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

Abrar K Thabit[1,2], Mordechai Grupper[1], David P Nicolau[1,3], Joseph L. Kuti[1]
[1]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA; [2] Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia;
[3] Division of Infectious Diseases, Hartford Hospital, Hartford, CT, USA

Joseph L. Kuti, PharmD
Center for Anti-Infective Research and Development
Hartford Hospital
80 Seymour Street
Hartford, CT 06102
Tel: 860-972-3612
Fax: 860-545-3992
Email: joseph.kuti@hhchealth.org

ABSTRACT (revised)

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

Methods: A 5,000-patient Monte Carlo simulation was conducted to determine the probability of achieving 50% free time above the minimum inhibitory concentration (*f*T>MIC) for piperacillin. Proposed regimens, all using solely 4.5g or 3.375g strengths, were compared with standard regimens listed in piperacillin/tazobactam prescribing information over CrCl ranges of 120 mL/min to hemodialysis. The probability of target attainment (PTA) at MICs≤16µg/mL was compared between study and standard regimens.

Results: At CrCl=41-120 mL/min, prolonged infusions of 4.5g and 3.375g q6h resulted in ≥95% PTA versus ≥76% for standard regimens. At CrCl=20-40 mL/min, 4.5g and 3.375g q8h as prolonged infusions achieved slightly higher PTA (≥98%) compared with standard regimens (≥93%). Similarly, PTA achieved with prolonged infusions of 4.5g and 3.375g q12h (≥93%) were comparable with those of standard regimens (≥91%) at CrCl=1-19 mL/min. In hemodialysis, 100% PTA was achieved with prolonged infusion regimens.

Conclusions: Piperacillin/tazobactam regimens designed around the 4.5g or 3.375g dose combined with prolonged infusions provided similar or better PTA at MICs≤16µg/mL compared with standard regimens. These observations may support the stocking and use of a single piperacillin/tazobactam strength to simplify dosing.

INTRODUCTION

- Piperacillin/tazobactam (TZP), 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, TZP is available in vials of different strengths including 4.5, 3.375, and 2.5 g, as well as in bulk vials (1). All of these vials must be stocked to meet the needs of current dosing regimens based on a patient's creatinine clearance (CrCL).
- Sterile preparations of intravenous medications that are available in vials of different strengths or in bulk vials were prone to errors, and an incorrect infusion rate was the most frequent serious error encountered at the time of dose administration (2-4).
- The pharmacodynamics (PD) of TZP is governed by the percentage of the dosing interval in which free concentrations of the piperacillin component remain above the minimum inhibitory concentration of the organism (%*f*T>MIC) with activity threshold of approximately 50% *f*T>MIC against most Gram-negative pathogens.
- We hypothesize that a single vial strength of TZP can be used to design dosing regimens spanning the CrCL range for potential patients.

OBJECTIVES

- To determine the probability of achieving 50% *f*T>MIC for the piperacillin component of TZP against a wide range of MICs using prolonged infusion of 4.5 or 3.375 g dosing regimens across a wide CrCL range
- To compare the probability of target attainment (PTA) and area under the curve (AUC) achieved by proposed regimens with standard regimens.

MATERIALS & METHODS

Piperacillin Pharmacokinetics

- Pharmacokinetic (PK) parameter estimates from a previously published two-compartment population PK model were used to predict the exposure of the piperacillin component of TZP resulting from dosing regimens proposed in the current study (5).
- This study included patients with a wide CrCl range of 14 to 257 mL/min (5), thereby allowing simulation of dosing regimens across the CrCl ranges listed in the TZP prescribing information (1).
- The PK of a single dose of piperacillin (as a component of TZP) in 5 hemodialysis (HD) patients was extrapolated from a previous study (6). Since this paper only reported a non-compartmental description of piperacillin PK, the mean concentrations were fit to one and two compartment models (Phoenix; version 6.3, Pharsight Corporation, Mountain View, CA) to determine final parameter estimates. Final model selection was discriminated based on visual inspection of the generated graphs of observed vs. predicted concentrations and the Akaike Information Criterion (AIC).

Dosing Regimens Simulated

- TZP regimens were simulated based on CrCl ranges reported in the prescribing information (1).
- Regimens simulated include standard regimens listed in TZP prescribing information, as well as proposed regimens given as prolonged infusion. Simulated regimens are presented in Table 1.

