Population Pharmacokinetics of Ganciclovir Following Administration of Valganciclovir in Pediatric Renal Transplant Patients

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Introduction and Objectives

Valganciclovir, the ester of ganciclovir and L-valine, is a prodrug of ganciclovir with an increased bioavailability. It has been used for prophylaxis, preemptive treatment of Cytomegalovirus (CMV) viremia and therapy of tissue-invasive CMV disease

There are no pharmacokinetic data in pediatric renal transplant patients

- The first objective was to develop a population pharmacokinetic model of valganciclovir in pediatric renal transplant patients
- The second objective was to identify the patients' characteristics that influence pharmacokinetic parameters
- The third objective was to define the dosage regimen that will allow efficient drug exposure for CMV prophylaxis in children

Patients

22 pediatric renal transplanted children which consisted of 11 males and 11 females, with a age of 10 ± 5 years and weight of 34 ± 19 kg

Population Modeling

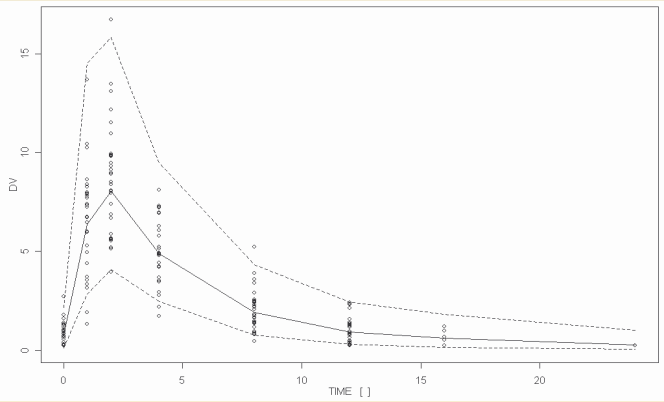
2-compartement model with a lag-time (ADVAN4, TRANS4). Inter-individual and residual variability were best described by exponential model. Inter-individual variability was then estimated for CL, V2 and KA

During the covariate analysis, a nonlinear relationship between CL and CL_{CR} and a linear relationship between CL and bodyweight significantly improved the model, with the equation:
$CL = \theta1 \times (CL_{CR}/median)\ \theta2 + \theta3 \times (WT/median)$

Model Validation

1- Visual Predictive Check

The 5th and 95th percentiles as well as the median 50th percentile of these simulations and the patients' data over a 24 hour interval were shown in figure . Exact Binomial Test, 9.2% out of limits observed, the 95% confidence interval [5.24 , 14.7] Pearson's Chi-squared test, p = 0.1492



2- Bootstrap

The PK parameters and results of 1000 bootstrap:
(87% successful run)

	Model final		Bootstrap n=1000	
Parametre	final estimate	SE(%)	Median	2.5th-97.5th
Absorption rate constant (h^{-1}) Ka	0.369	11.3	0.366	0.30 - 0.45
Lag-time(h)	0.743	14.4	0.752	0.56 - 0.96
Apparent central volume of distribution (L) V2	5.2	35.6	4.95	0.97 - 8.04
Apparent peripheral volume of distribution (L) V3	30.7	8.9	31	26.90 - 48.42
Inter-tissue clearance ($L\,h^{-1}$) Q	3.97	27.7	3.82	2.36 - 6.23
Apparent Systemic clerance ($L\,h^{-1}$) CL $\theta1*(CL_{CREA}/89)**\theta2+\theta3*(WT/28)$	8.04	10.6	8.04	5.82 - 9.66
	2.93	11.2	2.92	2.42 - 4.11
	3.62	17.4	3.51	2.67 - 5.62
Residual exponentiel	20.93	20.4	19.84	16.66 - 23.79
intersubject variance V2	58.22	58.4	58.99	28.10 - 95.39
intersubject variance Ka	32.25	42.9	31.04	19.25 - 43.31
intersubject variance CL	23.83	41.0	23.40	14.80 - 32.40

Simulation

24-hour maintenance dose required to achieve $AUC_{0\text{-}24}$ of 45 $\mu g.h.mL^{-1}$ in children of various creatinine clearances and weights

Weight(kg)	Creatinine clearance (mL min^{-1})					
	60	70	80	90	100	110
10	172	236	319	428	570	724
15	202	267	357	458	591	770
20	230	293	378	484	623	803
25	257	325	415	518	649	817
30	288	353	443	549	683	842
35	319	386	478	573	713	866
40	347	409	500	608	740	897
45	381	448	527	641	756	956
50	407	472	551	665	796	952
55	434	496	592	692	831	984
60	467	527	614	719	852	1033

CONCLUSION

In summary, the population pharmacokinetic model developed for ganciclovir after administration of valganciclovir in pediatric renal transplant patients was validated. Creatinin clearance and bodyweight were significant covariates influencing valganciclovir clearance. The dosage regimen of valganciclovir for CMV prophylaxis has been defined using the final population pharmacokinetic model based on weight and Creatinin clearance for the renal transplant children