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Correlation between pharmacokinetic/pharmacodynamic indices and clinical outcomes in Japanese patients with skin and soft tissue infections treated with daptomycin: analysis of a phase III study ☆

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ABSTRACT

The relationships between pharmacokinetic (PK)/pharmacodynamic (PD) indices and outcomes were investigated in patients with skin and soft tissue infection (SSTI) who received daptomycin at 4 mg/kg/day. Efficacy was evaluated in 55 patients from whom *Staphylococcus aureus* was isolated, with success rates of 94.5% and 69.1% for clinical and microbiological responses, respectively. The odds ratio for the relationship between the area under the day 1 concentration–time curve ($AUC_{0-24\ h}$) to the MIC and the probability of clinical success was 1.03 (95% confidence interval [CI] 0.73–1.45), and that for the relationship for probability of microbiological success was 0.94 (95% CI 0.81–1.09). In 82 patients in the safety analysis, only 1 met the creatine phosphokinase (CPK) elevation criteria, and this patient's minimum concentration (C_{min}) of plasma daptomycin was 5.37 μg/mL. No significant relationship was found between peak CPK and C_{min} (Pearson's correlation coefficient −0.0452). In conclusion, no clear correlation between PK/PD indices and the probability of efficacy or safety events was demonstrated when daptomycin was administered in SSTI patients using the clinically recommended dosage of 4 mg/kg/day.

1. Introduction

Daptomycin (Cubicin®) is a cyclic lipopeptide antibiotic that is approved for the treatment of skin and soft tissue infections (SSTIs) caused by gram-positive cocci and of bacteremia caused by *Staphylococcus aureus*. Several reports of pharmacokinetic (PK)/pharmacodynamic (PD) analyses of daptomycin based on an in vivo infection model described the ratio of area under the plasma concentration–time curve to the MIC ($AUC_{0-24\ h}$/MIC) as the PK/PD index associated with efficacy (Louie et al., 2001; Safdar et al., 2004). However, the magnitude of $AUC_{0-24\ h}$/MIC associated with efficacy based on data from clinical studies has not been described.

The relationship between daptomycin exposure and creatine phosphokinase (CPK) elevation has been reported previously, based on data from patients who received daptomycin at 6 mg/kg/day for the treatment of bacteremia or endocarditis (Bhavnani et al., 2010). The evaluation of the proposed cut-off points to adverse events, however, has not been performed in patients receiving daptomycin at 4 mg/kg/day for the treatment of SSTIs. The clinical outcomes of a phase III study in patients with SSTIs caused by methicillin-resistant *S. aureus* (MRSA) or other gram-positive cocci treated with daptomycin have been reported by Aikawa et al. (2013). Using data from a subpopulation of that study, we investigated the relationships between daptomycin exposure and clinical outcomes in patients with SSTIs who received daptomycin at 4 mg/kg/day.

2. Materials and methods

2.1. Study design and population for analysis

We analyzed data from a subset population of a phase III study of daptomycin in Japanese patients with SSTI caused by gram-positive cocci conducted between 2008 and 2010 (Aikawa et al., 2013). The study was reviewed and approved by the ethics committee of each institution, and written informed consent was obtained from the patients before enrollment. This study is registered at ClinicalTrials.gov

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(NCT00770341). Inclusion criteria for the phase III study were 1) isolation of MRSA from specimens obtained within 3 days before starting treatment or the detection of gram-positive cocci and a suspicion of MRSA infection and 2) presence of at least 3 of the following: drainage/exudate, erythema, fluctuance, localized warmth, pain/tenderness, swelling/induration, temperature >37.5 °C (oral) or 37 °C (armpit), white blood cell count outside the normal range, stab cells >15%, pulse rate >90/min, respiratory rate >20/min, and positive C-reactive protein.

In this study, patients were treated with 4 mg/kg/day intravenous daptomycin over 30 min for 7–14 days. CPK was measured twice a week in the treatment period. The population for each analysis was defined as follows: PK/PD analysis population for safety: patients who received at least 1 dose of daptomycin and at least 1 blood sample for plasma concentration measurement; PK/PD analysis population for efficacy: patients who 1) were included in the PK/PD analysis population for safety, 2) received at least 4 days of treatment, 3) had clinical or microbiological assessment data at test of cure (TOC), 4) did not receive any prohibited concomitant antibiotics, 5) did not have important deviations from the protocol, and 6) were infected with *S. aureus* (methicillin sensitive or resistant). The MIC of daptomycin against *S. aureus* at baseline was measured by microdilution methods in accordance with the Clinical and Laboratory Standards Institute (CLSI) testing guidelines (M7-A7, 2006).

2.2. PK sampling and measurement of plasma level

Daptomycin was intravenously infused over 30 min, and blood samples were collected at the following 5 time points: prior to and at the end of infusion, 30 min to 2 h, and 4–10 h postadministration on day 4 and prior to infusion on day 5. Blood was collected in Na–heparin tubes and stored on ice immediately. Plasma was obtained by centrifugation at approximately 3000–4000 rpm for 15 minutes within 2 h of blood collection. The plasma (1.5 mL) was then transferred to a polypropylene tube, which was stored frozen at −20 °C. The daptomycin concentration was measured at PPD® (Richmond, Virginia, USA). A 300-μL aliquot was used for reverse-phase high-performance liquid chromatography (Waters WISP 717 plus) with ultraviolet absorbance detection. The minimum quantifiable level was 3.0 μg/mL. The daptomycin standard for quantification was provided by Cubist Pharmaceuticals (Lexington, MA, USA).

