higher cost and less than optimum management of infectious diseases.

Objectives To determine the relative likelihood of true allergy in patients suspected to have a penicillin allergy and to investigate the risk factors involved. We hypothesized that the vast majority of self-reported penicillin allergies are less likely to be true allergies when proper immunological work up is performed.

Methods Paediatric patients aged 0–18 years presenting to the ADR clinic at the Children Hospital of Western Ontario (CHWO) with suspected antibiotic allergies were included. A retrospective review of charts was conducted to obtain demographic information and results from allergological and *in vitro* testing. Subjects were evaluated with a radioallergosorbent test (RAST) or the lymphocyte toxicity assay (LTA)/the *in vitro* platelet toxicity assay (*i*PTA) depending on whether the history was most consistent with an immediate allergy or a delayed hypersensitivity, respectively. Patients with negative RAST or LTA/iPTA were recommended to undergo confirmatory oral challenge test (OCT).

Results Ninety subjects were identified including 75 with possible penicillin allergy and 10 with suspected allergy to a non-penicillin antibiotic. Five subjects presented with a mixed allergy. Based on the results from RAST, *in vitro* testing and OCTs, the prevalence of a true allergy in the penicillin group was 6.25% vs. 66.67% in the non-penicillin group (p< 0.001). Patients presenting with severe reactions were more likely to be truly allergic (p< 0.01). In-patients were more likely to present with non-penicillin allergies and were subsequently more likely to have a true allergy (p< 0.001).

Conclusions True allergy is very rare in patients with suspected penicillin allergies and can be determined with a proper work-up including OCT. Shorter protocols for the evaluation of these patients would be beneficial.

Disclosure(s) Nothing to disclose

O04 FETAL OUTCOME FOLLOWING DYDROGESTERONE EXPOSURE IN PREGNANCY

G Koren*, D Gilboa. *Maccabi Research Institute, Tel Aviv*

Background The progestin dydrogesterone (DYD) is widely used for threatened and recurrent miscarriages, as well as for dysfunctional bleeding, infertility and other obstetric and gynecological indications. While its apparent efficacy has been compared to other progestins, its fetal safety has not been investigated.

Objectives To follow up fetal outcome after gestational exposure to DYD.

Patients and methods Using a 2.5 million patients' database, we compared congenital malformations among babies exposed *in utero* to DYD between 1999 and 2016, to a control group not receiving this medication. We adjusted for concomitant exposure to *in vitro* fertilization (IVF) and to other forms of assisted reproductive technology (ART).

Results There were 8508 children exposed *in uteo* to DYD (4417 males, 4091 females) out of 777,422 live births. After excluding cases with concomitant exposure to IVF and other forms of ART, DYD was associated with increased risk for hypospadias [OR 1.28(95% confidence interval 1.06–1.55)], overall cardiovascular malformations [OR 1.18 (1.06–1.33)], spina bifida [OR 2.29(1.32–3.97] and hydrpcephalus [OR 2.04

(1.28–3.25]. In additional analysis, including also those exposed to IVF and other forms of ART, there was also increased risk for cryptorchidism [1.37(1.19–1.58)] and congenital dislocation of the hip [OR 1.58(1.42–1.78)].

Conclusions DYD confers teratogenic effects after exposure to the recommended doses in pregnant women. Some of these adverse fetal effects are further augmented by concomitant use of IVF and other forms of ART. These independent teratogenic effects may have important implication for the child and family.

Disclosure(s) Nothing to disclose

O05 PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING TO CHARACTERIZE ACETAMINOPHEN PHARMACOKINETICS AND NAPQI FORMATION IN NON-PREGNANT AND PREGNANT WOMEN

[1,2]P Mian*[*], [3,4,5]JN van den Anker, [6,7]K van Calsteren, [8]P Annaert, [1]D Tibboel, [2,9]M Pfister, [3,11,12]K Allegaert, [13]A Dallmann. [1]*Pediatric Surgery and Intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands*; [2]*Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel, Basel, Switzerland*; [3]*Pediatric Surgery and Intensive Care, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands*; [4]*Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Basel, Switzerland*; [5]*Division of Pharmacology, Children's National Health System, Washington DC, DC, USA*; [6]*Department of Obstetrics and Gynecology*; [7]*Department of Development and Regeneration, University Hospitals Leuven*; [8]*Drug Delivery and Disposition, KU Leuven, Leuven, Belgium*; [9]*Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Basel, Switzerland*; [10]*Certara LP, Princeton, NJ, United States*; [11]*Department of Development and Regeneration, KU Leuven, Leuven, Belgium*; [12]*Department of Pediatrics, Division of Neonatology, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, The Netherlands*; [13]*Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Basel, Switzerland*

Background Little is known about the pharmacokinetics (PK) of acetaminophen during different stages of pregnancy. The aim of this study was to develop a physiologically based pharmacokinetic (PBPK) model to predict acetaminophen PK throughout pregnancy.

