Simplifying Piperacillin/Tazobactam Dosing: Pharmacodynamics of Utilizing 4.5g Doses for Patients with Normal and Impaired Renal Function

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ABSTRACT

Objectives: To evaluate the pharmacodynamic exposure of piperacillin/tazobactam across the renal function range using only 4.5g- or 3.375g-based dosing strategies.

Methods: A 5,000-patient Monte Carlo simulation was conducted to determine the probability of achieving 55% free drug time above the minimum inhibitory concentration (fMIC) for piperacillin. Regimens, all using solely 4.5g or 3.375g TAZ therapy, were compared with standard regimens listed in piperacillin/tazobactam prescribing information or CCI regional guidelines.

Results: At CCl<100 mL/min, prolonged infusions of 4.5g and 3.375g TAZ were comparable to 100% (99.7%) of 2.25g and 1.5g standard regimens, respectively. 4.5g, 3.375g q12h and 4.5g q8h regimens were simulated based on observed mean CrCl (Phoenix simulated pharmacokinetic model) and confirmed with available literature.

Conclusions: Piperacillin/tazobactam regimens designed around the C45-63q3.5 dose range combined with prolonged infusions provided similar or better pharmacodynamics compared with standard regimens. These observations may support the stocking and use of a single piperacillin/tazobactam strength to simplify dosing.

INTRODUCTION

Piperacillin-tazobactam (TAZ), a β-lactam-β-lactamase antibiotic possessing broad spectrum activity against many aerobic and anaerobic Gram-positive and Gram-negative organisms, including Pseudomonas aeruginosa and Enterobacteriaceae, is one of the most frequently prescribed intravenous antibiotics in the hospital setting.[1]

Commercially, TAZ is available in dosing strengths of 250 mg, 500 mg, 1 g, 2 g, and 4 g as a single energy source, and a single dose of 3.375 g or 4.5 g can be used for single-shot hemodialysis (HD) (post HD) (pre HD) and 4.5 g q12h (3h) in patients with normal renal function.[2]

Sterile preparations of intravenous medications are available in doses of 250 mg, 500 mg, 1 g, 2 g, and 4 g in both vials and 10 mL syringes. In one study, a lower creatinine clearance rate of 30 mL/min was observed to be the time of dose administration.[3]

The pharmacodynamics (PD) of TAZ is governed by the percentage of the dosing interval in which free concentrations of the piperacillin component remain above the minimal inhibitory concentration of the organism (MIC-90%) with activity threshold of approximately 50% of the MIC of each species.[4]

We hypothesize that a single vial strength of TAZ can be used to design dosing regimens across the CCR range for potential patients.

MATERIALS & METHODS

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RESULTS

Pharmacokinetics

For the non-hemolysis population, the Monte Carlo simulation resulted in PK parameter estimates similar to those reported by Fallon, et al. [5].

For the hemolysis population, a 2-compartment model provided the best fit for the mean concentration observed in the original study (6). The model was simulated with a CCl<100 mL/min, a CrCl 0.5-1.7 mL/min, and t1/2 = 1.13 h.

Monte Carlo Simulation

PTA pharmacokinetic parameters, as defined by CCI range, are presented in Table 1. Table 2. Probability of target attainment (50% fMIC) of standard and proposed piperacillin/tazobactam regimens across the CCI range.

Table 1. Probability of target attainment (50% fMIC) of standard and proposed piperacillin/tazobactam regimens across the CCI range.

Table 2. Area under the free drug concentration curve for 24-hour steady state and standard and proposed dosing regimens across the CCI range.

REFERENCES