work sharing was piloted by the development of a new monograph and the periodic revision of a monograph complying to the Dutch standard operating procedure by Germany. This pilot has shown the feasibility of work-sharing in developing and updating drug monographs.

Conclusion The Dutch framework has successfully been extended to the German situation. Work-sharing on the development of dosing recommendations is feasible. Similar extension to Norwegian and Austrian nation-wide formularies has started.

REFERENCES

1. van der Zanden T, De Wildt S, Liem T, Offringa M, de Hoog M. Developing a pediatric formulary for the Netherlands. *Arch Dis Child* 2017;Apr;**102**(4):357–61.

Disclosure(s) Tijtske van der Zanden is managing director of the Dutch Paediatric Pharmacotherapy Expertise Network; Saskia de Wildt is medical director of Dutch Paediatric Pharmacotherapy Expertise Network. The other authors have no financial disclosures relevant to this article.

P102 ALTERNATIVE SPLICING OF THE *SLCO1B1* TRANSPORTER IN PAEDIATRIC LIVER

¹BD van Groen*, ²C Bi, ²R Gaedigk, ²V Staggs, ¹D Tibboel, ^{1,3}SN de Wildt, ²JS Leeder. ¹Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands; ²Children's Mercy Hospital, Kansas City, MO, USA; ³Radboudumc, Nijmegen, The Netherlands

10.1136/archdischild-2019-esdppp.140

Background Alternative mRNA transcripts occur in >90% of human genes and may be triggered by developmental signals. The hepatic transporter OATP1B1 (gene name *SLCO1B1*) traffics substrates across the hepatic membrane, and shows age-related changes in protein expression. We aimed to predict novel isoforms of OATP1B1 by studying alternative splicing of *SLCO1B1* in human paediatric post-mortem liver tissue, and the relationship of their mRNA expression with age.

Methods mRNA expression of *SLCO1B1* transcripts was determined using RNA sequencing (HISAT2/StringTie). Novel mRNA transcripts were considered of relevance when (1) the expression was >5% of the annotated isoform, (2) it was a *SLCO1B7* and *SLCO1B1* hybrid transcript, or (3) when the expression was associated with age. The software packages ORF-finder, TMpred and TOPO2 were used to predict the protein sequence and structure of the novel isoforms. Relationship of expression with age was studied with the Kruskal-Wallis test for age groups (fetal, 0–1.5 year, 1.5–6 year, 6–12 year and 12–18 year) and with Spearman correlation tests for age on continuous scale.

Results In 97 hepatic post-mortem tissues (gestational age median 16.4 [range 14.7–41.3] weeks, postnatal age 0.36 [0–17] years) 27 novel mRNA transcripts were detected. Of these, 13 were relevant: 2 isoforms are predicted to translate into amino acid sequences similar to the annotated isoform for OATP1B1, 9 isoforms may translate into truncated versions, and the expression of 8 isoforms was associated with age. None of the isoforms had an ORF that covered the *SLCO1B7* region.

Conclusion We showed that novel *SLCO1B1* mRNA isoforms potentially translate into OATP1B1 protein with unknown function, and that alternative splicing may well be a regulatory mechanism for *SLCO1B1* expression during development. This data provides a better understanding of age-related changes in

the expression of OATP1B1, and, with that, potentially improves prediction of disposition of endogenous and exogenous substrates.

Disclosure(s) BG was supported, in part, by the Ter Meulen fund 2018 provided by the Royal Dutch Academy of Sciences. The National Institute of Child Health and Human Development Brain and Tissue Bank for Developmental Disorders at the University of Maryland is funded by the National Institutes of Health (NIH) contract HHSN275200900011C, reference number, N01-HD-9-0011 and the Liver Tissue Cell Distribution System is funded by NIH contract number N01-DK-7-0004/HHSN267200700004C.

