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Pharmacodynamic (PD) Profiling of Daptomycin (DAP) Against Methicillin Resistant *Staphylococcus Aureus* for the Treatment of Serious Infections in USA Medical Centers

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ABSTRACT

Background: Empiric dosing of Daptomycin (DAP) to achieve a Cumulative Fraction of Response (CFR) of > 90% based on the MIC distribution of US MRSA isolates at various levels of renal function has not been examined. Consequently, the optimal empiric dosing regimen for DAP in serious infections remains unclear.
Methods: Previously published pharmacokinetic data (AAC, 2004 Aug., n=282) and MIC data of 4513 MRSA isolates for DAP (IDSA 2010, Poster #246) were used in this analysis. Doses up to 12 mg/kg were evaluated for Probability of Target Attainment (PTA) with Monte Carlo Simulation (MCS, n=5000) for different levels of renal function at the MIC ranges of 0.125 to 2 mg/L. CFR was calculated for each regimen targeting an AUC/MIC necessary to achieve a killing of 2 $\log_{10}$ CFU. The minimum amount of drug and the respective dosing interval necessary to produce a CFR > 90% was then evaluated for safety using MCS and a two compartment model with constant intravenous input and first order output.
Results: DAP regimens expected to achieve the CFR > 90% at the renal function of 20, 40, 60, 80, 100, 120 ml/min are 10mg/kg q48h, 5mg/kg q24h, 6mg/kg q24h, 7mg/kg q24h, 8mg/kg q24h and 9mg/kg q24h, respectively. The MCS also showed that - based on the CFRs achieved by the manufacturer recommended dose and dosing intervals - it is likely that empiric dosing will result in sub-optimal PTAs for patients with creatinine clearance outside of the range of 30 – 60 ml/min.
Conclusion: We conclude that for the treatment of serious MRSA infections to achieve the killing of 2 $\log_{10}$ CFU, the revised dosing method would provide better empiric population PTA compared to manufacturer recommendations.

INTRODUCTION

DAP has been shown to exhibit concentration dependent killing in vitro[1] and in vivo[2,3,4] against MRSA. In vivo experiments[2,3,4] have shown that the AUC_{24h}/MIC was most closely related to the antimicrobial effect. While the optimal value of the PK and PD Index is yet to be established for DAP for infections caused by MRSA, previously published in vivo models[2,3,4] have yielded conflicting results. In single[2] and multi-strain[3,4] experiments, the magnitude of the ratio of AUC_{24h}/MIC needed to achieve similar results in killing effect seems to differ based on the size of pretreatment titer conditions. This phenomenon could be explained by the inoculum effect, which in the case of DAP is likely due to a density dependent decline in the effective concentration of DAP in the medium[5]. The aim of our work was to use MCS to integrate PK and PD with microbiology data to yield population PTA of DAP at different levels of renal function against the MIC distribution of recently reported MRSA isolates. Next, we established empiric dosing recommendations that would provide a CFR > 90% across renal function categories from 20 to 120 ml/min for infections where one would expect the presence of high inoculums. Last, since the chance of CPK elevation seems to be higher with Cp_{min} values $\geq$ 24.3 µg/ml[6], we compared the percentages of patients likely to achieve a Cp_{min} $\geq$ 24.3 µg/ml to assess for the safety of the proposed dosing regimens.

METHODS

Population Pharmacokinetic Model[7]

- Estimation of model parameters

  - CL_R = 0.807 + 0.00514 * (CrCl – 91.2)
  - CL_{DAP} = [CL_R + 0.14 * (TEMP – 37.2)] * y *(CV = 30.6 %)*
  - Q = 3.46 + 0.0593 * (WEIGHT – 75.1) *(CV = 65.2 %)*
  - V_P = [3.13 + 0.0458 * (WEIGHT – 75.1)] * 1.93 *(CV = 19.1 %)*
  - V_C = 4.8 L *(CV = 56.7 %)*

where CL_R (l/h) is DAP clearance as a function of the renal function only, ClCr (ml/min) is creatinine clearance, CL_{DAP} (l/h) is DAP clearance, TEMP (C^o) is body temperature, y is a constant based on sex, Q (l/h) is the intercompartmental clearance, V_P (l) is the volume of the peripheral compartment, V_C (l) is the volume of the central compartment presented here as the median population value *(CV is the coefficient of variation in percentages)*.