2.3. Population PK modeling

Our analysis included the data from 545 subjects who were enrolled in phase I and phase III studies conducted in Japan (127 subjects), which were reported by Dvorchik et al. (2004) (282 subjects), or who were enrolled in 3 other phase I and phase III studies in non-Japanese (136 subjects). A total of 5586 daptomycin samples for PK (1255 from Japanese and 4331 from non-Japanese) were included in the data set. Doses ranged from 2 to 12 mg/kg among the studies described by Dvorchik et al. (2004) and among the additional 20 studies evaluated. Plasma concentration data for daptomycin were analyzed using nonlinear mixed-effects modeling (NONMEM, version 6). The first-order conditional estimation with interaction method was used for all analyses. Our population PK model was further developed in reference to the published model (Dvorchik et al., 2004). We investigated the influence of the covariates reported by Dvorchik et al. (2004), namely, gender, body weight, temperature, infection status, disease diagnosis, dialysis and dialysis membrane type, creatinine clearance, and ethnicity, on daptomycin PK. In addition, a new covariate representing origin, Japan versus other countries, was also examined.

The final population PK model was used to generate the empirical Bayesian PK parameter estimates. The individual day 1 AUCs were calculated based on simulated daptomycin concentrations. Steady-state exposures were estimated using the individual empirical Bayes parameters. Estimated daptomycin exposure and PK parameters included minimum concentration (C_{min}), $AUC_{0-24\ h}$, weight-adjusted steady-state volume of distribution (Vss), weight-adjusted clearance (CL), and half-life ($t_{1/2}$). The predictability of the model was evaluated using a visual predictive check. One thousand data sets were simulated for daptomycin concentrations based on the final model. The observed and simulated data sets in a steady state were each divided into bins of approximately equal numbers of observations by ranges of time after dose and then stratified by dose (4 and 6 mg/kg). For each separate bin in the observed and simulated data, the 5th, 50th, and 95th percentiles were calculated. The observed data were compared to the 5th, 50th, and 95th percentiles of the observed and simulated data.

2.4. PD endpoints

Clinical and microbiological responses were evaluated at TOC. Clinical success was defined as resolution or partial resolution of signs and symptoms of SSTI in patients who did not receive additional antimicrobial agents that could potentially have been effective against the causative pathogen during the study period. Microbiological success was defined as "eradication" (admission pathogen absent in culture) or "presumed eradication" (no material available for culture due to the infection site being cured or improved). The Independent External Adjudication Committee (IEAC), consisting of 5 medical experts blinded to study therapy, reviewed and determined the final assessment of efficacy.

CPK elevation represented the safety endpoint of interest, with the upper limit of normal (ULN) for CPK concentration being defined as 200 U/L. Patients with CPK concentrations meeting either of the following conditions were classified as having elevated CPK: 1) no CPK elevation at baseline followed by CPK elevations $\geq 3 \times$ ULN based on 2 sequential measurements during the period from day 4 to 2 days after the end of therapy, with 1 of 2 CPK elevations $\geq 5 \times$ ULN or 2) baseline CPK greater than the ULN followed by CPK elevation $\geq 5 \times$ ULN based on 2 sequential measurements during the period from day 4 to 3 days after the end of therapy (Bhavnani et al., 2010).

2.5. PK/PD analyses

Summary statistics including the geometric mean (GM) and corresponding 95% confidence intervals (CIs), minimum, median, and maximum were provided for PK parameters. Clinical and microbiological responses were summarized by exposure grouped by quartiles. The relationship between response and exposure grouped in this manner was assessed using Mantel–Haenszel chi-square test. In addition, logistic regression models with day 1 and steady-state $AUC_{0-24\ h}$ and $AUC_{0-24\ h}$/MIC evaluated as continuous covariates were used to investigate the effect of exposure on the clinical and microbiological responses. Similarly, the relationship between CPK elevation and C_{min} grouped by quartiles and as a continuous covariate was evaluated. Pearson's correlation coefficient was calculated for the relationship between C_{min} and peak CPK. SAS version 9.3 for Windows (SAS, Cary, NC, USA) was used to perform all analyses. All statistical tests were conducted at the 0.05 significance level (2 sided).

3. Results

3.1. Patient population and daptomycin susceptibility for S. aureus

A total of 82 patients were included in the PK/PD analysis population for safety, and 55 patients were included in the PK/PD analysis population for efficacy. The patient characteristics for the PK/PD analysis populations for safety and efficacy are shown in Table 1. The distribution of daptomycin susceptibility for *S. aureus* stratified by methicillin-resistant and methicillin-susceptible isolates is shown in Table 2. All isolates were found to be susceptible to daptomycin according to the CLSI criterion (1 μg/mL).

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