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Short Communication

Pharmacodynamics of daptomycin in combination with other antibiotics for the treatment of enterococcal bacteraemia

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ABSTRACT

Daptomycin is commonly prescribed in combination with other antibiotics for treatment of enterococcal bacteraemia. Whilst a free drug area under the concentration–time curve to minimum inhibitory concentration (*f*AUC/MIC) ratio >27.4 is associated with 30-day survival with daptomycin monotherapy, it is unknown whether receipt of other antibiotics affects this threshold. Data were pooled from seven published trials assessing outcomes in daptomycin-treated enterococcal bacteraemia, including patients receiving daptomycin (≥72 h) and any β-lactam, intravenous aminoglycoside, linezolid, tigecycline and/or vancomycin. Exposures were calculated using a published population pharmacokinetic model based on creatinine clearance, 90% protein binding and daptomycin Etest MIC. The *f*AUC/MIC threshold predictive of 30-day survival was determined by classification and regression tree analysis. Following pooling of data, 240 adults were included; 137 (57.1%) were alive at 30 days. A majority of patients were immunosuppressed (65.8%) and received a β-lactam (94.6%). Examining the threshold in low-acuity patients ($n = 135$) to control for co-morbidities, these patients were more likely to survive when *f*AUC/MIC >12.3 was achieved (63.2% vs. 20.0%; $P = 0.015$). The difference remained significant in a multivariable logistic regression model that controlled for infection source and immunosuppression ($P = 0.017$). This threshold is 2-fold lower than that observed with daptomycin monotherapy. Probabilities of threshold attainment using a 10 mg/kg/day dose were 100% for isolates with MICs ≤ 2 mg/L and 95.2% for a 12 mg/kg/day dose for MICs of 4 mg/L. These data support the use of high-dose daptomycin in combination with another antibiotic for treatment of enterococcal bacteraemia.

1. Introduction

Systemic enterococcal infections have become increasingly challenging to manage as these pathogens circulate the global healthcare system with an ability to acquire resistance to nearly all

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anti-enterococcal antibiotics. With established clinical efficacy and bactericidal properties, daptomycin is frequently used to treat enterococcal bacteraemia, and improved outcomes are associated with regimens that exceed approved (4–6 mg/kg/day) doses [1]. However, mutations in genes encoding the LiaFSR regulatory system may still render doses >6 mg/kg/day inadequate, as evidenced by a fatal case of recurrent bacteraemia in a patient treated with 8 mg/kg/day [2]. In fact, in vitro investigations suggest that ≥10 mg/kg/day is required to sustain bactericidal activity without regard to the isolate's genotypic profile [3]. Furthermore, decreased susceptibility to daptomycin has been associated with microbiological failure in vancomycin-resistant *Enterococcus faecium* bacteraemia [4]. Based on these observations and a recent pharmacokinetic/pharmacodynamic (PK/PD) analysis of daptomycin monotherapy [5], the Clinical and Laboratory Standards Institute (CLSI) designated enterococci with daptomycin minimum inhibitory concentrations (MICs) of 2–4 mg/L as 'susceptible-dose-dependent' (S-DD) [6].

Combination antibiotic therapy with daptomycin and other agents that are intrinsically or synergistically active may be an option for S-DD infections. Although isolate-specific synergistic interactions between daptomycin and various β-lactams are frequently demonstrated in vitro [7], accounts of treatment failures serve as important reminders that translation to clinical success is not guaranteed [8]. We examined the missing link between these in vitro and clinical observations in patients treated with daptomycin combination therapy for enterococcal bacteraemia. Our previous findings in daptomycin monotherapy-treated patients indicate that pharmacodynamic threshold attainment, in terms of the free drug area under the concentration–time curve to MIC ratio (*f*AUC/MIC) >27.4, is associated with 30-day survival [5]. Thus, the aim of this study was to identify the daptomycin *f*AUC/MIC threshold associated with 30-day survival in patients who received other antibiotics during daptomycin therapy in order to determine daptomycin doses that achieve the required exposure.