P103 TARGET ATTAINMENT OF AMIKACIN THERAPY IN CRITICALLY ILL CHILDREN

¹J Verbruggen*, ²K Jakipbayeva, ^{1,2}T Van Der Heggen, ^{2,3}E Dhont, ²L Dhondt, ^{4,5}J Vande Walle, ^{6,7}P De Paepe, ⁸I Herck, ^{2,3,4}P De Cock. ¹Department of Pediatrics, Ghent University Hospital; ²Heymans Institute Of Pharmacology, Ghent University; ³Department of Pediatric Intensive Care, Ghent University Hospital; ⁴Department of Internal Medicine and Pediatrics, Ghent University; ⁵Department of Pediatric Nephrology; ⁶Department of Emergency Medicine, Ghent University Hospital; ⁷Department of Basic and Applied Medical Sciences, Ghent University; ⁸Department of Cardiac Intensive Care, Ghent University Hospital, Ghent, Belgium

10.1136/archdischild-2019-esdppp.141

Background Research regarding the optimal amikacin (AMI) dosing regimen in critically ill children is scarce.¹ Optimal AMI efficacy has been observed with plasma peak over minimal inhibitory concentration of the suspected pathogen (peak/MIC) ratios of 8 to 10. Plasma trough levels (C_{min}) >5mcg/ml are related to its toxicity.

The objectives of this pilot study were to: (1) evaluate target attainment rate and occurrence of supratherapeutic concentrations in early and assumed steady-state dose conditions, and (2) investigate the correlation between AMI clearance and estimated glomerular filtration (eGFR).

Methods Children admitted to the ICU receiving intravenous AMI (20 mg/kg once daily) were included. Serial blood samples were obtained from early (1st/2nd) and assumed steady-state (SS) doses. The evaluated target peak concentration range was 54–64 mcg/ml, assuming a *Pseudomonas aeruginosa* infection with Eucast MIC breakpoint of 8 mg/L, and a C_{min} threshold of 5 mcg/L. eGFR was estimated using the modified Schwartz formula. AMI clearance was calculated using non-compartmental PK analysis. Correlation was assessed by means of a scatter plot and Pearson Correlation Coefficient (r).

Results

Twenty-one patients (median age 1,5 years; range:0,5 months–14 year, median eGFR 162 ml/min/1,73m² (range:107–475 ml/min/1,73m²) were included. In early dose conditions, 69% of patients had therapeutic peak concentrations (median: 60 mcg/ml; range:26–73 mcg/ml). In SS conditions, 60% of patients had therapeutic peak concentrations (median: 59 mcg/ml; range:35–83 mcg/ml). Only one supratherapeutic C_{min} was observed. AMI clearance (median 0.08L/h/kg; range: 0.05–0.91 L/h/kg) was comparable to what has been previously reported but showed no correlation with eGFR (r=0.1; p=0,66) [1].

Conclusion This pilot study suggest that the current AMI dosing regimen may lead to subtherapeutic concentrations in patients infected with less susceptible pathogens. Supratherapeutic C_{min} were far less of a concern. Dose adjustments of

renally cleared drugs based on eGFR may not be reliable in this patient population.

REFERENCES

1. Illamola SM, Sherwin CM, van Hasselt JGC. Clinical Pharmacokinetics of Amikacin in Pediatric Patients: A Comprehensive review of Population Pharmacokinetic Analysis. *Clin Pharmacokinet* (2018) **57**:1217.

Disclosure(s) Nothing to disclose

P104

PHARMACOLOGIC DIFFERENCES OF ADALIMUMAB, INFlixIMAB AND ETANERCEPT: DO WE NEED SPECIFIC VACCINATION RECOMMENDATIONS FOR PRENATALLY EXPOSED INFANTS?

^{1,2}T Welzel*, ¹V Gotta, ³N Rakhmanina, ^{1,4}JN van den Anker. ¹Pediatric Pharmacology and Pharmacometrics; ²Pediatric Rheumatology, University Children's Hospital Basel, University of Basel, Basel, Switzerland; ³Division of Infectious Diseases; ⁴Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, WA, USA

10.1136/archdischild-2019-esdppp.142

Background In pregnancy adalimumab (ADA) and infliximab (IFX) should preferentially be stopped at gestational week 20 and etanercept (ETN) at weeks 30–32¹ because of their steadily increased transplacental transfer during the late second and third trimester. Pregnant women with chronic inflammatory diseases are often treated throughout their entire pregnancy to prevent negative impact on pregnancy outcomes from the disease. Therefore, more infants are born with prenatal exposure and the question arises if and when live vaccines can be administered safely.

