Piperacillin/tazobactam Therapeutic Drug Monitoring: True Inter-patient Variability or Compound Instability?

Ryan L. Crass[1], Praveen Kumar[1], Twisha S. Patel[2], Manjunath P. Pai[1]

[1]University of Michigan College of Pharmacy, Ann Arbor, MI, USA; [2]Michigan Medicine, Ann Arbor, MI, USA

Abstract

Background: Beta-lactam exposure is frequently documented to be inadequate in critically ill patients implying that therapeutic drug monitoring (TDM) may be necessary to optimize efficacy. Practical barriers to implementation of TDM for beta-lactam/beta-lactamase inhibitor combinations include potential chemical instability as well as the need to assay both drug components.

Methods: First, ex-vivo stability studies of piperacillin/tazobactam (PIP/TZB) were performed at 1, 10, and 100 mg/L concentrations in human plasma. Spiked plasma samples were stored at room temperature for 4 hours and then at 4˚C for 72 hours to mimic the conditions of routine handling. Second, a pilot study using discarded clinical laboratory samples was conducted to ascertain the feasibility of such a method for PIP/TZB TDM. Consecutive patients initiated on PIP/TZB within 24 hours of admission to the medical intensive care unit were screened for enrollment. Patients receiving less than 48 hours of therapy and those requiring renal replacement therapy were excluded. Laboratory samples were collected following their intended use and assayed for PIP and TZB using LC-MS/MS. Clinical patient data were obtained retrospectively.

Results: In the ex-vivo studies, both PIP and TZB were stable at 100 mg/L for up to 48 hours at 4˚C; however, at lower drug concentrations there was unacceptable (>15%) loss after 24 hours. Thirty-two subjects contributed a total of 136 clinical samples for secondary analysis. Patients were a median (IQR) of 69 (54, 72) years old with estimated creatinine clearance of 75.6 (61.5, 111.7) mL/min. The assay was linear over a range of 1-100 mg/L and 0.5-50 mg/L for PIP and TZB, respectively. The median (5th, 95th percentile) PIP and TZB concentrations were 26.30 (1.78, 112.00) and 7.55 (0.95, 23.00) mg/L, respectively. A strong linear relationship (R^2 0.84) was found between TZB and PIP concentrations.

Conclusions: PIP and TZB concentrations are strongly correlated permitting evaluation of PIP as the key analyte. Samples for PIP/TZB should be frozen soon after collection for batch assay methods. “Real world” studies documenting high interpatient variability in PIP/TZB pharmacokinetics in the critically ill should account for pre-analytical variation with clear sample handling protocols.

Background

- Pharmacokinetic studies of piperacillin/tazobactam (PIP/TZB) in critically ill patients have demonstrated higher inter-patient variability in drug exposure[1]
- Most of these studies measure PIP without quantifying TZB
- Compound instability under standard sample handling conditions may be a significant contributor to this observed variability[2,3,4]

Objectives

- To characterize the stability of PIP/TZB in human plasma
- To determine the concentrations of PIP and TZB in secondary use clinical samples obtained from critically ill patients

Results

Figure 1: Stability of piperacillin in human plasma at various concentrations when stored at room temperature for 4 hours then at 4˚C for a total of 72 hours.

