Physiologic changes associated with pregnancy may have a large impact on drug disposition. The goal of this study was to build PBPK maternal-fetal models to predict the fetal exposure to antiviral drugs including emtricitabine and acyclovir. PBPK models were built in the Open Systems Pharmacology Software Suite version 7.3. The maternal-fetal PBPK model structure was developed in MoBi and exported to PK-Sim for population simulations. Placental transfer was parameterized based on data from ex vivo cotyledon perfusion experiments. The predictive performance of the PBPK models was evaluated via comparison with in vivo data. The pregnancy data for those drugs were from in vivo maternal and fetal blood samples taken at delivery. Results In the acyclovir ex vivo experimental data simulation, the fitted was 0.056 L/h (95% confidence interval: 0.043 - 0.069 L/h) and the fitted was 0.056 L/h (95% confidence interval: 0.043 - 0.069 L/h) and the fitted was 0.49 (95% confidence interval: 0.39 - 0.59). The predicted ratio between acyclovir in vivo concentrations in the umbilical vein plasma and the maternal plasma ranged from 0.37 - 0.77, whereas the observed ratios were slightly higher and ranged from 0.61 - 1.1. The previously published, and CLpl (1.49 L/h) parameters were applied to the emtricitabine maternal-fetal PBPK model, and the emtricitabine concentrations in the umbilical cord were adequately predicted. Conclusion These results increase the confidence in applying PBPK models to predict maternal and fetal drug exposure. Improved maternal-fetal PBPK models may streamline and accelerate the performance of pharmacokinetic and safety studies for drugs in pregnant women.

References

Disclosure(s) Nothing to disclose

Physiologically Based Pharmacokinetic Models to Predict Fetal Exposure to Antiviral Drugs

Background Human toxocariasis is highly prevalent and its global importance may be greatly underestimated. Toxocariasis occurs mainly in childhood by ingestion of parasite eggs from contaminated environment. During migration in human tissues the Toxocara larvae can cause several symptoms including eye involvement, but the majority of patients are asymptomatic. Eosinophilia is a marker of activity of this disease. There are no studies supporting the treatment of asymptomatic patients. Methods To evaluate the effectiveness of albendazole (10–15 mg/kg/day BID for 15 days) a randomized, placebo-controlled trial was carried out in asymptomatic children (ClinicalTrials.gov #NCT00755560). Treatment response was defined as mean absolute reduction in eosinophil counts, 12 months after treatment. Demographic, complete blood count, liver and renal function and stool parasite exam were assessed at diagnosis, and every 4 months during follow up. Inclusion criteria: age 2 to 15 years, reactive toxocara excretory-secretory substances (TES) by ELISA, eosinophils >1100/mm3, normal fundoscopy and non geo-helminthic infection. Results The 45 enrolled subjects, median age 5.3 years (range 2–13), were randomized in a 1:1 relationship. At 12-month follow-up, eosinophil median was: 1088/mm³ (IQ 25-75 680 to 2023) in placebo group and median of 1360/mm³ (IQ 25-75 761 to 2226) in albendazole group (p = 0.37). Kinetics of specific antibody titers by the ELISA showed an erratic pattern. No differences were observed in the values between the 2 treatment groups. Both groups had minor adverse events and no patient needed to discontinue medication. In asymptomatic patients with toxocariasis, albendazole was not effective to reduce eosinophil counts. Conclusion Given that toxocariasis is a neglected disease, in order to evaluate the effectiveness of albendazole or other drugs, further studies need to be conducted. Disclosure(s) Nothing to disclose

Population Pharmacokinetics of Ganciclovir After Oral Valganciclovir in Renal Transplant Children

Abstracts

Disclosure(s) The opinions expressed in this article are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration or of the National Institutes of Health. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Background Cytomegalovirus (CMV) infection is a major cause of morbidity in solid organ transplant recipients. Valganciclovir (ValG), prodrug of the antiviral ganciclovir, is used to prevent or treat CMV infection in this population. In children, as the percentage of patients reaching the pharmacological target is too low with currently used ValG dosing regimens, our aim was to determine ganciclovir population pharmacokinetics in renal transplant children receiving ValG and propose an appropriate dosage regimen.

Methods After transplantation, children receiving ValG were monitored for plasma ganciclovir concentrations using high performance liquid chromatography. Population pharmacokinetics analysis was performed with NONMEM.

Results 1212 samples from 104 renal transplant patients, aged 2 to 20 years, received ValG to prevent (n=80), treat (n=12), or both prevent then treat (n=12) CMV infection. ValG was administered orally at a daily dose of 19.8 ± 10.1 mg/kg (mean ± SD). A two-compartment model with first-order elimination best fitted the data. At steady-state, AUC_{24h-ss} was 64.5 ± 23.4 μg/mL.h, apparent clearance (CL/F) was 0.39 ± 0.14 L/h/kg, apparent volume of distribution at steady-state (VD_{ss}) was 2.4 ± 0.48 L/kg. Ganciclovir CL/F increased with body surface area, decreased with increasing creatinine concentration and was 15% higher in boys. Central volume of distribution increased with body surface area (BSA) and showed a 14% increase in boys. Internal validation was performed.

Conclusion We have successfully built a pharmacokinetic model allowing to propose dosages adapted individually to the characteristics of renal transplanted children.

Disclosure(s) Nothing to disclose

REFERENCES

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Poster Presentations

E001 APPLICATION OF FETO-PLACENTAL-MATERNAL PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO PREDICT TENOFOVIR CONCENTRATION DURING PREGNANCY
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Background Tenofovir is a drug used in combination with other anti-HIV drugs to treat patients with HIV-1 infection. It is used during pregnancy to reduce the risk of HIV transmission to the child. The aim of this work is to use a Physiologically-Based Pharmacokinetic (PBPK) model for prediction of maternal and fetal tenofovir concentration at birth.

Methods A full Feto-Placental-Maternal PBPK model that includes placenta as a 3-compartment permeability limited organ and 14 compartments for different fetal organs was developed using physiological1,2 and drug specific parameters3.