Methods We reviewed pharmacologic properties of ADA, IFX and ETN with regards to prenatal exposure and vaccine recommendations.

Results IFX is a chimeric and ADA a human anti-TNF-alpha antibody. Both have high binding affinity to the neonatal Fc receptor (FcRn).² ETN is a TNF-alpha receptor fusion protein with a 5–10 fold lower binding affinity to the FcRn compared with IFX/ADA.²

At delivery neonatal drug concentrations compared with maternal ones seem to be higher in prenatally exposed infants to IFX^{3–5} (median ratio of 1.97) and ADA (median ratio of 1.21),³ whereas neonatal ETN concentrations are lower.^{6,7} The mean time to drug clearance in IFX or ADA exposed infants is 7.3 months and 4 months, respectively.³ Drug concentrations are undetectable for IFX or ADA after 12 and 9 months of life, respectively.³ In infants exposed throughout the entire pregnancy ETN is undetectable after 3 months.⁷

Infants exposed to ADA, IFX and ETN before gestational week 22 can follow the normal vaccination schedule including live vaccines,¹ whereas live vaccines in infants exposed in the late second and third trimester should be avoided for 6–12 months of life.^{1,3}

Conclusion Pharmacologic differences of ADA, ETN and IFX require specific live vaccine recommendations for infants exposed prenatally to these drugs.

REFERENCES

1. Götestam Skorpen C, Hoeltzenbein M, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;**75**(5):795–810.

2. Porter C, Armstrong-Fisher S, et al. Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): Consequences for FcRn-mediated in vitro transcytosis and ex vivo human placental transfer. *J Reprod Immunol* 2016; **116**:7–12.
3. Julsgaard M, Christensen LA, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 2016;**151**(1):110–9.
4. Mahadevan U, Wolf DC, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*, 2013. **11**(3):286–92;quiz e24.
5. Zelinkova Z, de Haar C, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther*, 2011. **33**(9):1053–8.
6. Berthelsen BG, Fjeldsøe-Nielsen H, et al. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology (Oxford)* 2010; **49**(11):2225–7.
7. Murashima A, Watanabe N, et al. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. *Ann Rheum Dis* 2009; **68**(11):1793–4.

Disclosure(s) Nothing to disclose

P105

AMBULATORY STUDY CENTER AT THE UNIVERSITY OF BASEL CHILDREN'S HOSPITAL (UKBB)

C Werner*, R Santoro, J Bielicki. UKBB, Basel, Switzerland

10.1136/archdischild-2019-esdppp.143

Background Many drugs authorized in Europe and the United States are inadequately studied in children. SwissPedNet Funding has boosted the development of specialized and professional pediatric centers for clinical studies in Switzerland tasked with executing compliant, reliable and family-centered clinical research. The University of Basel Children's Hospital (UKBB) is one of the pediatric clinical study centers.

Methods The Department for Clinical Research in Basel consists of the study center for adults at University Hospital Basel (USB) and the Ambulatory Study Center (ASZ) focusing on pediatric studies at the UKBB. The latter was established in 2015, and consists of a specialized team, including a medical director, medical coordinator, medical specialists in pediatrics as well as a team of study nurses.

The ASZ supports and promotes clinical studies with and for infants and children for external and internal sponsors in various therapeutic areas such as oncology, cardiology, pneumology, nephrology, neuropsychiatry, orthopaedics and infectious diseases. The full range of activities for executing the approved clinical study protocol can be offered, including planning, implementation, budgeting, coordinating, monitoring and archiving as well as collaboration with all required hospital departments.

Results Up to now, the ASZ has enrolled around 600 children in clinical trials, with 6 studies completed and 12 studies ongoing. A comprehensive Quality Management system was established and SOPs were jointly created with the adult study center. A digital clinical study request form is available for sponsors via the website.

Conclusion We see an increased demand for pediatric clinical studies across all age ranges and therapeutic areas. We envision a center of excellence with a pool of fully trained study nurses to accommodate and centrally organize all pediatric studies in the UKBB. Parent engagement and patient inclusion is one critical step to further improving healthcare for pediatric patients through highest quality clinical research.