2. Materials and methods

2.1. Patients

Previously collected, de-identified data were pooled from seven observational studies of daptomycin-treated enterococcal bacteraemia for re-analysis [4,9–14]. Patients received ≥72 h of daptomycin therapy for enterococcal bacteraemia with documented administration of (i) any β-lactam, (ii) an intravenous aminoglycoside, (iii) linezolid, (iv) tigecycline and/or (v) vancomycin (for vancomycin-susceptible isolates). These antibiotics were administered on the same day as daptomycin, however the prescribed dosage schedule or duration of therapy was unavailable. The total population was further categorised by acuity. Low-acuity patients were those who did not meet any of the criteria among Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥21, Charlson comorbidity index ≥5 or Pitt bacteraemia score ≥4, as these scores were associated with mortality in a critically ill population [15]. Patients were excluded if they had received continuous renal replacement therapy during treatment and/or if documentation of negative blood cultures preceded the receipt of daptomycin. Only the first episode of enterococcal bacteraemia was included.

2.2. Calculation of daptomycin *f*AUC/MIC

These methods and those outlined in Sections 2.3 and 2.4 have been previously described in detail [5]. Daptomycin total body clearance (CL) for each patient was calculated using a validated population pharmacokinetic model [16]. Briefly, daptomycin *f*AUC was determined by multiplying the dose in milligrams by the free fraction (10%) in human plasma and dividing by the calculated CL. If daptomycin was administered every 48 h, the dose was divided in half to reflect average 24-h exposure. The *f*AUC was divided by the baseline daptomycin Etest MIC provided by the study site to determine the *f*AUC/MIC.

2.3. Identification of daptomycin *f*AUC/MIC threshold

The *f*AUC/MIC threshold associated with 30-day survival, assessed from the first day of daptomycin therapy or time of bacteraemia diagnosis, was determined by recursive partitioning (rpart) using R v.3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Classification and regression trees were constructed with a root node and a single terminal node containing no fewer than 10 observations. The association of survival with threshold attainment was confirmed to be independent of other variables using multivariable logistic regression (Sigma Plot v.13.0; Systat Software Inc., San Jose, CA). The model included all covariates with a bivariate *P*-value of <0.2 determined by *t*-test or Mann–Whitney rank-sum test for continuous variables and χ^2 or Fisher's exact test for categorical variables using Sigma Plot v.13.0.

2.4. Probability of threshold attainment (PTA)

Monte Carlo simulations were performed using Crystal Ball v.11.1 (Oracle, Redwood Shores, CA) to determine the PTA for an *f*AUC/MIC as described previously [5] for daptomycin dosages of 6, 8, 10 and 12 mg/kg daily. Simulated parameters were the unbound daptomycin fraction and creatinine clearance, which varied according to uniform distributions from 0.07–0.10 and 30–150 mL/min, respectively. In addition, body weight varied as a log-normal distribution from 37–180 kg according to the observed mean ± standard deviation in the pooled study cohort. Each *f*AUC/MIC was forecast using the calculation method described in Section 2.2. Simulations were performed separately for 5000 females and 5000 males to account for sex disparity in the pharmacokinetic model used to calculate CL, where a factor of 0.80 was applied for simulated females [16].

3. Results

3.1. Patients

Among 460 cases of daptomycin-treated enterococcal bacteraemia identified, 240 patients met the inclusion criteria and were assessed. The contribution of patients from the original studies was as follows: 67 from Egli et al. [9]; 22 from Casapao et al. [10]; 20 from Shukla et al. [4]; 28 from DiPippo et al. [12]; 77 from Chuang et al. [13]; and 26 from Britt et al. [14]. The vast majority of patients (94.6%) received β-lactams with daptomycin (Table 1). The distribution of daptomycin Etest MICs is provided in Fig. 1.

