Considerations for Higher Doses of Daptomycin in Critically Ill Patients With Methicillin-Resistant Staphylococcus aureus Bacteremia

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Background

– IDSA guidelines: high-dose (10 mg/kg) daptomycin in persistent MRSA bacteremia with vancomycin failure; experts suggest 8–10 mg/kg daptomycin in infective endocarditis

– recommendations based on the PK/PD profile of daptomycin; sub-optimal daptomycin AUC/MIC values linked to clinical failure, C_{min} concentrations correlated with skeletal muscle toxicity

– marked variability in PK in acutely ill patients, but dose currently only increased for weight, decreased for eCLcr <30 mL/minute, and not adjusted for any surrogate markers of critical illness

Aim of the study

– to characterize daptomycin use in critically ill patients, to identify subgroups with augmented daptomycin CL

– to estimate the probability of target attainment (PTA= in Monte Carlo simulations, the probability that at least a specific value of a pharmacodynamic index is achieved at a certain minimum inhibitory concentration) and toxicity of alternate dosing regimens

Methods

– *Study design*

- open-label, prospective study, carried out in the Policlinico Umberto I of Rome, Italy, between November 2009-2011
- daptomycin selected on the personal judgment of the attending physician
- patient demographics, clinical and laboratory findings, microbiological data, duration of daptomycin therapy, and outcome information collected

– *Selection criteria*

- adults (≥18 years) with a blood culture or other sterile site positive for a gram-positive pathogen
- exclusion criteria: 1)hypersensitivity to daptomycin; 2)meningitis or osteomyelitis; 3)pneumonia; 4)daptomycin-resistant organism; 5)treatment with gram-positive bacteria–active antimicrobial in the 7 days prior the study; 6)pregnant or lactating; 7)dialysis; 8)rhabdomyolysis; 9)myopathy
- healthcare-associated infections defined according to CDC, bloodstream infections according to standard international criteria, bacteremia defined as microorganism in ≥2 separate blood cultures with evidence of infection, infective endocarditis diagnosed according to the modified Duke criteria

– *Daptomycin dosing and plasma concentration measurement*

- daptomycin was infused intravenously over 30 minutes every 24 hours based on a clinician-chosen dosage of 6 or 8 mg/kg/day
- sampling was done prior to the first dose, at 30 minutes (end of infusion), and at 1, 2, 4, 8, 12, and 24 hours after the initial dose

– *Population Pharmacokinetic Analysis*

- population pharmacokinetic (POP-PK) systems analysis was performed with ADAPT 5, based on Akaike information criterion (AIC= measure of the relative quality of a statistical model)
- blinded analysis

– *Model Validation and Dosing Simulations*

- after final model validation, individual patient estimates and actual doses were used to compute individualized C_{max}, C_{min}, $AUC_{0\text{-}24}$ and $AUC_{0\text{-}inf}$ values
- various dosing regimens were simulated (n = 5000) to ascertain PTA and toxicity
- a daptomycin $AUC_{0\text{-}24}$/MIC ratio of <666 has been associated with worse clinical outcomes. MIC range: 0.016–2 mg/L (EUCAST)
- evaluation of PTA of an $AUC_{0\text{-}24}$/MIC ratio of ≥666 ± 1 SD (≥579, ≥666, ≥753) for weight-based doses (6–10 mg/kg) and fixed doses (500–1000 mg) by Monte Carlo simulation (MCS) (n = 5000)

- probability of C_{min} ≥ 24.3 mg/L (associated with skeletal muscle toxicity)

– *Statistical analysis*
- the upper quartile of daptomycin CL compared to the rest of the population
- Fisher exact test, Mann-Whitney test and logistic regression for the relationship between PK-PD indices and mortality

Results
– 69 patients screened, 58 patients enrolled, 50 patients included (**Figure 1**)
– demographic characteristics in **Table 1**, type of infections: bloodstream (42%), skin and soft tissue (40%), isolate identified in 88% of patients, 2/3 MRSA, patients treated with daptomycin 6 mg/kg (n = 32) or 8 mg/kg (n = 18)
– 590 plasma samples analyzed (median 12/patient), 1-compartment linear model
– individual median CL: 0.845 (0.662, 1.36) L/hour (**Figure 2**), a distinct subpopulation with augmented CL was observed (**Figure 3**), distinct over body weight and eCLcr
– patients with augmented CL had significantly (P < .001) lower C_{max}, AUC_{0-24}, and AUC_{0-inf} values (**Table 1**, **Figure 4**)
– **Table 2**: patients with augmented CL had all bacteremia and/or infective endocarditis. Eleven/13 were infected with MRSA, severe sepsis or septic shock was in 100% of cases (compared to 24% of the rest of the population), in- hospital mortality was significantly (P < .001) higher
– **Table 3**: in-hospital mortality only in patients with MRSA bloodstream infections
– in sepsis the median CL was 0.98 (0.601, 2.10) L/hour compared to 0.769 (0.528, 1.92) L/hour without sepsis (**Figure 5A**), mean SOFA scores were higher in augmented CL, with significant but poor (R2 = 0.22) relationship (**Figure 5B**)
– **Table 4** (patients without sepsis): cumulative fraction of response (CFR=expected population probability of target attainment for a specific drug dose and a specific population of microorganisms) >90% for all targets with the 8 and 10 mg/kg/day but not the 6 mg/kg/day doses. CFR increases with increasing weight-based dose; C_{min} values ≥24.3 mg/L is 11.0% with 10 mg/kg/day doses. In contrast, with 500 mg/day, CFR > 90% for all targets, and C_{min} values are ≥24.3 mg/L in 1.38%
– **Table 5** (patients with sepsis): lower PTA and CFR, and lower C_{min} values ≥24.3 mg/L. CFR >90% for all targets with 10 mg/kg/day or doses >750 mg/day. However, with 750 higher CFR and lower C_{min} values ≥24.3 mg/L

Discussion
– daptomycin exposures are lower in critically ill patients with sepsis (primarily with MRSA-related bacteremia) when treated with standard doses
– a subpopulation of critically ill patients with augmented daptomycin CL exists; however, it is not easily identified by demographic, anthropometric, laboratory, or severity of illness markers
– higher weight-based doses may achieve the target exposure, but a minimum threshold dose (500 mg or 750 mg) is necessary
– higher empiric fixed doses in the first 96 hours of therapy are associated with a lower probability of skeletal muscle toxicity than use of 10 mg/kg
– use of an empiric fixed dose of 500 mg (nonsepsis) or 750 mg (sepsis) ensures that underweight patients are not underdosed, taking into account that daptomycin is weight-dosed, but daptomycin CL is independent of weight

Limitations
– small sample size to identify markers predictive of augmented daptomycin CL
– time-course and management of critically ill patients are highly variable
– TDM could be used, but the study was not adequately powered or designed to validate the role of TDM

Conclusion
– strong rationale for the prospective comparison of a fixed empiric dose (750 mg/day) to weight-based (8–10 mg/kg) dosing of daptomycin in critically ill patients
– higher doses are likely necessary at the onset of therapy in critically ill patients