Monte Carlo Simulation

- A 5,000-patient Monte Carlo simulation was conducted using Crystal Ball (Oracle Corp., Redwood City, CA) to recreate free drug concentration-time profiles for the above regimens based on a 2-compartment model with zero-order input and first order elimination.
- Piperacillin clearance (CL), volume of the central compartment (V_1), and intercompartment transfer constants (k_{12} and k_{21}) were assumed to follow log-Gaussian distributions.
- CrCl was simulated as a uniform distribution with equal likelihood of values in between the simulated ranges.
- Body weight was simulated as a Gaussian distribution that recapitulated the body weight in the original PK study (5).
- Regimens were simulated at steady-state, no earlier than after 4 doses for each regimen, except with q24h regimens, where a steady-state was determined after at least 2 doses.
- For the HD simulation, all PK parameter estimates were considered as log-normal distributions with a 15% CV in line with the variability documented during the study in HD patients (6).
- All HD regimens were simulated for 72h where doses were administered after HD with incorporation in the simulation the assumption that the HD filter removed 30% of unbound piperacillin during each dialysis cycle (6).
- Piperacillin protein binding was fixed at 30% (1).
- PTA was calculated using 50% *f*T>MIC as the PD exposure target over a wide range of TZP MICs (0.008-256 µg/mL) with focus on MIC of 16 µg/mL (susceptibility breakpoint of Enterobacteriaceae and *P. aeruginosa*) (7).
- An *a priori* PTA threshold of ≥ 90% was defined as optimal for the purpose of inference.
- In order to confirm comparable exposures, the area under free drug concentration-time curve over 24h at steady state ($fAUC_{0\text{-}24}$) was calculated for each patient. Also, the mean ± SD, 10th, and 90th percentiles for all 5,000 simulated patients were calculated and compared between the proposed and the standard dosing regimen at each CrCl range.

RESULTS

Piperacillin Pharmacokinetics

- For the non-hemodialysis population, the Monte Carlo simulation resulted in PK parameter estimates similar to those reported by Felton, et al (5).
- For the hemodialysis population, a 2-compartment model provided the best fit for the mean concentration data observed in the original study (6).
- The resulting PK parameter estimates were as follows: CL = 3.7 L/h, V1 = 7.4 L, k_{12} = 0.8 h^{-1}, and k_{21} = 1.3 h^{-1}.

Monte Carlo Simulation

- PTA results for all regimens, as defined by CrCl range, are presented in Table 1.
- Estimated *f*AUC values resulting from simulated regimens are presented in Table 2.

Table 1. Probability of target attainment (50% *f*T>MIC) of standard and proposed piperacillin/tazobactam dosing regimens against different MICs

Simulated CrCl Range (mL/min)	Dosing Regimen (infusion duration)	Probability of Target Attainment (%) at each MIC (µg/mL)									
		≤ 0.5	1	2	4	8	16	32	64	128	256
41 – 120	4.5g q6h (0.5h)[a]	100	100	100	99.2	95	76	38.1	9.5	1.5	0.1
	3.375g q6h (0.5h)[b]	100	100	99.6	97.3	89.7	61.3	23.8	5.0	0.5	0.1
	4.5g q6h (3h)[c]	100	100	100	100	100	99.3	67.2	18.4	2.7	0.2
	4.5g q8h (4h)[c]	100	100	100	100	100	93.4	43.9	8.6	1	0
	3.375g q6h (4h)[c]	100	100	100	100	100	95.2	46.6	9	1	0
	3.375g q8h (4h)	100	100	100	100	100	76.8	24.4	3.9	0.2	0
20-40	3.375g q6h (0.5h)[a]	100	100	100	100	99.8	98.1	82.2	25.8	2.7	0.2
	2.25g q6h (0.5h)[b]	100	100	100	100	99.4	93.1	50.1	7.2	0.6	0
	4.5g q8h (0.5h)	100	100	100	100	99.5	96.4	75.7	22	2.4	0.2
	4.5g q8h (3h)[c]	100	100	100	100	100	99.1	87.6	31.6	3.4	0.2
	3.375g q8h (4h)[c]	100	100	100	100	100	99.6	89.1	33.3	3.9	0.2
	3.375g q12h (4h)	100	100	100	100	98	82.3	27	3.2	0.2	0
1-19	2.25g q6h (0.5h)[a]	100	100	100	100	100	96.6	80.6	35.9	6.7	0.5
	2.25g q8h (0.5h)[b]	100	100	100	99.7	98.1	91.0	62.1	18.4	2.2	0
	4.5g q12h (0.5h)	100	100	99.7	99.3	97.1	91.6	71	29.8	5.6	0.4
	4.5g q12h (3h)[c]	100	100	100	100	99.1	95.8	78.3	35.8	6.9	0.4
	4.5g q24h (3h)	≥ 99	97.8	95.7	91.2	80.2	56.3	22.6	4.1	0.2	0
	3.375g q12h (4h)[c]	100	100	100	100	99	92.8	65.6	20	2.3	0
HD (on and post-dialysis)	2.25g q8h (0.5h)[a]	100	100	100	100	100	100	61.6	0.1	0	0
	2.25g q12h (0.5h)[b]	100	100	100	100	100	71.3	1.5	0	0	0
	4.5g q12h (0.5h)	100	100	100	100	100	99.7	71.3	1.5	0	0
	4.5g q12h (3h)[c]	100	100	100	100	100	100	97.7	11.5	0	0
	4.5g q24h (3h)	100	100	100	97.9	74.9	17.0	0.1	0	0	0
	3.375g q12h (4h)[c]	100	100	100	100	100	100	91.6	0.6	0	0