3.2. Survival threshold in all patients

In the total population ($n = 240$), 30-day survival was achieved in 137 patients (57.1%). The pharmacodynamic threshold identified was *f*AUC/MIC > 12.2, where 132/225 patients (58.7%) with exposures exceeding this threshold survived compared with 5/15 patients (33.3%) with *f*AUC/MIC ≤ 12.2 ($P = 0.099$). In patients who received a β-lactam ($n = 227$; 94.6%), the threshold was similar (30-day survival, 59.0% if *f*AUC/MIC > 12.3 vs. 33.3% if *f*AUC/MIC ≤ 12.3; $P = 0.095$).

3.3. Survival threshold in low-acuity patients

To account for non-infectious syndromes that may confound mortality, an analysis of low-acuity patients ($n = 135$) was

Table 1
Characteristics of included patients with enterococcal bacteraemia treated with daptomycin[a].

Characteristic	All patients ($n = 240$)	Low-acuity patients ($n = 135$)
Age (years)	62.8 ± 15.9 (64.4)	60.7 ± 16.4 (61.5)
Female sex [*n* (%)]	97 (40.4)	57 (42.2)
Serum creatinine (mg/dL)	1.5 ± 1.3 (1.1)	1.3 ± 1.2 (0.9)
Weight (kg)	72.4 ± 22.8 (68.0)	72.9 ± 22.2 (68.0)
Daptomycin dose (mg/kg/dose)	7.2 ± 1.7 (7.0)	7.3 ± 1.7 (7.0)
Other antibiotic received [*n* (%)]		
Aminoglycoside	22 (9.2)	14 (10.4)
β-Lactam	227 (94.6)	127 (94.1)
Linezolid	21 (8.8)	11 (8.1)
Tigecycline	8 (3.3)	2 (1.5)
Vancomycin	9 (3.8)	7 (5.2)
Received 1 other antibiotic	199 (82.9)	112 (83.0)
Received 2 other antibiotics	35 (14.6)	20 (14.8)
Received 3 other antibiotics	6 (2.5)	3 (2.2)
Enterococcus faecium bacteraemia [*n* (%)]	235 (97.9)	131 (97.0)
Daptomycin Etest MIC (mg/L) [median (range)]	2 (0.094–96)	2 (0.094–48)
Immunosuppressed [*n* (%)][b]	158 (65.8)	81 (60.0)
Infection source		
Catheter	67 (27.9)	35 (25.9)
Endocarditis	6 (2.5)	3 (2.2)
Gastrointestinal	73 (30.4)	44 (32.6)
Urinary tract	30 (12.5)	18 (13.3)
Other or unknown	64 (26.7)	35 (25.9)
Intermittent haemodialysis [*n* (%)]	28 (11.7)	10 (7.4)
Low-acuity [n (%)][c]	135 (56.3)	135 (100.0)
APACHE II score	13.1 ± 5.7 (13.0)	11.6 ± 4.9 (12.5)
Charlson comorbidity index	4.1 ± 2.8 (4.0)	2.3 ± 1.3 (2.0)
Pitt bacteraemia score	3.1 ± 2.7 (3.0)	1.3 ± 1.2 (1.0)
Survived at 30 days [*n* (%)]	137 (57.1)	81 (60.0)

MIC, minimum inhibitory concentration; APACHE, Acute Physiology and Chronic Health Evaluation.
[a] Data are presented as the mean ± standard deviation (median) unless otherwise stated.
[b] Immunosuppressed patients were those with active malignancy, history of solid organ/bone marrow transplantation, neutropenia (absolute neutrophil count <500/μL), human immunodeficiency virus (HIV) infection, or those receiving chemotherapy, mycophenolate, tacrolimus, cyclosporine, biological therapy or corticosteroids.
[c] Low-acuity indicates that none of following conditions were met: APACHE II score ≥21 (available for 48 patients in the total population and 28 in the low-acuity cohort), Charlson comorbidity index ≥5 (available for 213 patients in the total population and 115 in the low-acuity cohort) and Pitt bacteraemia score ≥4 (available for 75 patients in the total population and 31 in the low-acuity cohort); these scores were previously associated with in-hospital mortality in critically ill patients with sepsis [15].

