Population Pharmacokinetics of Piperacillin-Tazobactam Extended Infusions in Paediatric Population

Jean Lavigne (1), Nastya Kassir (1), Céline Thibault (2,3,4,6), Catherine Litalien (2,3,4), Julie Autmizguine (2,3,4,5)

(1) Certara Strategic Consulting, Canada, (2) Department of Pediatrics, CHU Sainte-Justine, Montreal, Canada, (3) Clinical Pharmacology Unit, CHU Sainte-Justine, Montreal, Canada, (4) Research Center, CHU Sainte-Justine, Montreal, Canada, (5) Department of Pharmacology and Physiology, Université of Montréal, Montreal, Canada, (6) Research Institute, Children's Hospital of Philadelphia, Philadelphia, USA

Background

- Piperacillin-tazobactam (TZP) is frequently used to treat severe hospital-acquired infections in children
- Efficacy correlates with the time that free piperacillin concentration is above the minimum inhibitory concentration (MIC) over the dosing interval (*f*T > MIC)
- TZP extended infusions optimize *f*T > MIC.

Methods

- Single-center prospective pharmacokinetic-pharmacodynamic study
- Infants and children 2m-6y on TZP per standard of care received:
  - **2-5m old: 80 mg/kg/dose q6h infused over 2h**
  - **6m-6y old: 90 mg/kg/dose q8h infused over 4h**
- Opportunistic sampling (maximum of 4 PK plasma samples/patient)
- Two population PK models developed (piperacillin and tazobactam) using nonlinear mixed effect modeling (NONMEM v7.3)
- Weight (WT) included in the base model *a priori* (allometric scaling with fitted exponents) centered around our population median (11.4 kg)
- Covariate analysis: stepwise forward selection ($p<0.05$) and backward elimination ($p<0.01$)
- Piperacillin simulations were performed using the final PK model, over a range of MICs from 4-32 mg/L
- Surrogate pharmacodynamic (PD) piperacillin efficacy target was *f*T > MIC ≥ 50% (free concentration = 70% of total concentration)
- Probability of target attainment (PTA) ≥ 90% was considered optimal

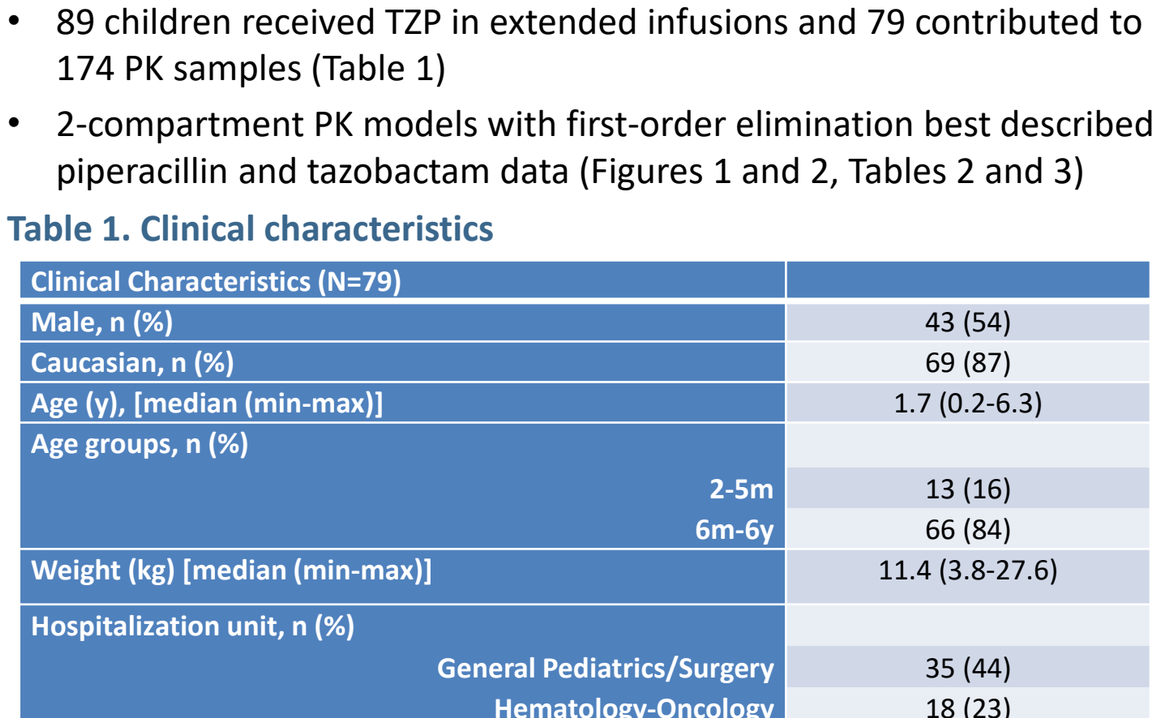
Results

- 89 children received TZP in extended infusions and 79 contributed to 174 PK samples (Table 1)
- 2-compartment PK models with first-order elimination best described piperacillin and tazobactam data (Figures 1 and 2, Tables 2 and 3)

Table 1. Clinical characteristics

Clinical Characteristics (N=79)	
Male, n (%)	43 (54)
Caucasian, n (%)	69 (87)
Age (y), [median (min-max)]	1.7 (0.2-6.3)
Age groups, n (%)	
2-5m	13 (16)
6m-6y	66 (84)
Weight (kg) [median (min-max)]	11.4 (3.8-27.6)
Hospitalization unit, n (%)	
General Pediatrics/Surgery	35 (44)
Hematology-Oncology	18 (23)
PICU	26 (33)
Duration of TZP treatment (days) [median (min-max)]	3.7 (0-14.7)
Co-medication, n (%)	
Furosemide	20 (25)
Vancomycin	13 (16)
Tobramycin	23 (29)

Figure 1. Piperacillin goodness-of-fit and visual predictive check plots



Results (Con't)

- 1000 virtual paediatric patients were simulated with age between 2m-6y and *f*T > MIC were calculated.