METHODS

Monte Carlo Simulation

- 5000 trial Monte Carlo Simulation (Crystal Ball Fusion Edition,v.11.1.2.1.000; Oracle Corp. Redwood Shores, CA, USA)
  - Total body CL_{DAP} estimates for each simulated patients were based on using the explanatory variables of CrCl , sex and body temperature
  - Volume of the peripheral compartment and the intercompartmental clearance were estimated as a function of the total body weight and the presence of bacterial infection
  - CrCl was fixed at 20 ml/min intervals between the ranges of 20 to 120 ml/min, temperature was assumed to follow triangular distribution, the probability of male and female sex was set to appear in equal proportions in the simulated population, while all pharmacokinetic parameter estimates were assumed to follow lognormal distribution. Patients weight was obtained from published data[8] and was simulated with Weibull distribution. Protein binding was set at 90% to simulate free drug concentrations, while infusion time was set at 30 minutes
  - A two compartment model with constant intravenous input and first order output was used to estimate concentration – time profiles for each simulated patient at 1 h increments until steady state was reached. The trapezoidal rule was used to calculate AUC, then the AUC was divided by the MIC to obtain the value for the desired PK/PD Index of the selected time interval
- Pharmacodynamic Target
  - PK/PD Index of the free or total drug AUC_T/MIC ratio necessary to achieve stasis, 1 $\log_{10}$ kill and 2 $\log_{10}$ kill was utilized at "Low"[4] (LI) and "High"[3] (HI) pretreatment titer conditions as the goal of evaluation
- Safety analysis
  - Percent of patients expected to have their Cp_{min} value equal to or exceeding 24.3 µg/ml at steady state with the proposed new doses and dosing intervals compare to that of the currently recommended 6 mg/kg every 24 hours for patients with a CrCl of 60 ml/min
- Population Probability of Target Attainment
  - Cumulative Fraction of Response was calculated for select regimen evaluated by multiplying the Probability of Target Attainment at the given MIC with the percentage of isolates found at that MIC, then the sum of this data yielded the CFR for the simulated regimen

Organism	Percent Occurrence at DAP MIC (µg/ml) of:					
MRSA	≤ 0.06	0.12	0.25	0.5	1	2
	< 0.1	2.3	70.3	26.4	0.9	< 0.1

Table 1. DAP MIC Distribution of US MRSA Isolates (2007-2008)[9]

RESULTS

	Renal Function Category Based on CrCl (ml/min)					
	20*	40	60	80	100	120
AUC_{0-T} (mg/l*hr)	1052.2 (483.8, 2225.1)	867.7 (408.9, 1776.6)	736.3 (352.7, 1499.1)	639.1 (309, 1301.8)	564.4 (273.7, 1148.2)	505.3 (245.2, 1024.1)

Table 2. Summary statistics of simulated DAP AUC_{0-T} for manufacturer recommended 6 mg/kg doses every 24 h [data presented as median (5th percentile, 95th percentile),*48 h dosing interval]

