Population pharmacokinetics(PK)/Pharmacodynamics(PD) modeling and simulation of vancomycin for pediatric infectious patients

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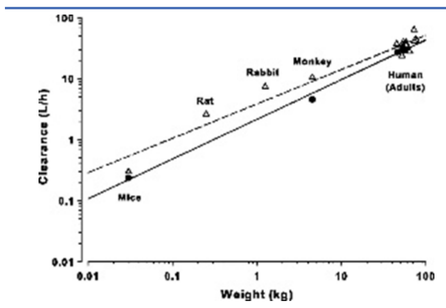
Introduction



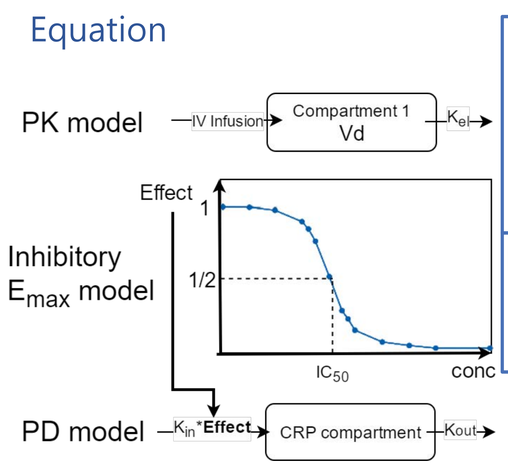
The aim of this study is to develop population PK/PD model of vancomycin in pediatric infectious patients for dose optimization of vancomycin. Allometric scaling is available for extrapolation about size. The maturation function can reflect the maturity of an organ or tissue function for age. Allometric scaling and maturation function were used to apply vancomycin dosage to pediatric patients. Using two factors, it is possible to optimize the dosage with low toxicity and high efficacy.

Method

81 pediatric patients' PK and clinical laboratory data as PD data were obtained from Electronic Medical Record (EMR) at Chungnam National University Hospital. 81 demographics of patient were tested by PK covariates (postnatal age(PNA), postconceptional age(PCA), gestational age(GA), weight, etc). C-Reactive protein(CRP) was selected as PD because this parameter is representative to infectious factor. Plasma concentrations were fitted with one-compartment and indirect response model(IDR) was selected to connecting between PK and PD model. Kin was defined CRP synthesis rate. Kout was defined CRP degradation rate.

Results

Equation



PK

$$\mathrm{Cl} = \mathrm{Cl}_{TV} \times \left(\frac{weight}{70}\right)^{0.75} \times \frac{\mathrm{PCA}^{Hill}}{PCA^{Hill} + TM_{50}{}^{Hill}}$$

$$\mathrm{V} = \mathrm{V}_{TV} \times \frac{Weight}{70} \quad K = \frac{Cl}{V}$$

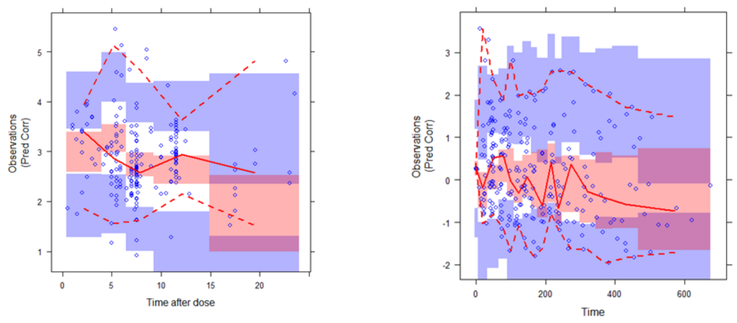
PD $\mathrm{K}_{in} = \mathrm{K}_{in_{TV}}$ $\mathrm{K}_{out} = \mathrm{K}_{out_{TV}}$ $\mathrm{IC}_{50} = \mathrm{IC}_{50_{TV}}$

$$\mathrm{C}_p = \frac{\mathrm{Comp}_1}{\mathrm{V}} \quad \mathrm{Effect} = \frac{\mathrm{C}_p}{IC_{50} + \mathrm{C}_p}$$

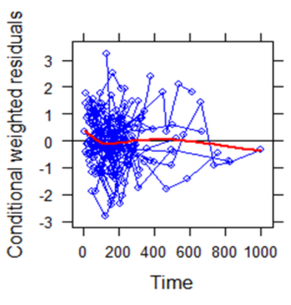
$$\frac{dComp_1}{dt} = -K \times Comp1$$

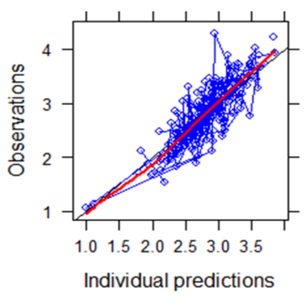
$$\frac{dComp_{CRP}}{dt} = \mathrm{K}_{in}(1 - \mathrm{Effect}) - \mathrm{K}_{out} \times Comp_{CRP}$$

VPC (PK (left), PD(Right))