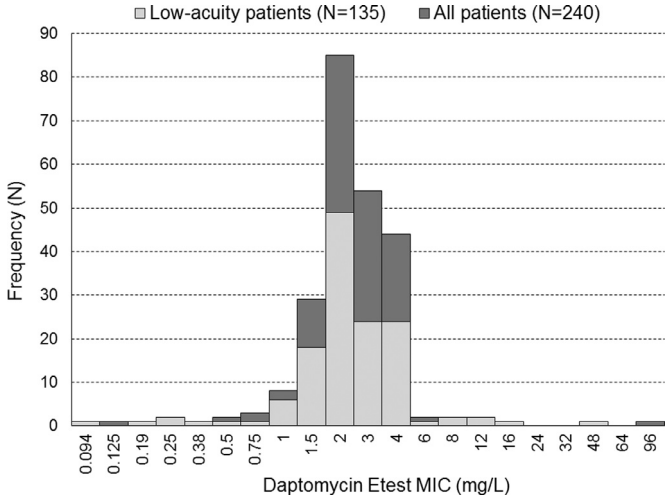

Fig. 1. Daptomycin Etest minimum inhibitory concentration (MIC) distribution. MIC distributions were constructed using baseline daptomycin Etest MICs, as reported by each original study site, for all patients ($n = 240$) and for the low-acuity population ($n = 135$).

conducted as previously described [5]. Whilst acuity scores were lower in this subpopulation as a corollary of the definition, the 30-day mortality rate remained high at 40.0% (Table 1) compared with a mortality rate of 46.7% in high-acuity patients. The median daptomycin dose (7.4 mg/kg/dose vs. 6.4 mg/kg/dose; $P = 0.068$) and *f*AUC/MIC (32.4 vs. 27.5; $P = 0.357$) was higher in surviving patients than in those who died, respectively, but the differences were not statistically significant. The median MIC was 2 mg/L both in surviving and deceased patients ($P = 0.742$). Low-acuity patients with *f*AUC/MIC > 12.3 ($n = 125$) were more likely to survive (63.2% vs. 20.0%; $P = 0.015$). As removal of eight patients who did not receive a β-lactam produced an identical threshold ($P = 0.014$), statistical analysis was completed in the entire low-acuity subpopulation. In the multivariable model, achievement of the pharmacodynamic threshold remained associated with 30-day survival (multivariable odds ratio for survival = 7.50, 95% confidence interval 1.44–39.06; $P = 0.017$) when controlling for urinary source, other/unknown source and immunosuppressed status, as these were the only parameters with bivariate *P*-values of <0.2 (Table 2).

The PTA for *f*AUC/MIC > 12.3 is presented in Fig. 2.

4. Discussion

A daptomycin *f*AUC/MIC threshold of >12.3 was identified as being associated with 30-day survival ($P = 0.017$) in low-acuity patients with enterococcal bacteraemia treated with daptomycin in combination with another antibiotic. This association was mainly driven by co-administration of a β-lactam antibiotic. The PTA for MIC ≥ 4 mg/L was suboptimal when the standard bacteraemia dose (6 mg/kg/day) and a medium dose (8 mg/kg/day) were

Table 2
Effect of characteristics on 30-day survival in the low-acuity cohort ($n = 135$).