[a] Standard piperacillin/tazobactam dose for nosocomial pneumonia per prescribing information
[b] Standard piperacillin/tazobactam dose for indications other than nosocomial pneumonia per prescribing information
[c] Proposed piperacillin/tazobactam dose based on PTA and AUC analyses

Table 2. Area under the free drug concentration curve for 24h period at the steady state for standard and proposed piperacillin/tazobactam dosing regimens

Simulated CrCl Range (mL/min)	Dosing Regimen (infusion duration)	*f*AUC, mean ± SD (mg·h/L)	10th, 90th percentiles
41 - 120	4.5g q6h (0.5h)[a]	1121 ± 743	533, 1864
	3.375g q6h (0.5h)[b]	841 ± 557	400, 1398
	4.5g q6h (3h)[c]	1121 ± 743	533, 1864
	4.5g q8h (3h)[c]	854 ± 569	404, 1422
	3.375g q6h (4h)[c]	841 ± 557	400, 1398
	3.375g q8h (4h)	640 ± 427	303, 1067
20-40	3.375g q6h (0.5h)[a]	1434 ± 772	733, 2272
	2.25g q6h (0.5h)[b]	956 ± 515	489, 1514
	4.5g q8h (0.5h)	1425 ± 761	733, 2273
	4.5g q8h (3h)[c]	1474 ± 802	762, 2365
	3.375g q8h (4h)[c]	1096 ± 593	559, 1737
	3.375g q12h (4h)	717 ± 386	367, 1137
1-19	2.25g q6h (0.5h)[a]	1543 ± 975	629, 2730
	2.25g q8h (0.5h)[b]	1158 ± 734	471, 2043
	4.5g q12h (0.5h)	1548 ± 984	629, 2730
	4.5g q12h (3h)[c]	1567 ± 997	635, 2759
	4.5g q24h (3h)	787 ± 505	317.5, 1386
	3.375g q12h (4h)[c]	1160 ± 736	471, 2046
HD (post-dialysis)	2.25g q8h (0.5h)[a]	1152 ± 161	956, 1361
	2.25g q12h (0.5h)[b]	784 ± 113	646, 930
	4.5g q12h (0.5h)	1568 ± 226	1292, 1860
	4.5g q12h (3h)[c]	1591 ± 223	1288, 1849
	4.5g q24h (3h)	793 ± 118	651, 945
	3.375g q12h (4h)[c]	1167 ± 166	964, 1382

[a] Standard piperacillin/tazobactam dose for nosocomial pneumonia per prescribing information
[b] Standard piperacillin/tazobactam dose for indications other than nosocomial pneumonia per prescribing information
[c] Proposed piperacillin/tazobactam dose based on PTA and AUC analyses

CONCLUSIONS

- Prolonged infusion regimens of TZP designed around only a 4.5g or 3.375g dose provide similar or better PTA, particularly at MIC ≤ 16 µg/mL, compared with current standard dosage regimens, without significantly increasing daily *f*AUC exposure across the simulated renal dysfunction range.
- In the era of focusing antimicrobial stewardship efforts on effective and safe utilization of antibiotics, our study supports the use of a single strength of TZP to simplify regimens.
- Our 5 hospital health system moved to stocking of a single 4.5g vial strength of TZP based on these results. Our recommended dosing regimens include: CrCL > 40 ml/min: 4.5g q6h (3h infusion), CrCL 20-40 ml/min: 4.5g q8h (3h infusion), CrCL < 20 ml/min including hemodialysis: 4.5g q12h (3h infusion) with doses administered after hemodialysis.

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