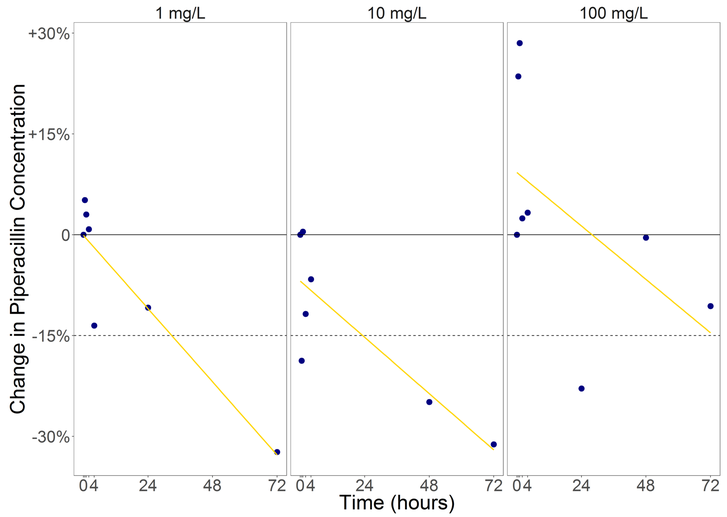


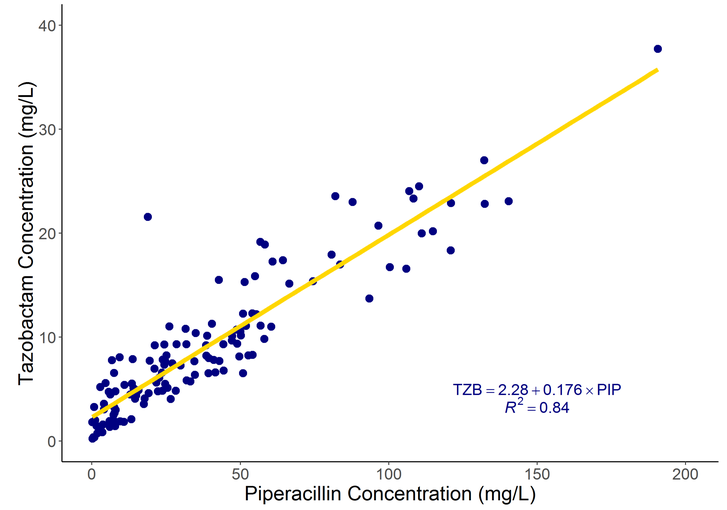
Table 1: Accuracy and Intra-Batch Precision of the LC-MS/MS Assays

Drug	Nominal Concentration (mg/L)	Mean Concentration (mg/L)	Precision (%CV)	Accuracy (%)
Piperacillin	0.50	0.52	8.6 %	104.5 %
	2.50	2.27	2.1 %	90.7 %
	10.00	10.52	11.0 %	105.2 %
	50.00	50.67	6.4 %	101.3 %
Tazobactam	0.50	0.52	20.7 %	103.4 %
	2.50	2.04	11.3 %	81.4 %
	10.00	9.41	11.3 %	94.1 %
	50.00	47.06	8.6 %	94.1 %

Table 2: Characteristics of Patients Contributing Samples

Variable	Median (IQR) or *n* (%)
N	32
Age (years)	69 (54, 72)
Female Sex	19 (59.4%)
Caucasian Race	25 (78.1%)
Height (in)	67.0 (64.0, 70.3)
Weight (kg)	88.3 (68.4, 109.6)
Body Mass index (kg/m^2)	30.3 (24.4, 36.0)
Estimated Creatinine Clearance (mL/min)	75.6 (61.5, 111.7)

Figure 2: Relationship between piperacillin and tazobactam concentrations obtained from secondary use samples from critically ill patients



Methods

Ex-vivo Stability

- Human plasma was spiked with 1, 10, and 100 mg/L concentrations of PIP/TZB
- Plasma was stored at room temperature for 4 hours, then placed at 4˚C for a total of 72 hours to mimic routine storage conditions in the clinical laboratory
- Aliquots were sampled at the following time points: 0, 0.5, 1, 2, 4, 24, and 72 hours
- Compound instability was assessed as the proportion of drug lost relative to the initial concentration

Secondary Use Clinical Samples

- Discarded clinical laboratory samples were collected form consecutive patients initiated on PIP/TZB within 24 hours of medical intensive care unit admission
- Subjects who received PIP/TZB for < 48 hours or those on any form of extra-corporeal organ support were excluded
- The relationship between TZB and PIP concentrations was assed using linear regression

Assay: Concentrations of PIP and TZB were determined using liquid chromatography – tandem mass spectrometry. The assay was linear over a range of 1 – 100 mg/L and 0.5 – 50 mg/L for PIP and TZB, respectively.

Conclusions

- Piperacillin is not sufficiently stable under routine storage conditions to permit secondary use sampling for therapeutic drug monitoring (TDM).
- Samples should be processed and either frozen or assayed within 24 hours in clinical studies measuring concentrations of PIP/TZB.
- Piperacillin and TZB concentrations from clinical samples are highly correlated suggesting measurement of PIP alone is likely to be sufficient for TDM

References

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