Predicting the Developmental PK/PD of Cyclosporine (CsA) in Paediatrics

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Background

Physiologically Based Pharmacokinetic (PBPK) models have previously been used to predict drug exposure across the paediatric age range but to the best of our knowledge have not been applied in the modelling of developmental changes in the concentration–response relationship. Few studies have investigated changes of pharmacodynamics (PD) with age in children. One study has shown that the development of the immune system was an important determinant of variation in CsA therapy in the paediatric population[1]. The PD changes coupled with the age related changes in PK, due to developmental physiology and the ontogeny of CYP3A4 will result in both altered exposure and response in children.

Objectives

To simulate the developmental immunosuppressive effect of CsA in a virtual healthy paediatric population stratified for their ages using the Simcyp paediatric simulator.

Methods

Prior *in vitro* and *in vivo* information on the metabolism and kinetics of CsA and developmental knowledge on physiology of paediatric population were incorporated into the Simcyp Simulator. Simulations of CsA PK and the decrease in Peripheral Blood Monocyte (PBM) effects were performed in infant (0 – 1 yr), pre-adolescent (4 – 12 yrs) and adult (>12 yrs) populations using Paediatric Simcyp V11 Release 2. The PK model specification used in Simcyp is based on HLM *in vitro* enzyme kinetics data of CYP3A4 for the elimination phase, while the distribution model is the minimal PBPK together with a first order absorption rate constant.

The proliferation of PBM *in vitro* was used as a PD marker of the immunosuppressive effect of CsA. The PK-PD relationship was taken from Marshall & Kearns 1999[1] in the form of an E_{max} model.

No fitting was done for the drug profiles. The simulated PK and PD profiles were compared to original observations[1&2].

Results

PK: The simulated CsA blood concentration time profile together with the clinical data are given in Figure 1. Simulated/observed ratios for trough blood level at steady-state C_{0h}, and after 2 hours C_{2hr}, together with $AUC_{0\text{-}8hr}$ are given in Table 1 and, are 1.17, 0.75, and 1.06 - fold, respectively for the pre-adolescent group.

Simulated $AUC_{0\text{-}24,ss}$ for blood concentrations showed no significant difference between this group and adults, but was about 2-fold lower than that of infants (Table 2).

PD: Simulated concentration-response profile for the infant and pre-adolescents groups are given in Figure 2.

By accounting for the difference in the sensitivity of PD in infants compared with older children and adults, the simulation predicted an increase in the area under response curve (AUCR) by about 26% in infants, but was only 6% lower in adults compared with the pre-adolescent group (Figure 3 and Table 3).

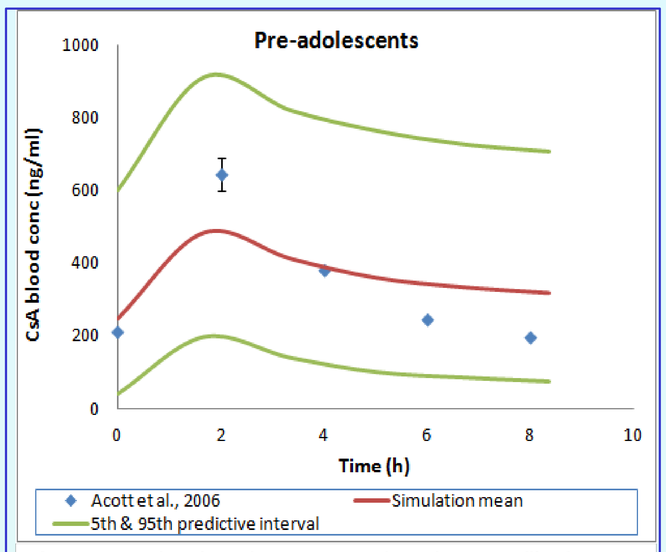

Figure 1. Simulated concentration time profile for CsA level in blood at steady state in pre-adolescent group after 1.7 mg/kg daily dose. Observations are shown by triangles, the error bars represent the standard error.

	C_{0h} (ng/ml)	C_{2h} (ng/ml)	$AUC_{0\text{-}8h}$ (ng/ml.h)
Observed	213	646	2955
Simulated	249	484	3142
Ratio	1.17	0.75	1.06

Table1. PK Parameters for the simulated and actual concentration time profiles for CsA level in blood at steady state in pre adolescent group.
Ratio = Simulated/Observed

	$AUC_{120\text{-}144h}$ (ng/ml.h)
Adult	10650
Pre-adolescents	11200
Infant	26210

Table 2. Simulated CsA area under the blood concentration for paediatric *vs* adult populations at steady state.

