUC₀₋₂₄ on day 7 of 494 μg · h/ml (13). In pediatric patients with cSSTI, comparable exposures were obtained following administration of 7 mg/kg QD and 5 mg/kg QD in those aged 7 to 11 yrs and 12 to 17 yrs, respectively (5). Despite administration of a higher dose of daptomycin (10 mg/kg QD), the AUC_{0-∞} values obtained on day 1 for the three septic patients in our study (patients 2, 3, and 4) were either comparable (patient 3) or markedly lower (patients 2 and 4) than those reported for pediatric cSSTI patients. These findings are consistent with the significantly higher clearance values obtained for daptomycin in these patients compared to those in the pediatric cSSTI patients (16 and 13 ml/h/kg for those aged 7 to 11 and 12 to 17 yrs, respectively) (5). Taken together, these results suggest an alteration of pharmacokinetics of daptomycin in pediatric patients with sepsis, characterized by increased clearance and suboptimal AUC values. Falcone et al. have previously demonstrated augmented daptomycin clearance associated with decreased AUC_{0-∞} and AUC₀₋₂₄ values in critically ill adult patients receiving daptomycin (8). Di Paolo et al., in a population pharmacokinetic study of adult patients with severe infections, also demonstrated a higher volume of distribution and lower plasma concentrations of daptomycin compared with those in healthy volunteers (7).

In healthy adult volunteers receiving daptomycin, the accumulation index between days 1 and 7 of therapy was approximately 1.2 (13). In our patients, a more pronounced increase was observed in AUC₀₋₂₄ values on day 5 compared to the AUC_{0-∞} values on day 1 (as in patient 4; Table 2), which correlates nicely with a decrease in daptomycin clearance. These findings reflect alterations in patients' hemodynamic status associated with recovery from sepsis. From a practical point of view, however, these changes in drug exposure, both from day 1 to day 5 and among patients treated with the same dose of daptomycin, underscore the importance of therapeutic drug monitoring (TDM)

in order to avoid subtherapeutic levels or dose-related adverse events. This need for TDM has recently been highlighted for adult patients receiving daptomycin for bone and joint infections (14).

The findings of this study were based on a small number of patients and should therefore be interpreted with caution. However, they set the basis for a more comprehensive study of daptomycin pharmacokinetics in critically ill patients.

In summary, we herein demonstrated significantly lower drug exposure in pediatric septic patients treated with daptomycin compared to that in healthy volunteers or patients with milder infections. This suboptimal exposure appears to be associated with augmented daptomycin clearance and was more pronounced in the burn patient. Therefore, higher-than-recommended doses of daptomycin may be required for children with sepsis in order to ensure appropriate exposure. The observed interpatient and interday variability suggests a role for therapeutic drug monitoring.

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