**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. 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 in the form of an $E_{\text{max}}$ model.

No fitting was done for the drug profiles. The simulated PK and PD profiles were compared to original observations.

**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 $C_{\text{p}}$ and after 2 hours $C_{2\text{hr}}$, together with $AUC_{0-24\text{hr}}$ are given in Table 1 and are 1.17, 0.75, and 1.06 - fold, respectively for the pre-adolescent group.

Simulated $AUC_{0-24\text{hr}}$ 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).

**Conclusions**

Simulated results for the reduction of PBM 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**