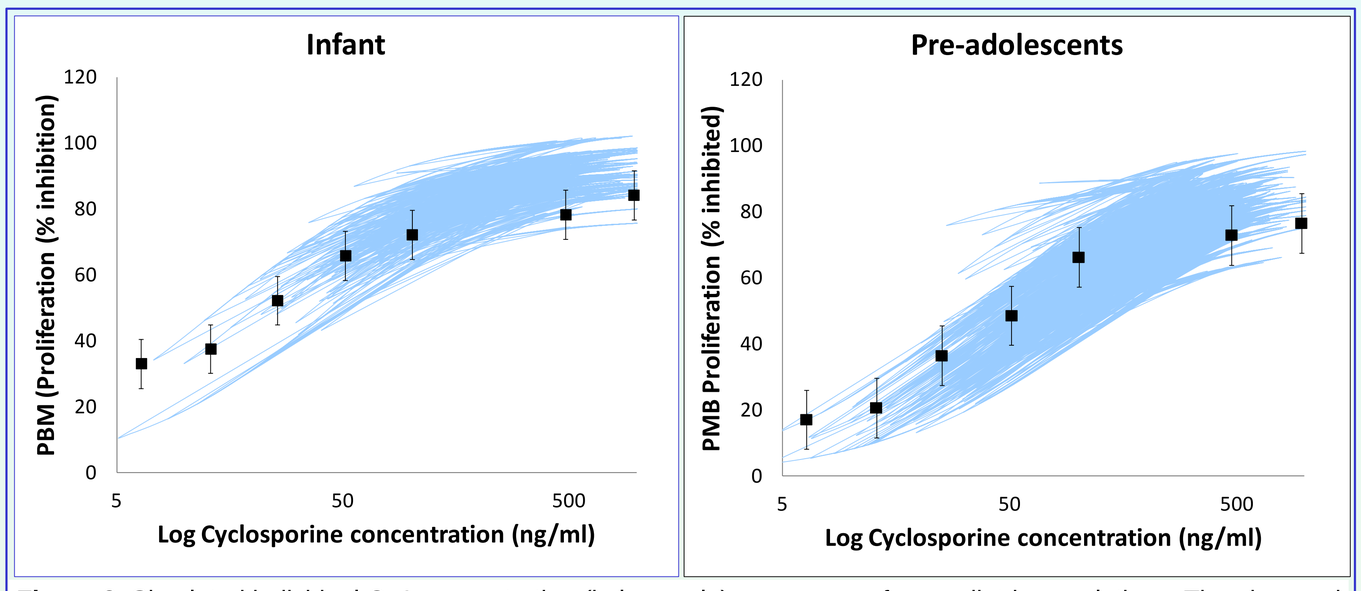

Figure 2. Simulated individual CsA concentration (in log scale) *vs* response for paediatric populations. The observed data from Marshall & Kearns (1999) are given as black squares, the error bars represent the standard error.

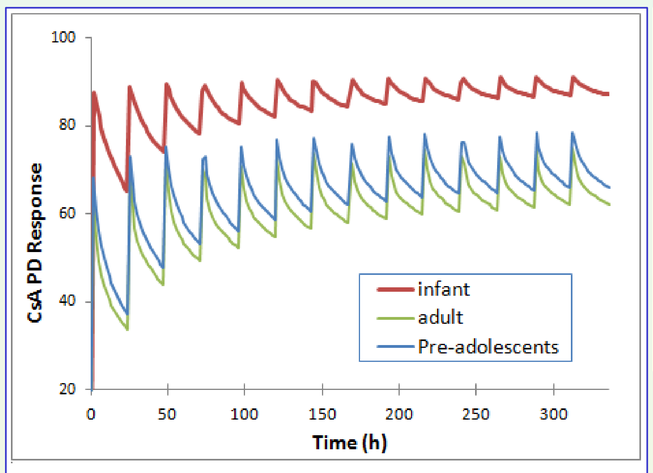

Figure 3. Simulated mean response time profiles for paediatric *vs* adult populations.

	From (h)	To (h)	R_{max}	t_{Rmax}	AUCR
adult	312	336	75	312.5	1656.5
Pre-adolescents	312	336	78	312.5	1767.0
infant	312	336	91	312.5	2230.3

Table 3. PD parameters for the last dose simulated mean response time profiles of CsA for paediatric *vs* pred-adolescents and adult populations.

Conclusions

Simulated results for the reduction of PBMs following CsA in neonates compared with the pre-adolescence and adult populations showed consistency with clinical observations in terms of the different effects of age on drug exposure and effect. The higher sensitivity in neonates to CsA may necessitate reduction of the drug dose in this population. Clinical trial simulations similar to the one shown in this study can be used to investigate the design of POPPK-PD studies in different ages and their power.

References

1. Marshall JD, Kearns GL. *Clin Pharmacol Ther*. 1999; 66: 66-75.
2. Acott PD, Crocker JF, *Transplant Proc*. 2006; 38: 2835-41.