Evaluation of Piperacillin/Tazobactam Regimens in Patients with SHIFT Renal Replacement Therapy

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Introduction

- No pharmacokinetic (PK) data exist to guide piperacillin/tazobactam dosing for critically ill patients receiving hybrid types of renal replacement therapy (RRT).
- Piperacillin/tazobactam dosing regimens prescribed for these patients vary, ranging from 2.25g q12h to 4.5g q6h, up to a four-fold difference in daily doses. [1]
- SHIFT RRT, a daily prolonged intermittent RRT, is employed to treat critically ill patients with acute kidney injury.
- Monte Carlo simulations can be used to predict the optimal piperacillin/tazobactam dosing regimens in critically ill patients receiving SHIFT RRT.

Objective

To evaluate the probability of target attainment of conventional piperacillin/tazobactam regimens and to determine initial optimal dosing recommendations in critically ill patients receiving SHIFT RRT.

Methods

Mathematical PK Model Development

- One compartment PK model with the first elimination order was structured to predict piperacillin and tazobactam disposition for 48 hours of initial therapy.
- Literature-derived demographic/PK data with their variability and four common SHIFT RRT regimens were incorporated into the models.

Methods

Table 1. Input Parameters Used in In-Silico PK Trials [2-9]

	Parameters	Hemofiltration (HF)		Hemodialysis (HD)	
SHIFT RRT	Qblood	300 ml/min	300 ml/min	300 ml/min	300 ml/min
	Qeffluent	5 L/h	4 L/h	5 L/h	4 L/h
	Duration	8 h	10 h	8 h	10 h
	Frequency	Daily	Daily	Daily	Daily
Piperacillin Mean±SD [Range]	Weight	86.6±29.2 kg [≥40 kg]			
	Volume of Distribution	0.40±0.21 L/kg [0-1.11 L/kg]			
	Unbound Fraction	0.76±0.20 [0-1]			
	Non-renal Clearance	48.5±37 mL/min [0-187 mL/min]			
	SC or SA	0.50±0.30 [0-1]		0.60±0.28 [0-1]	
Tazobactam Mean±SD [Range]	Weight	86.6±29.2 kg [≥40 kg]			
	Volume of Distribution	0.50±0.37 L/kg [0-2.13 L/kg]			
	Unbound Fraction	0.74±0.27 [0-1]			
	Non-renal Clearance	40.4±70 mL/min [0-381 mL/min]			
	SC or SA	0.76±0.26 [0-1]		0.80±0.36 [0-1]	

- Daily SHIFT RRT regimen was modelled to be instituted either at the beginning of (early SHIFT) or 14-16 hours after initial drug administration (late SHIFT) to ensure a broad range of clinical scenarios.
- Range limits and correlation on input parameters estimated from the data were included in the models to construct a realistic virtual population.

Monte Carlo Simulation (MCS)

- MCS was performed to generate free individual piperacillin and tazobactam concentration profiles in 5,000 virtual patients.
- Ten piperacillin regimens (2-4g q6-8h) and three tazobactam regimens (0.5g q6h) with intermittent (30-minute) or prolonged infusion (4-hour extended or 24-hr continuous) were simulated.

Prediction of Probability of Target Attainment (PTA)

- The PTA was evaluated by the fraction of virtual patients attaining >50% free piperacillin concentration above 4 times minimum inhibitory concentration (MIC) (50% *f*T ≥ 4xMIC) of *Pseudomonas aeruginosa* (16 µg/mL) *and* >50% free tazobactam concentration above the corresponding threshold concentrations (4 µg/mL) (50% *f*T ≥ Threshold) during the first 48 hours of therapy. [10,11]
- Optimal regimens were those that achieved PTA ≥ 90% using the smallest daily dose.

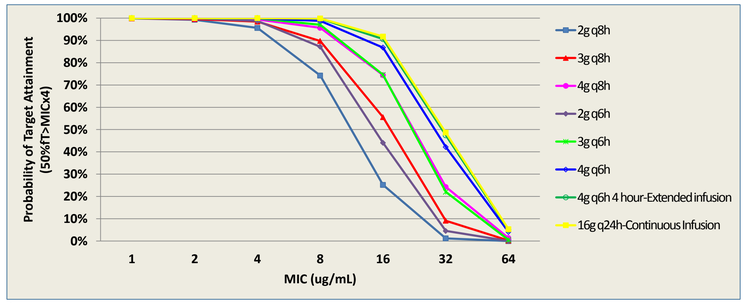
Results

- The attainment of ≥ 90% of PTA required piperacillin 16g/day during the initial 48 hours of therapy in all SHIFT RRT settings. The corresponding tazobactam dose of 2g/day attained ≥ 90% of PTA in all SHIFT regimens.
- Prolonged infusion did not yield substantially better PTA than intermittent infusion in patients receiving SHIFT RRT.
- Mean piperacillin clearance and half-life was 5.5±2.1 L/h and 5.0±3.8 h during SHIFT, and 2.8±1.8 L/h and 13.1±14.3 h off-SHIFT, respectively.

Table 2. PTA and the Proportion of *f*T≥4xMIC in 5000 Virtual Patients Receiving Different Piperacillin Regimens

Dosing	Early SHIFT RRT		Late SHIFT RRT	
	%PTA (>50% *f*T>4xMIC)	%*f*T>4xMIC (mean±SD)	%PTA (>50% fT>4xMIC)	%*f*T>4xMIC (mean±SD)
2g q8h	0.25	0.27 ± 0.27	0.25	0.28 ± 0.29
3g q8h	0.56	0.51 ± 0.30	0.56	0.53 ± 0.31
4g q8h	0.74	0.66 ± 0.26	0.74	0.69 ± 0.28
2g q6h	0.44	0.41 ± 0.31	0.47	0.45 ± 0.33
3g q6h	0.75	0.65 ± 0.27	0.76	0.69 ± 0.28
4g q6h	**0.87**	**0.78 ± 0.22**	**0.89**	**0.82 ± 0.22**
2g q6h extended infusion	0.47	0.40 ± 0.33	0.45	0.42 ± 0.35
3g q6h extended infusion	0.80	0.67 ± 0.28	0.74	0.67 ± 0.31
4g q6h extended infusion	**0.91**	**0.79 ± 0.22**	**0.90**	**0.81 ± 0.23**
16g/day continuous infusion	**0.92**	**0.78 ± 0.22**	**0.89**	**0.80 ± 0.24**

Figure. PTA of Selected Piperacillin Regimens at Different MICs



*Figures illustrate 8H HD in early SHIFT RRT but is illustrative of all modelled SHIFT settings.

Discussion/Conclusion

- Many conventional piperacillin/tazobactam dosing regimens did not attain the pharmacodynamic target for optimal efficacy in patients receiving daily SHIFT RRT.
- Piperacillin/tazobactam 16 g/day is required to attain pharmacodynamic target in critically ill patients receiving daily 8 or 10 hour SHIFT.
- Piperacillin/tazobactam 16 g/day is more than what has been recommended for CRRT (12g/d) or intermittent HD (6-7g/d).
- Extended (4-hour) or continuous infusions (24-hour) did not result in substantially higher PTA than intermittent (30-minute) infusions.
- Application of our dosing recommendation should be limited to SHIFT patients within the demographic profile of our virtual patients.
- Future clinical studies should validate these simulation results.

References

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