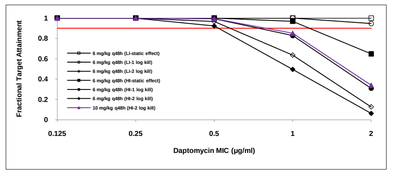


Figure 1 A. DAP PTA at CrCl of 20 ml/min

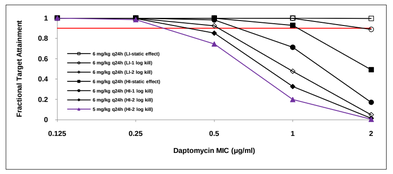


Figure 1 B. DAP PTA at CrCl of 40 ml/min

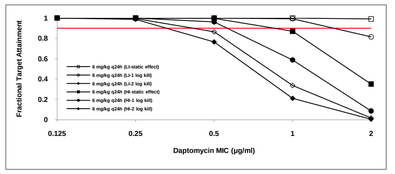


Figure 1 C. DAP PTA at CrCl of 60 ml/min

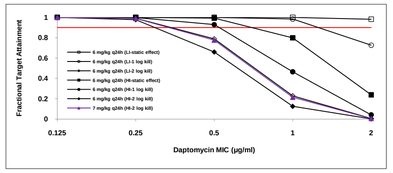


Figure 1 D. DAP PTA at CrCl of 80 ml/min

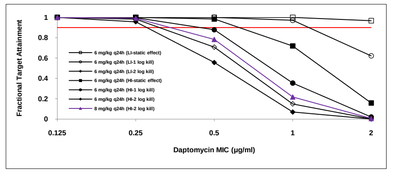


Figure 1 E. DAP PTA at CrCl of 100 ml/min

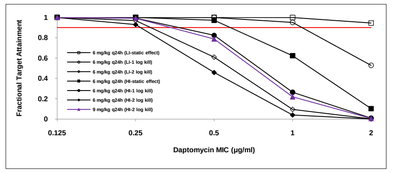


Figure 1 F. DAP PTA at CrCl of 120 ml/min

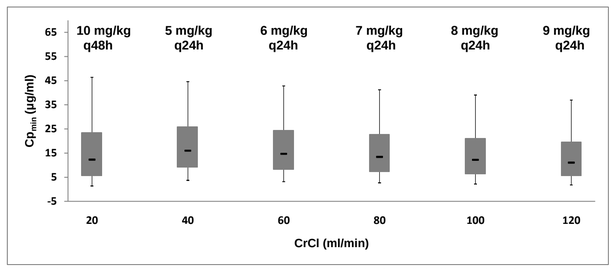
	Renal Function by Category					
CrCl (ml/min)	20	40	60	80	100	120
Dose and Dosing Interval	10 mg/kg q48h	5 mg/kg q24h	6 mg/kg q24h	7 mg/kg q24h	8 mg/kg q24h	9 mg/kg q24h
% Cp_{min} ≥ 24.3 µg/ml	23.3	27.7	24.5	21.3	18.6	15.9

Table 3. Percentage of simulated DAP Cp_{min} greater than or equal to 24.3 µg/ml for selected dosing regimens

RESULTS

CrCl (ml/min)	Dose	Dosing Interval	CFR (%) for Regimen Evaluated	
20	6 mg/kg	every 48 hours	AUC_{48h}/MIC 94.2	AUC_{48h}/MIC 45.7
	10 mg/kg		AUC_{48h}/MIC 99.2	AUC_{48h}/MIC 67.7
40	6 mg/kg	every 24 hours	94.9	
	5 mg/kg		91.3	
60	6 mg/kg	every 24 hours	92	
80	6 mg/kg	every 24 hours	88.5	
	7 mg/kg		92.4	
100	6 mg/kg	every 24 hours	84.2	
	8 mg/kg		92.8	
120	6 mg/kg	every 24 hours	79.7	
	9 mg/kg		92.9	

Table 4. CFR for select DAP regimens and PI doses to achieve a total AUC_{24h}/MIC of 1061 or more



The edges of the grey boxes extend from the 25th through the 75th percentiles, the intersecting line in black is the 50th percentile, the whiskers extend to the 5th and 95th percentiles.

Figure 2. Summary statistics of simulated DAP Cp_{min} (µg/ml) across renal function categories

CONCLUSION

- For patients with CrCl of 30 to 60 ml/min to achieve the target total drug AUC_{24h}/MIC ratio of 1061, DAP PI recommended doses and dosing intervals should provide optimal population probability of target attainment empirically against recently documented MRSA isolates in US medical centers. For renal function categories outside of this range, higher doses at similar to PI recommended dosing intervals should be considered.
- The new dosing regimens proposed here should result in the percentage of patients having their Cp_{min} value $\geq$ 24.3 µg/ml similar to or less than that of the currently recommended 6 mg/kg every 24 hours for patients with a CrCl of 60 ml/min
- Although our simulation data would suggest the use of higher daily DAP doses at similar dosing intervals to achieve the total drug AUC_{24h}/MIC of at least 1061, the safety and efficacy of these regimens for the treatment of MRSA infections must be validated by clinical trials

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