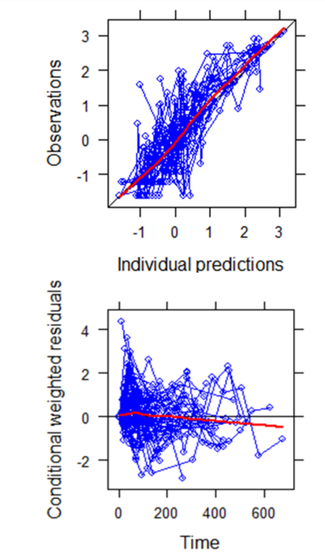
PK model





Theta	Estimate	SE	RSE	95% CI
Vd	50.9	9.71	0.191	31.868 - 69.932
CL	3.42	0.224	0.065	2.981 - 3.859
Additional error	0.387	0.0358	0.093	0.317 - 0.457
TM50	31.2(FIX)	0	0	31.2 - 31.2
HILL	3.68(FIX)	0	0	3.68 - 3.68
Omega	1	2	p val	Shrinkage
1 Vd	0.194 (84%)		0.1159	0.763
2 CL	0.0159 (371.7%)	0.306 (28.4%)	0.9016	0.122
Omega	(on SD scale) 1	2	Sigma	Shrinkage
1 Vd	44%(42%)		1	20.10%
2 CL	-6.5%	55.3% (14.2%)		

PD model



Theta	Estimate	SE	RSE	95% CI
Vd	50.9 FIX	0	0%	50.9 - 50.9
CL	3.42 FIX	0	0%	3.42 - 3.42
TM50	31.2 FIX	0	0%	31.2 - 31.2
Hill	3.68 FIX	0	0%	3.68 - 3.68
KOUT	0.0125	0.002	15.90%	0.009 - 0.016
KIN	0.0173	0.0077	44.20%	0.002 - 0.032
IC50	15.2	14	92.10%	-12.24 - 42.64
ADD ERROR	0.684	0.0551	8.10%	0.576 - 0.792

Omega	1	2	3	4	p val	Shrinkage
1 Vd	0.194(FIX)					
2 KCL	-	0.306(FIX)				
3 KOUT	-	-	0.0605(123.6%)		0.2043	68.4%
4 KIN	-	-	-	0.92 (35.40%)	0.5534	32.1%
Omega	(on SD scale)1	2	3	4	Sigma	Shrinkage
1 Vd	44%				1	8.20%
2 KCL	-	55.30%				
3 KOUT	-	-	24.6%(61.8%)			
4 KIN	-	-	-	95.9%(17.7%)		

Covariate

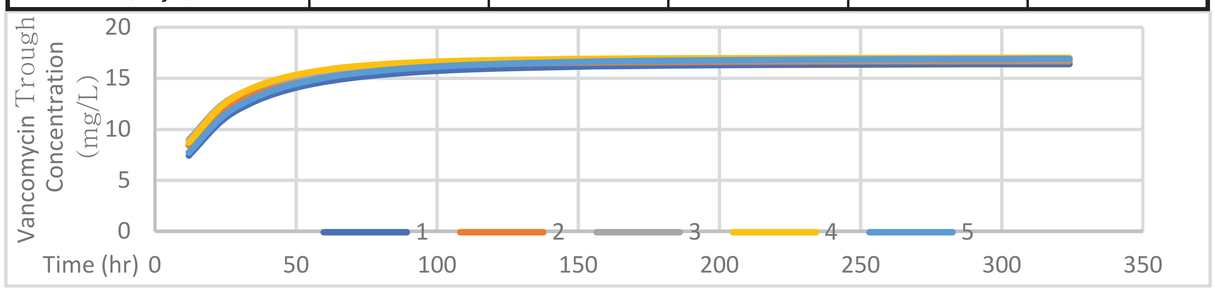
PK final model was explained by Allometric scaling and maturation function. Allometric scaling was applied to Vd and CL. And maturation function was applied to CL. Maturation function's parameters that were TM50 and Hill were not estimated but gotten from reference.

PD model didn't have valid covariate. The parameters with the largest correlation in the PD model were K_{in} and PCA. but p value was less than 0.05.

Simulation

Five virtual populations were set up and 1000 simulations on each population were carried out as shown below. And the average value was taken. The initial CRP value was set at 10 mg / L and the point at which the CRP value fell below 2 mg / L was used as the endpoint. The target blood concentration of vancomycin was set at 16 mg / L to avoid toxicity. The trough concentration trend was as shown in the graph below.

Population	1	2	3	4	5
Weight (kg)	2	4	8	16	32
PCA (weeks)	30	40	60	230	520
Dose (mg/kg)	13.5	20	23.1	20.3	15.2
Traditional dose (mg/kg)	15mg/kg				
Endpoint (CRP<2mg/L) (days)	9.2	9	8.7	8.6	9.4



Conclusions

CRP is one of acute infection markers. In humans, plasma levels of CRP may rise rapidly and markedly, as much as 1000-fold or more, after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes. and this PK/PD model is valid during dosing vancomycin. therefore this model can be used for effect prediction for a short time(1-2 weeks).

Acknowledgment

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