Assessment of AUC-Based Therapeutic Drug Management Algorithms for Plazomicin Therapy in Patients with Bloodstream Infection

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INTRODUCTION

- Variability of antibiotic pharmacokinetics (PK) in certain patient populations, including the critically ill, may lead to subtherapeutic or elevated drug exposures. Therapeutic drug management (TDM) allows for individualized drug dosing in patients at high risk of PK variability [1,2].
- TDM is recommended to optimize exposures and clinical outcomes in certain patients treated with aminoglycosides (AG) [3,4]. Plazomicin is an AG that was engineered to overcome aminoglycoside-modifying enzymes, the most common aminoglycoside-resistance mechanism in Enterobacteriaceae.
- An area under the concentration-time curve (AUC)-based approach for TDM was used in the CARE clinical trial evaluating plazomicin therapy for patients with serious infections due to carbapenem-resistant Enterobacteriaceae to help achieve plazomicin $AUC_{0–24}$ exposures within a target range.
- The objectives of these analyses were to evaluate the performance of the AUC-based TDM algorithms used in the CARE clinical trial among the subset of patients with bloodstream infections (BSI) and to assess the performance of this TDM approach in simulated patients with BSI.

METHODS

- The performance of the TDM algorithms that were employed in the CARE clinical trial was evaluated using individual fitted plazomicin exposures for enrolled patients based on the actual dosage regimens administered and observed treatment duration.
- Using the subset of patients with BSI from the CARE clinical trial, a population of simulated patients was generated by replicating the demographics for each patient a sufficient number of times in order to generate a population of at least 3,000 simulated patients.
- A plazomicin population PK model [5] and a plazomicin exposure-response model that characterized creatinine clearance (CLcr) changes during therapy were utilized to simulate plazomicin concentration-time profiles for each simulated patient receiving 14 days of therapy.
- Initial plazomicin dosing regimens were based on baseline renal function (**Table 1**) and subsequent doses were either maintained at the starting dose (without TDM) or periodically adjusted consistent with the dosage adjustments used by patients in the CARE trial (with TDM).

Table 1. Initial plazomicin dosage regimens based on renal function

Renal Function[a]	Plazomicin Dosage Regimen[b]
CLcr ≥60 mL/min	15 mg/kg q24h
CLcr 30 to <60 mL/min	10 mg/kg q24h
CLcr 15 to <30 mL/min	10 mg/kg q48h

a. Determined using the Cockcroft and Gault equation.
b. Adjusted body weight (ABW) was used in place of total body weight (TBW) if TBW was ≥ 25% higher than ideal body weight (IBW). ABW was calculated as follows: ABW (kg) = IBW + 0.4 • (TBW - IBW).

Table 2. Plazomicin AUC-based TDM algorithm, including TDM sampling time points and equations for estimated AUC_{0-24} and adjusted plazomicin dose

AUC-Based TDM Algorithm			
Adjusted Dose (mg/kg) = Current Dose (mg/kg) × 262/Estimated AUC_{0-24h}[b,c]			
Dosage regimen	TDM Sampling Timepoints C1	TDM Sampling Timepoints C2	Equation for Estimated AUC_{0-24} (mg•h/mL)
q12h[a]	2 ± 1 hours	8 ± 2 hours	[(3.7 × C1) + (10 × C2) - 3.5] × 2
q24h	2 ± 1 hours	10 ± 2 hours	[(3.3 × C1) + (20 × C2) - 11]
q48h	2 ± 1 hours	18 ± 2 hours	[(1.7 × C1) + (50 × C2) - 21] × 0.5

a. Every 12 hour dosage regimen interval may result from a dosage adjustment based on TDM.
b. If the adjusted dose is >15 mg/kg, divide into two equal doses and shorten the dosage interval by half (e.g., an adjusted dose of 20 mg/kg every 24 hours should be administered as 10 mg/kg every 12 hours).
c. If the adjusted dose is <7.5 mg/kg, double the dose and the dosage interval (e.g., an adjusted dose of 5 mg/kg every 24 hours should be administered as 10 mg/kg every 48 hours).