Characteristic	*n* (%) of patients		Bivariate analysis		Multivariable analysis	
	Survived ($n = 81$)	Deceased ($n = 54$)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Immunosuppressed	43 (53.1)	38 (70.4)	0.48 (0.23–0.99)	0.045	0.70 (0.32–1.54)	0.374
Intermittent haemodialysis	5 (6.2)	5 (9.3)	0.65 (0.18–2.34)	0.520		
Bacteraemia source						
Gastrointestinal	24 (29.6)	20 (37.0)	0.72 (0.35–1.48)	0.368		
Urinary tract	6 (7.4)	12 (22.2)	0.28 (0.10–0.80)	0.013	0.30 (0.10–0.91)	0.033
Catheter-related	23 (28.4)	12 (22.2)	1.39 (0.62–3.10)	0.423		
Endocarditis[a]	3 (3.7)	0 (0.0)	–	0.275		
Other or unknown	25 (30.9)	10 (18.5)	1.96 (0.85–4.52)	0.109	1.69 (0.68–4.15)	0.258
*f*AUC/MIC > 12.3[a,b]	79 (97.5)	46 (85.2)	6.87 (1.40–33.74)	0.015	7.50 (1.44–39.06)	0.017

OR, odds ratio; CI, confidence interval; *f*AUC, free drug area under the concentration–time curve; MIC, minimum inhibitory concentration.
[a] Bivariate statistical analysis performed using Fisher's exact test.
[b] Dose was not included as a covariate in multivariable modelling as it varies co-linearly with *f*AUC/MIC.

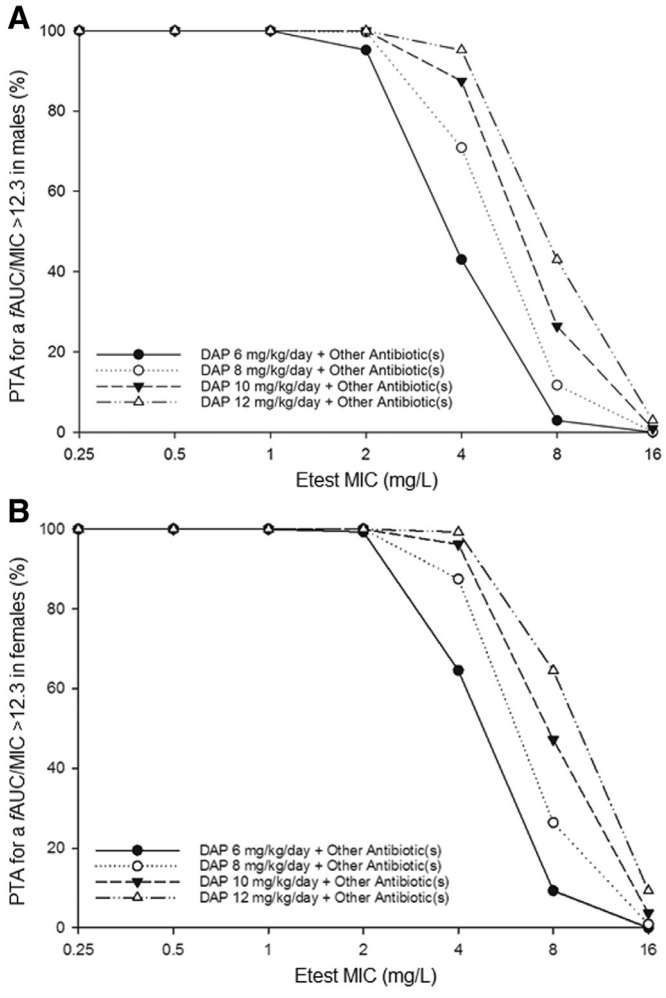

Fig. 2. Monte Carlo simulation results for (A) males and (B) females of the PTA for *f*AUC/MIC > 12.3. The PTA was higher for female simulated patients because calculated DAP clearance was 20% slower in simulated females. DAP, daptomycin; *f*AUC, area under the free drug concentration–time curve; MIC, minimum inhibitory concentration; PTA, probability of threshold attainment.

simulated. Overall, the data support daptomycin dosages of 10–12 mg/kg/day in combination therapy regimens to cover enterococcal isolates in the S-DD range (MIC = 2–4 mg/L). The standard dose (6 mg/kg/day) in combination therapy regimens was satisfactory for isolates now considered susceptible by the CLSI (MIC ≤ 1 mg/L) [6].

