ABSTRACT/REVISED

Methods: Population pharmacokinetic (popPK) models of DAP in HD patients and patients with bacteremia were used in this analysis. Daily doses of 3 and 4 mg/kg given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis were evaluated with Monte Carlo Simulation (MCS, n=10000) to assess the magnitude of drug exposure with daily 2, 3, 4, and 5 hours HD sessions. To select the optimal regimen based on the duration of dialysis provided, the simulated mean ± SD trough levels at 72 hours and AUC_{DAP} were simulated with the suggested mean ± SD trough levels at 72 hours and AUC_{DAP} for the dose of 6 mg/kg every 24 hours using the popPK model developed in the bacteremia trial.

Results: Manufacturer recommended 6 mg/kg DAP regimens should result in mean ± SD trough levels and AUC_{DAP} values of 9.5 ± 8.1 μg/mL and 441.1 ± 275 mgL/h, respectively. Comparing these mean ± SD values to be achieved by the suggested daily dialysis regimens, percentage differences of 38% to 64% and 5% to 14% in magnitude were noted, for trough levels and AUC_{DAP}, values, respectively. Summary of optimized dosing recommendations are presented in Table 1.

Conclusion: We conclude that the DAP dosing strategies presented here would provide adequate coverage from the efficacy standpoint in daily HD, as compared to the exposure achieved by the patients of bacteremia trial. Our analysis also showed a definite increase in the magnitude of the expected trough levels using these methods of dosing DAP, which may lead to an increase in the probability of drug related adverse events. Clinicians should carefully weigh benefits and harms of all treatment related effects when managing their patients with the above suggested dosing regimens.

RESULTS

CONCLUSION

Model based optimization of Daptomycin dosing during high – intensity renal replacement therapy

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Introduction

RRT has dramatically evolved during the past couple of decades and is often individualized to patient specific clinical status and tolerance. As the patient’s condition changes, the strategy for RRT should be frequently altered to meet the current clinical needs and to maintain efficacy. Technical aspects of IHD, including the length of dialysis, may have significant effects on the extent by which a drug is removed during dialysis. Drugs that are known to be removed by IHD to a meaningful degree may result in inadequate drug levels in the plasma as a consequence of the changes in dialysis length or intensity, and provide inadequate systemic drug exposure. DAP clearance during IHD using high – flux membranes has been shown to be similar, while during the off – dialysis period is reduced by about 75%, as compared to the clearance by the patients in the bacteremia and infective endocarditis trial. It was suggested for clinicians to consider the dose of 9 mg/kg instead of 6 mg/kg when the interval length is about 72 hours to ensure drug exposures comparable to the 48 hours intermittent periods. Other investigations have investigated the relationship between daptomycin exposure and the probabilities of CPK elevations. Based on their findings, C_{ss} at the beginning of 24.3 mgL was most significantly associated with clinically important CPK elevations. The aim of our work was to use Monte Carlo simulation to evaluate the magnitude of daptomycin exposure and resulting trough levels when select doses are given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis. Then, we compared the exposures and trough levels with that of the model from the bacteremia and endocarditis trial to select the dosing method that may be considered most appropriate for daily administration.

Methods

Monte Carlo Simulation

- Monte Carlo Simulation with Pmetrics (V.0.25), without covariance matrices and 2 compartment IV pharmacokinetic models characterized by 4

| Parameter | Monte Carlo Simulation (MCS, n=10000) |
|-----------|---------------------------------|--------|
| V_{1} (L) | 5.52 (1.90) | 6.56 (3.10) |
| K_{p} (L/h) | 0.24 (0.06) | 0.98 (0.47) |
| K_{u} (h^-1) | 1.61 (1.91) | 1.67 (3.94) |
| K_{D} (h^-1) | 1.17 (1.13) | 1.34 (3.40) |
| C_{ss} (LH) | 1.30 (0.63) | NA |

V_{1}, volume of the central compartment; Cl_{n}, nonrenal clearance of DAP from the central compartment; K_{u}, transfer rate constant from the central to the peripheral compartment; K_{D}, transfer rate constant from the peripheral to the central compartment; C_{ss}, hemodialysis clearance of DAP from the central compartment

Patient weights for simulation was obtained from anthropometric reference data for children and adults in the United States and was simulated with a discrete distribution. Daily doses of 3 and 4 mg/kg given 1 hour prior, 1 hour into, and 1 hour before the end of dialysis were evaluated for exposure, then compared with the exposure likely to be achieved by patients with similar body weights using the population pharmacokinetic model developed in the bacteremia and infective endocarditis trial. The simulated mean ± SD trough levels and AUC_{DAP} served as the bases of comparison for the two populations.

Results

- Daptomycin concentrations were simulated for 48h, 72h, and 96h after starting the infusion as shown in Figure 1.

Figure 1. A–C Histograms of simulated AUC_{DAP} for B – E model and 2 hours daily intermittent hemodialysis sessions

Figure 2. A–C Histograms of simulated AUC_{DAP} for B – E model and 3 hours daily intermittent hemodialysis sessions

Figure 3. A–C Histograms of simulated AUC_{DAP} for B – E model and 4 hours daily intermittent hemodialysis sessions

Figure 4. A–C Histograms of simulated AUC_{DAP} for B – E model and 5 hours daily intermittent hemodialysis sessions

Figure 5. A–D Box plots of simulated Trough levels at 72 hours

- Conclusions:
  - Dosing of DAP for the treatment of serious infections in daily intermittent hemodialysis greatly depends on the length of dialysis treatment and the timing of drug administration. For dialysis sessions lasting from 2 to 5 hours daily, 3 and 4 mg/kg doses would be sufficient to ensure likely adequate mean ± SD AUC_{DAP} values. The best practice strategies for administration times are to give the dose 1 hour after the start of or 1 hour before the end of the dialysis session.
  - As a result of decreased DAP clearance while off dialysis, practitioners should be aware of the increased chance for drug accumulation when DAP is given according to these dosing methods. After 72 hours of therapy, the mean value for trough concentrations may reach levels of up to 64% higher, as compared to patients with normal renal function.

References

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