METHODS

- The AUC-based TDM algorithm involved sampling on Day 1, Day 4 (± 1 day), and Day 8 (± 1 day). Two TDM samples were obtained, based on the patient's dosing schedule (**Table 2**).
- The estimated AUC_{0-24} was determined by inputting the TDM sample concentrations into the corresponding equation based on the simulated dosing schedule (**Table 2**).
- If the estimated AUC_{0-24} was not within the target AUC range of 210-315 mg•h/mL (±20% of AUC_{0-24} target of 262 mg•h/mL), an adjusted dose equation was utilized to calculate the new dose (**Table 2**). The adjusted dose was implemented 48 hours after the dose on which the TDM samples were based.
- Summary statistics for average AUC_{0-24} over 48 hours by study day with and without TDM and the percentage of AUC_{0-24} values below, within, and above the recommended target AUC range were compared for simulated patients.

RESULTS

- Evaluations of the performance of the TDM algorithms in the subset of patients with BSI in the CARE trial (n=23) demonstrated a higher percentage of post-dose total-drug plasma AUC_{0-24} values within the specified AUC_{0-24} range after the administration of increasing numbers of TDM-adjusted plazomicin doses.
  - The percentage of plazomicin doses with total-drug plasma AUC_{0-24} values that were ≥ 210 to ≤ 315 mg•h/L for doses 1, 3 to 5, 6 to 9, and > 9 was 30.4, 50.7, 59.3, and 57.8%, respectively.
- Comparisons of AUC_{0-24} metrics for simulated patients with BSI who did and did not undergo TDM are provided in **Table 3**. Distributions of AUC_{0-24} are shown in **Figure 1**.
  - Following initial dosing based on renal function, 47.3% of simulated patients had exposures within the targeted AUC range, with 31.9% of simulated patients having exposures above the target range.
  - With AUC-based TDM, the variability in average total-drug plasma AUC_{0-24} was notably reduced from a percent coefficient of variation (%CV) of 31.7 after initial dosing to 17.3% after doses administered on Days 9 to 11. Without AUC-based TDM for subsequent doses, the variability increased from a %CV of 31.7% to 47.5% after doses administered on Days 9 to 11.
  - With the use of TDM, the percentage of simulated patients who had AUC_{0-24} values within the target range increased to 79.9% ; <12% of simulated patients had exposures above the target AUC range on Days 9 to 11.
  - Without the use TDM for subsequent doses, the percentage of simulated patients with AUC_{0-24} values in and above the target range decreased to 36.8% and increased to 47.2%, respectively, on Days 9 to 11.

