dk), where midazolam dose is adjusted to total body weight or age, may lead to both supra- and subtherapeutic doses respectively, in children with obesity. However, confirmatory studies are needed.

REFERENCES

1. Smith R, Brown J. Midazolam for status epilepticus. *Aust Prescr*. februar 2017;**40** (1):23–5.
2. Ulvi H, Yoldas T, Müngen B, Yigiter R. Continuous infusion of midazolam in the treatment of refractory generalized convulsive status epilepticus. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol* oktober 2002;**23**(4):177–82.

Disclosure(s) Nothing to disclose

036 PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS TO PREDICT FETAL EXPOSURE TO ANTIVIRAL DRUGS

[1]X Liu, [2]J Momper, [1]N Rakhmanina, [1]J van den Anker, [3]D Green, [4]G Burckart, [2]B Best, [5]M Mirochnick, [2]E Capparelli, [6]A Dallmann*. *[1]Children's National Health System, Washington D.C., DC; [2]University of California, San Diego Skaggs Schol of Pharmacy and Pharmaceutical Sciences, La Jolla, CA; [3]Office of Pediatric Therapeutics; [4]Office of Clinical Pharmacology, US Food and Drug Administration, Silver Spring, MD; [5]School of Medicine, Boston University, Boston, MA, USA; [6]University of Basel Children's Hospital, UKBB, Basel, Switzerland*

10.1136/archdischild-2019-esdppp.36

Background 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.

Methods PBPK models were built in the Open Systems Pharmacology Software Suite version 7.3 (www.open-systems-pharmacology.org). 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 0.49 (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.[1] The previously published, and CLpl (1.49 1/h) parameters[2] 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

1. Frenkel LM, *et al*. Pharmacokinetics of acyclovir in the term human pregnancy and neonate. *Am J Obstet Gynecol* 1991;**164**:569–76.
2. De Sousa Mendes M, *et al*. Prediction of human fetal pharmacokinetics using ex vivo human placenta perfusion studies and physiologically based models. *Brit J Clin Pharmacol* 2016;**81**:646–57.

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.

037 USE OF ALBENDAZOLE IN CHILDREN WITH ASYMPTOMATIC TOXOCARIASIS

[1]F Garcia Bournissen*, [2]S Moroni, [2]N Gonzalez, [2]G Moscatelli, [2]G Ballering, [2]J Altcheh. *[1]Parasitology and Chagas, Buenos Aires Children Hospital, Ciudad de Buenos Aires; [2]Parasitology and Chagas, Buenos Aires Children Hospital, Buenos Aires, Argentina*

10.1136/archdischild-2019-esdppp.37

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 geohelmintic 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: 1008/mm^3 (IQ $_{25\text{-}75}$680 to 2023) in placebo group and median of 1360/mm^3 (IQ $_{25\text{-}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

038 POPULATION PHARMACOKINETICS OF GANCICLOVIR AFTER ORAL VALGANCICLOVIR IN RENAL TRANSPLANT CHILDREN

[1]A Facchin, [1]V Elie*, [1]N Benyoub, [2]V Baudouin, [1]A Maisin, [1]S Magreault, [1]E Jacqz-Aigrain. *[1]Pediatric Pharmacology and Pharmacogenetics; [2]Nephrology, Assistance Publique – Hopitaux de Paris, Hopital Robert Debré, Paris, France*

10.1136/archdischild-2019-esdppp.38

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. is controversial in children, As the percentage of patients reaching the pharmacological target is too low with currently used ValG dosing regimen, 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 pharmacockinetics 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, $AUC_{24}h_{-ss}$ 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 (VDss/F) 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

O39 DEFINING SERUM CCL22 AND TREFOIL FACTOR 3 (TFF3) AS PHARMACODYNAMIC BIOMARKERS FOR USE IN A PROOF-OF-CONCEPT CLINICAL TRIAL OF VAMOROLONE IN PAEDIATRIC ULCERATIVE COLITIS

