

P0868 **Individualizing piperacillin/tazobactam dosing in adult patients with cystic fibrosis: can tobramycin measurements help?**

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Background: The dosing of piperacillin (PIP)/tazobactam(TAZ) and tobramycin (TOB) in adults with cystic fibrosis is complicated by enhanced renal elimination and reduced pathogen susceptibility relative to other populations. Given the extensive renal elimination of these compounds, information from therapeutic drug monitoring of TOB could in theory be used to predict exposure of PIP/TAZ. Our objective was to identify pharmacokinetic relationships between TOB and PIP/TAZ using mathematical modeling in order to validate this approach to individualized dosing.

Materials/methods: A non-interventional, open-label, pharmacokinetic study was performed in hospitalized adult patients with cystic fibrosis receiving TOB and PIP/TAZ concomitantly. Six serum samples were collected and assayed. Pharmacokinetic analyses were performed using non-parametric adaptive grid methods with the PMetrics™ package in R. Models were developed and compared iteratively with discrimination based on goodness-of-fit statistics and the Akaike Information Criterion (AIC).

Results: Nine subjects were enrolled. Mean (%CV) population parameter estimates of Model 1 (1-compartment, independent), Model 2 (1 and 2 compartment with parallel first order and Michaelis-Menten (MM), independent), and Model 3 (Model 2 with TOB co-model) are reported in the table. The volume of the central compartment (Vc), elimination rate (Ke), transfer rate (Kcp, Kpc), and MM constants (Vmax, Km) are reported. Model 3 minimized AIC and maximized goodness-of-fit.

Drug	Parameter	Model 1 (AIC = 1084)	Model 2 (AIC = 1051)	Model 3 (AIC = 1044)
TOB	V _{C_{TOB}} (L)	8.34 (12.6)	8.36 (12.7)	8.41 (12.7)
	Ke _{TOB} (hr ⁻¹)	0.49 (13.2)	0.49 (13.8)	0.48 (12.7)
PIP	V _{C_{PIP}} (L)	18.94 (38.7)	12.79 (42.5)	15.28 (50.0)
	Ke _{PIP} (hr ⁻¹)	0.89 (35.7)	1.23 (82.9)	Ke _{TOB} × 0.14 (71.8) + 0.77 (60.0)
	Kcp _{PIP} (hr ⁻¹) Kpc _{PIP} (hr ⁻¹)			1.08 1.80 (60.6) (64.0)
				0.54 1.86 (87.2) (64.7)
	V _{max_{PIP}} (mg/hr) Km _{PIP} (mg/L)		135.3 11.45 (54.4) (113.4)	
			159.6 4.88 (34.5) (95.8)	
TAZ	V _{C_{TAZ}} (L)	14.53 (24.8)	15.17 (25.4)	14.86 (29.6)
	Ke _{TAZ} (hr ⁻¹)	0.63 (24.6)	0.61 (27.4)	Ke _{TOB} × 0.26 (68.6) + 0.5 (22.9)

Conclusions: A relationship between the elimination rate constants of TOB and PIP/TAZ was identified and modeling of PIP/TAZ using this relationship improved model fit. Validation of this relationship creates an opportunity for individualized dosing of PIP/TAZ in patients with cystic fibrosis