Tobramycin in paediatric CF patients - TCI or "One dose fits all"

S Hennig[1], R Norris[2], C Kirkpatrick[1]

1. School of Pharmacy, University of Queensland, Brisbane, Australia
2. Australian Centre for Paediatric Pharmacokinetics, Mater Pharmacy Services, Brisbane, Australia.

Introduction

- **Intravenous tobramycin is a mainstay in the treatment of *Pseudomonas aeruginosa (PA)* infections in patients with cystic fibrosis (CF)**
- **Once-daily dosing (OD) approach provides**
  - **high c_{max} concentration to improve *PA* killing and extends the post-antibiotic effect**
  - **reduced risk of nephro- and ototoxicity due to low through concentrations**
  - **reduced impact of adaptive resistance**
- **Even though the pharmacokinetics (PK) of tobramycin and other aminoglycoside antibiotics have been described in several patient populations, to our knowledge, no dosing and target concentrations intervention (TCI) guidelines have been established for paediatric CF patients**
- **TCI is recommended when**
  - **variability of drug concentrations in the target population cannot be explained by covariates alone**
  - **between subject variability (BSV) is larger than between occasion variability (BOV)**
  - **BOV is relatively small compared to the safe and effective variability (SEV).** (Matthews I, et al. Br J Clin Pharmacol 2004) **SEV is a subjective definition of an acceptable degree of variability of concentration in the target population** (Holford NHG. Br J Clin Pharmacol 1999)

Aims

1) **To estimate the population pharmacokinetic parameters of once-daily intravenous tobramycin in paediatric CF patients**
2) **To investigate the influence of covariates on the PK model**
3) **Assess use of TCI from the quantified random and predictable components of variability**

Methods

- **Retrospective data were collected from paediatric CF patients**
- **Tobramycin concentrations were determined using an immunoassay (TDx)**
- **A nonlinear mixed-effect modelling approach was used to describe the pharmacokinetics of tobramycin. Modelling was performed using the first order conditional estimation (FOCE) method with interaction in NONMEM, version 5.1.1.**
- **1000 Monte Carlo simulations were performed with NONMEM and analysed with S-Plus. The simulations were done using weight based dosing (mg/kg) for each tested dosing regimen with a weight from a covariate distribution model**

Results

- **318 tobramycin concentrations were recorded retrospectively from 35 CF patients aged 0.5 – 17.8 years old (See Table 1)**
- **A 2-compartment model best described the tobramycin data (See Table 2)**

Table 1: Demographics of patient population

Characteristics	Mean	(Range)
Age (years)	9.5	(0.5 – 17.9)
Total body weight (kg)	34.0	(6.0 – 72.6)
Height (cm)	131.0	(60.0 – 178.0)
Serum Creatinine (µmol/L)	44.0	(20.0 – 73.0)
Creatinine Clearance (ml/min)	105.7	(23.0 – 194.7)
Observations/ patient	9.0	(2.0 – 26.0)
Occasions/patient	4.6	(1.0 – 14.0)
Dose (mg)	311.7	(70.0 – 560.0)
Dose (mg/kg)	9.6	(6.92 – 15.2)

- **The final model was evaluated using goodness of fit plots, visual predictive check and a bootstrap (Figure 2, Table 2)**
- **The inclusion of total body weight allometricaly scaled as a covariate reduced the random component of BSV in CL from 50.1% to 11.7% and in V_c from 62.2% to 11.6%**
- **No relationship between serum creatinine concentrations as a marker for renal function and tobramycin clearance was identified**
- **The between occasion variability on CL was estimated in the final model as 6.47% and was smaller than the BSV on CL**

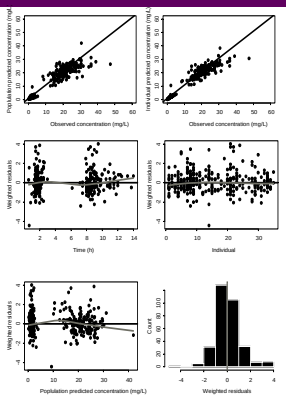

Figure 1: Goodness of Fit Plots for the final model including: Population and individual predicted tobramycin concentrations versus observed tobramycin concentrations (mg/L), weighted residuals versus time (h) after dose, individual and versus population predicted concentrations (mg/L) including a loess fit (grey) and a histogram of the weighted residuals.