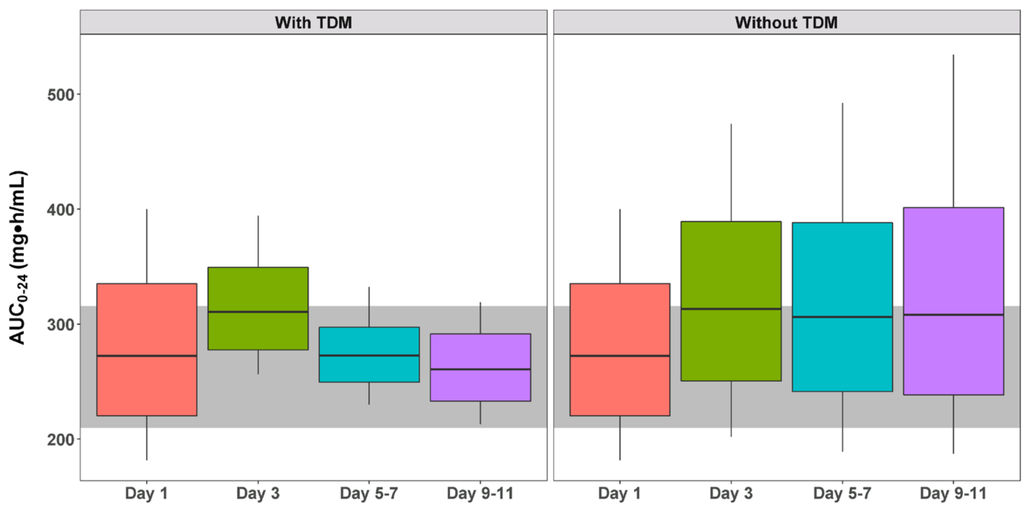
RESULTS

Table 3. Percentage of simulated patients with BSI below, within or above the targeted AUC range[a] with estimated median (%CV) plazomicin AUC_{0-24} values by study day

AUC_{0-24} Metric	Study Day: Day 1	Day 3	Day 5 to 7	Day 9 to 11
With TDM[b]				
Percentage below range	20.8	0	4.0	8.6
Percentage within range	47.3	53.1	80.9	79.7
Percentage above range	31.9	46.9	15.1	11.7
Median $AUC_{0–24}$ [%CV] (5^{th}, 95^{th} percentile)	272 [31.7] (161, 450)	311 [18.1] (246, 424)	272 [15.3] (216, 357)	261 [17.3] (203, 344)
Without TDM[c]				
Percentage below range	20.8	12.0	15.7	16.0
Percentage within range	47.3	38.7	37.3	36.8
Percentage above range	31.9	49.3	47.0	47.2
Median $AUC_{0–24}$ [%CV] (5^{th}, 95^{th} percentile)	272 [31.7] (161, 450)	313 [34.2] (178, 541)	306 [38.7] (166, 560)	308 [47.5] (160, 646)

$AUC_{0–24}$: Average total –drug plasma $AUC_{0–24}$ (mg•h/mL) over 48 hours; TDM: therapeutic drug management; %CV: percent coefficient of variation.
a. Assessed using a target AUC_{0-24} range of 210-315 mg•h/mL
b. With TDM results shown by Study Day correspond to exposures after dosing based on baseline renal function (Day 1; **Table 1**) and exposures based on doses administered after the first (Day 3), second (Day 5 to 7), and third (Day 9 to 11) AUC-based TDM dosage adjustments, respectively (**Table 2**).
c. Without TDM results shown by Study Day correspond to exposures after dosing based on baseline renal function alone (**Table 1**).

Figure 1. Box-and-whisker plots of $AUC_{0–24}$ by study day among simulated patients with BSI, with and without TDM



$AUC_{0–24}$: Average total-drug plasma $AUC_{0–24}$ over 48 hours. Box-and-whisker plots display the summary statistics for $AUC_{0–24}$ over the course of plazomicin treatment in simulated patients who received initial plazomicin dosing regimens based on baseline renal function (**Table 1**) and subsequent doses that were either periodically adjusted (with TDM; left panel) or maintained at the starting dose (without TDM; right panel). Grey band represents target AUC range (210-315 mg•h/mL). Box-and-whisker plot definition: The horizontal line represents the median, the box shows the 25th-75th percentiles, and whiskers extend to the 5^{th} and 95^{th} percentiles.

CONCLUSIONS

- Simulations with AUC-based TDM resulted in exposures that were consistent with those observed when TDM was implemented in patients with BSI in the CARE trial.
- Relative to dosing based on baseline renal function alone, results of assessments based on data from simulated patients with BSI demonstrated the benefit of using an iterative AUC-based TDM approach that consisted of two-sampling time points and dose adjustment equations.
  - The AUC-based TDM approach results in decreased variability in exposures and an increased percentage of $AUC_{0–24}$ values within the targeted range of 210 to 315 mg•h/mL.
- Results of simulations suggest that AUC-based TDM may prevent sustained high plasma exposures of plazomicin.

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