[1,2]LS Conklin*, [3]A Panigrahi, [4]H Gordish-Dressman, [2,5]EP Hoffman, [5]Y Hathout, [2,4]JN van den Anker, [1]L Diaz-Calderon. *[1]Gastroenterology, Hepatology, and Nutrition, Children's National Medical Center, Washington, DC; [2]ReveraGen BioPharma, Rockville, MD; [3]Center for Cancer and Immunology Research; [4]Center for Translational Medicine, Children's National Medical Center, Washington, DC; [5]School of Pharmacy and Pharmaceutical Science, Binghamton University-SUNY, Binghamton, NY, USA*

10.1136/archdischild-2019-esdppp.39

Background Paediatric ulcerative colitis (UC) patients would be well-served by a non-steroidal drug to control mucosal inflammation, without long-term and costly commitment to biologics. Vamorolone is a first-in-class alternative to glucocorticoids (GCs), under development for children with Duchenne muscular dystrophy (DMD); preliminary findings demonstrate improved safety compared with GCs[1,2]. We sought to define NFkB-regulated, GC-responsive serum biomarkers for use in a proof-of-concept pilot trial of vamorolone in UC, focusing on TFF3 (produced by intestinal epithelia, GC-responsive in UC), and CCL22 (produced by macrophages, GC-responsive in UC and other inflammatory diseases)[3,4].
Methods Sera from 10 children with IBD (7 UC, 3 CD) were tested pre and post prednisone/prednisolone (1 mg/kg/day, max 40 mg, 1–4 weeks); 210 proteins responsive to GCs in UC [3] were analyzed using SOMAscan. Proteins that showed significant change over time were correlated with change in Paediatric Ulcerative Colitis Activity Index (PUCAI) ($p < 0.05$ significance). Percent change in circulating CCL22 was compared with percent change in DMD patients treated with vamorolone (2 and 6 mg/kg/day, 2 weeks)[2]. Immunoassays were utilized to validate SOMAscan data.
Results CCL22 and TFF3 validated as decreased by GCs in IBD ($p=0.005$, $p < 0.001$). Decrease in TFF3 correlated with decrease in PUCAI ($r=0.741$, $p=0.022$); decrease in CCL22 did not correlate with change in PUCAI. Magnitude of CCL22 decrease in GC-treated UC patients was comparable to that seen in DMD patients treated with 6 mg/kg of vamorolone (47% vs. 33%). SOMAscan findings in UC validated by immunoassays.
Conclusion Decreases in serum CCL22 likely reflect effect on innate immune response, while decreases in serum TFF3 may reflect intestinal-specific effects of GCs in UC. CCL22 and TFF3, measured by immunoassays, may be useful as objective secondary outcomes reflective of NFkB inhibition and anti-inflammatory activity in a proof-of-concept trial of vamorolone in paediatric UC.

REFERENCES

1. Hoffman EP, *et al*. Phase 1 trial of vamorolone, a first-in-class steroid, shows improvements in side effects via biomarkers bridged to clinical outcomes. *Steroids*. 2018 Jun;**134**:43–52.
2. Conklin LS, *et al*. Phase IIa trial in Duchenne muscular dystrophy shows vamorolone is a first-in-class dissociative steroidal anti-inflammatory drug. *Pharmacol Res*. 2018 Oct;**136**:140–150.
3. Heier CM, *et al*. Identification of pathway-specific serum biomarkers of response to glucocorticoid and infliximab treatment in children with inflammatory bowel disease. *Clin Transl Gastroenterol*. 2016 Sep 15;**7**(9): e192.
4. Conklin LS, *et al*. Serum biomarkers of glucocorticoid response and safety in anti-neutrophil cytoplasmic antibody-associated vasculitis and juvenile dermatomyositis. *Steroids*. 2018 Dec; **140**:159–166.

Disclosure(s) LSC, JNvdA, and EPH are employees of ReveraGen BioPharma. LSC and JNvdA own stock options of ReveraGen. EPH is a co-founder of ReveraGen and owns founder shares.

ESDPPP 2019

Poster Presentations

P01 APPLICATION OF FETO-PLACENTAL-MATERNAL PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO PREDICT TENOFOVIR CONCENTRATION DURING PREGNANCY

K Abduljalil, TN Johnson, M Jamei. *Certara UK Limited, Simcyp Division, Sheffield, UK*

10.1136/archdischild-2019-esdppp.40

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-comparment permeability limited organ and 14 compartments for different fetal organs was developed using physiological[1,2] and drug specific parameters[3]