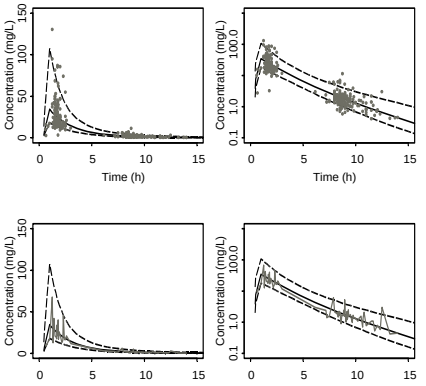

Figure 2: Visual Predictive Check showing the observed concentrations as grey points (top graphs) or as grey 50th percentile line of the observed concentrations (bottom graphs) with either a logarithmic scale on the y-axis (right side) or a non-logarithmic scale (left side)

Table 2: Parameter estimates of the base model, the covariate model and the 1000 bootstrap runs (median and 95th percentile).

Parameter	*Base Model*	*Covariate Model*	**1000 bootstrap replicates** Median (95th Percentiles)
Objective Function Value	636.194	531.507	513.29 (355.93 – 702.08)
Fixed Parameters			
CL ($L.h^{-1}$)	2.98	6.37[a]	6.26[a] (5.37 – 6.98)
V_c (L)	8.22	18.70[a]	18.60[a] (16.00 – 20.56)
Q ($L.h^{-1}$)	0.12	0.39	0.40 (0.25 – 0.79)
V_{per} (L)	9.93	1.32	1.57 (1.00 – 4.90)
t_{lag} (h)	0.39	0.40	0.40 (0 – 0.60)
D_c (h)	0.5c	0.5c	0.5c
Random Parameters (CV %)			
BSV CL	55.23	11.70	11.45 (6.74 – 15.94)
BSV V_c	61.97	11.66	10.63 (3.19 – 18.80)
BSV V_{per}	182.76	41.95	53.29 (17.43 – 109.20)
R (CL, V_c)	0.98	0.73	0.74 (0.47 – 0.79)
R (CL, V_{per})	0.39	0.49	0.77 (-5.91 – 0.58)
R (V_c, V_{per})	0.52	0.27	0.34 (-13.97 – 0.44)
BOV CL	6.44	6.47	6.60 (3.06 – 8.98)
Residual variability *(CV %)*	18.65	19.00	18.55 (15.42 – 21.91)

CL = Typical clearance from central compartment, V_c = Typical volume of central compartment, Q = Typical intercompartemetal clearance, V_{per}= Typical volume of peripheral compartment, t_{lag} = Typical lag-time between time of hanging infusion and drug entering the patients vein, D_c = Duration of infusion into the central compartment, BSV = Between subject variability, BOV =Between occasion variability, a = The typical value of clearance and volume refer to a patient with a total body weight of 70 kg for comparison to adult values, c = fixed, R = correlation coefficient between BSV's.
Typical value = Typical parameter estimate* (total body weight/70)^f, f = ¾ for clearance, f = 1 for volume.

- **From simulations an initial treatment dose of 10 mg/kg was established as the safest and most efficient, however only 72% of patients will achieve an AUC within 80-125% of the target (Table 3)**
- **Tobramycin trough concentrations after OD dosing do not correlate with c_{max} concentrations or AUC values**

Table 3: Results from simulations of several once daily dosing regimens.

Dosing Regimen	**350 mg***	**7.5 mg/kg**	**8.5 mg/kg**	**10 mg/kg**	**11 mg/kg**	**12 mg/kg**
	Percentage of patients					
Within AUC range (80-125 mg.h/L)	37.9	21.7	44.2	72.1	76.9	69.4
Outside AUC range (80-125 mg.h/L)	62.1	78.3	55.8	27.9	23.2	30.6
Below AUC 80 mg.h/L	36.6	78.1	55.0	22.2	10.3	4.4
Above AUC of 125 mg.h/L	25.5	0.2	0.8	5.7	12.9	26.2
Below 1 mg/L at 24 h (trough)	100	100	100	100	100	100
Below 0.3 mg/L (LOQ) at 24 h (trough)	97.2	100	99.8	99.7	99.6	99.6
Within c_{max} range (24-38 mg/L)	29.8	17.3	55.8	91.6	92.5	80.2
Below c_{max} of 24 mg/L	39.0	82.7	44.2	7.1	1.3	0.4
Above c_{max} of 38 mg/L	31.2	0	0	1.3	6.2	19.4

*same dose for all patients

Conclusions

- **One dose does not fit all**
- **Adjustment of the dose according to total body weight is not enough**
- **TCI and dose adjustment is required**