Figure 2. Tazobactam goodness-of-fit and visual predictive check plots

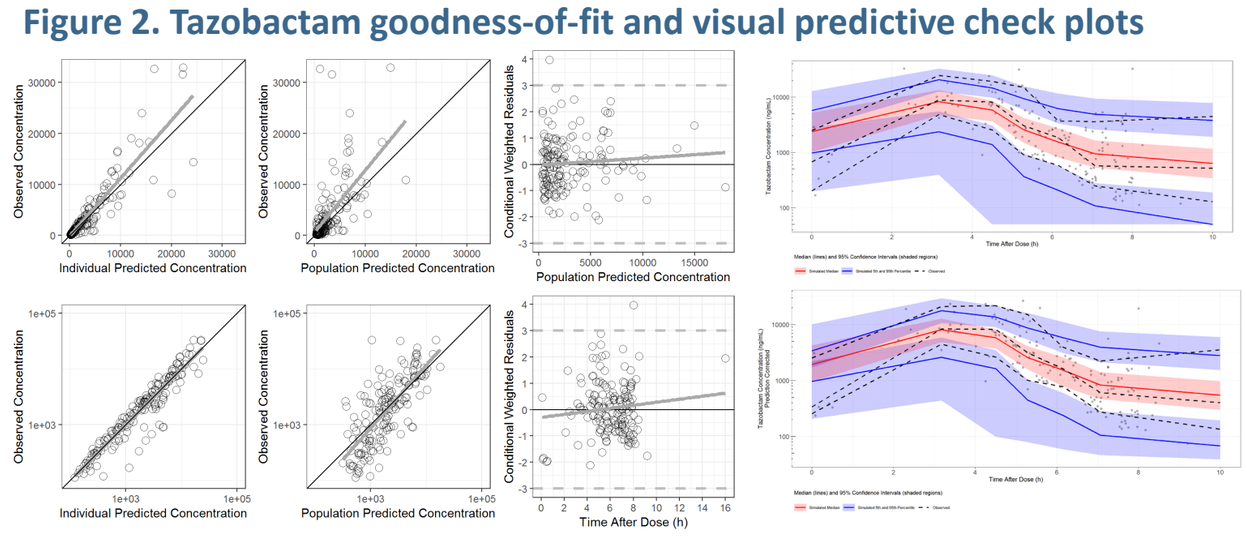


Table 2 . Final Piperacillin Model

Parameter	Estimate	RSE%	Bootstrap median	Bootstrap 95% CI
Typical values				
CL, Clearance (L/h)	3.92	17.4	3.72	2.74 – 5.35
Vc, Central volume of distribution (L)	4.87	27.2	4.35	2.47 – 8.24
CLd, Intercompartmental clearance (L/h)	0.252	86.2	0.205	0.0482 – 1.24
Vp, Peripheral volume of distribution (L)	0.488	47.9	0.656	0.192 – 8.46
Covariate effects				
Weight on CL (exponent)	1.40	13.2	1.36	0.946 – 1.78
Furosemide on CL	-0.284	97.7	-0.292	-0.638 – -0.0585
Weight on V (exponent)	1.26	23.4	1.16	0.318 – 1.95
Interindividual Variability				
Std. dev. of η on CL	0.438	17.6	0.420	0.271 – 0.570
Residual Variability				
Std. dev. of ε Proportional	0.461	10.5	0.205	0.130 – 0.286

Table 3. . Final Tazobactam Model

Parameter	Estimate	RSE%	Bootstrap median	Bootstrap 95% CI
Typical values				
CL, Clearance (L/h)	3.15	12.7	3.10	2.34 – 4.15
Vc, Central volume of distribution (L)	3.79	19.7	3.69	2.25 – 5.97
CLd, Intercompartmental clearance (L/h)	0.204	45.0	0.198	0.0596 – 0.481
Vp, Peripheral volume of distribution (L)	3.65	46.6	3.19	0.302 – 7.85
Covariate effects				
Weight on CL (exponent)	1.24	16.1	1.24	0.771 – 1.69
Furosemide on CL	-0.286	66.3	-0.297	-0.549 – -0.0400
Weight on V (exponent)	1.06	31.4	1.09	0.300 – 1.85
Interindividual Variability				
Std. dev. of η on CL	0.374	19.8	0.366	0.230 – 0.510
Residual Variability				
Std. dev. of ε Proportional	0.430	10.1	0.172	0.105 – 0.240

Conclusions

- Piperacillin and tazobactam were both best described with a 2-compartment PK model with weight on clearances and volumes and furosemide on clearance.
- Optimal piperacillin dosing to treat bacteria with MICs up to 16 mg/L:
  - <6m: 75 mg/kg/dose every 4h given over 0.5h
  - ≥ 6m: 130 mg/kg/dose every 8 hour given over 4h

PAGE, 11-14 June 2019, Stockholm, Sweden

II-008