The difference observed in 30-day survival is plausibly explained by achievement of the pharmacodynamic threshold, as neither daptomycin dosage (mg/kg/dose) nor MIC were independently associated with survival. It is interesting, though not unexpected, that this threshold identified in daptomycin combination therapy-treated enterococcal bacteraemia is approximately 2-fold lower than the threshold identified in low-acuity monotherapy-treated patients (*f*AUC/MIC > 27.4) [5]. Robust in vitro data support the presence of in vitro synergistic interactions between daptomycin and various β-lactams in susceptible and non-susceptible enterococcal strains [7]. Although the precise mechanisms are not fully elucidated, the finding of a lower threshold may be a consequence of increased β-lactam activity following daptomycin-induced cell envelope changes [17] or of enhanced daptomycin surface binding in the presence of β-lactams [7]. Furthermore, Kebriaei et al. observed suppression of daptomycin resistance that occurred with monotherapy (6, 8 and 10 mg/kg/d) in a simulated endocardial vegetation model with the addition of ampicillin, ertapenem or ceftaroline against an isolate (MIC = 2 mg/L) harbouring LiaS and LiaR mutations [18]. A lower pharmacodynamic threshold identified in combination therapy-treated patients also provides a potential mechanism responsible for improved end-of-treatment survival in enterococcal bacteraemia recently observed with high-dose (≥9 mg/kg/day) daptomycin plus a β-lactam compared with daptomycin monotherapy, high-dose monotherapy, or low-dose daptomycin plus a β-lactam [19].

In the cohort of patients in this study who received additional antibiotics with daptomycin, it was not possible to precisely indicate which β-lactam antibiotics were associated with survival as this information was unavailable. Moreover, β-lactams may have been intended for empirical Gram-negative coverage, and the number of doses and administration schedules of the other antibiotics received remain unknown. Other limitations inherent to the use of a retrospective study design have been described previously [5]. As such, the observed relationship between calculated pharmacodynamic exposure and survival is an association and may not be causal. It should also be recognised that *f*AUC/MIC values in this study were calculated with Etest MICs, and a threshold derived with MICs determined by other testing methods may be different. However, we chose not to explore this possibility as the methodological shortcomings of the MIC test for daptomycin and enterococci are well established [20] and gradient diffusion methods are commonly used in clinical laboratories in place of the more cumbersome reference testing method (i.e. broth microdilution).

Finally, a major gap in the field of translational pharmacokinetics/pharmacodynamics is that currently there is no established model for verifying that findings of in vitro synergy translate to

improved clinical outcomes. An ideal model to do so likely involves an amalgamation of in vitro, in vivo and clinical studies. Until this science is thoroughly validated, it will remain difficult to justify specific breakpoints for antibiotics when used in combination with other antibiotics. As such, it is important that the clinical PK/PD threshold ($fAUC/MIC > 12.3$) reported in this study is not confused with targets derived from clinical data describing antibiotic monotherapy, the latter of which should be the preferred method used for breakpoint assessment.

5. Conclusions

This human pharmacodynamic analysis provides support for prescription of daptomycin 10–12 mg/kg/day in combination therapies, particularly those containing a β-lactam, for bacteraemia caused by S-DD enterococci. Use of high doses should always be accompanied by careful monitoring for drug-related toxicities. In contrast to our previous data evaluating daptomycin monotherapy regimens [5], the high-dose combination therapy regimens achieved high PTAs for strains demonstrating elevated MICs as high as 4 mg/L. Clinical studies evaluating daptomycin pharmacodynamics with special attention to individual β-lactams are needed.

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Declaration of Competing Interest

None declared.

Ethical approval

Not required.

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