Methods PBPK models for acetaminophen and its metabolites were developed in non-pregnant and pregnant women. Physiological and enzymatic changes in pregnant women expected to impact acetaminophen PK were considered. The models were evaluated using goodness-of-fit-plots and through comparison of predicted PK profiles with in-vivo PK data. Predictions were performed to illustrate the concentrations at steady state ($C_{ss-mean}$), used as indicator for efficacy of acetaminophen achieved following 1000 mg q6h. Furthermore, as measurement for potential hepatotoxicity, the molar dose fraction of acetaminophen converted to NAPQI was estimated.

Results PBPK models successfully predicted the PK of acetaminophen and its metabolites in populations of non-pregnant and pregnant women. Predictions resulted in lowest $C_{ss-mean}$ in the third trimester (4.5 mg/L), while $C_{ss-mean}$ was 6.7, 5.6 and 4.9 mg/L in non-pregnant, first and second trimester populations, respectively. Assuming a constant increased activity of CYP2E1 throughout pregnancy, the molar dose fraction of acetaminophen converted to NAPQI was highest during the first (11.0%), followed by second (9.0%) and third trimester (8.2%), compared to non-pregnant women (7.1%).

Conclusion Risk for drug related hepatotoxicity in pregnant women might be increased as more NAPQI is produced during pregnancy compared to non-pregnant women, especially

during the first trimester. However, lack of information on the detoxifying capacity precludes any strong conclusions.
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O06 **METHADONE DOSING STRATEGIES IN PRETERM NEONATES CAN BE SIMPLIFIED**

[1]T van Donge*, [2]S Samiee-Zafarghandy, [1,3]M Pfister, [1]G Koch, [4]M Kalani, [4]A Bordbar, [1,5,6]J van den Anker. [1]*Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel (UKBB), Basel, Switzerland*; [2]*Department of Pediatrics, McMaster University, Ontario, ON, Canada*; [3]*Certara LP, Princeton, NJ, USA*; [4]*Department of Pediatrics, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran*; [5]*Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands*; [6]*Division of Clinical Pharmacology, Children's National Health System, Washington, DC, USA*

Aims A dramatic increase in newborn infants with neonatal abstinence syndrome has been observed and these neonates are frequently treated with complex methadone dosing schemes to control their withdrawal symptoms. Despite its abundant use, hardly any data on the pharmacokinetics of methadone is available in preterm neonates. Therefore we investigated developmental pharmacokinetics of methadone and evaluated current dosing strategies and possible simplification in this vulnerable population.
Methods A single center open-label prospective study was performed to collect pharmacokinetic data after a single oral dose of methadone in preterm neonates. A population pharmacokinetic model was built to characterize developmental pharmacokinetics of methadone and to assess the effects of weight and age on clearance and volume of distribution. In addition, simulation techniques were applied to evaluate reported dosing scenarios, investigate methadone exposure levels and examine the feasibility of simplified dosing recommendations.
Results In total, 121 methadone concentrations were collected from 31 preterm neonates. The median weight and gestational age amounted 1.6 kg and 32 weeks, respectively. A one-compartment model with first order absorption and elimination kinetics best described the data for (R)- and (S)-methadone. Clearance was observed to be higher for the (R)-enantiomer as compared to the (S)-enantiomer (0.244 versus 0.167 L/h). Target exposures, based on simulations, can be maintained with a simplified dosing strategy during the first four days of treatment. It is therefore questionable if there is a need for the currently used more extended dosing regimen of methadone in neonates.
conclusions This clinical investigation demonstrates that the clearance of methadone increases with advancing gestational age and higher clearance values and volumes of distribution can be observed for (R)-methadone as compared to (S)-methadone in preterm neonates. Simulations that account for developmental pharmacokinetics indicate that a simplified

methadone dosing strategy can maintain target exposure to control withdrawal symptoms in preterm neonates.
Disclosure(s) Nothing to disclose

O07 **PREDICTIVE PERFORMANCE OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL OF CAFFEINE IN THE PRETERM POPULATION**

A Pansari*, K Abduljalil, T Johnson. *Simcyp Division, Certara UK Limited, Sheffield, UK*

Background Caffeine has been extensively used in the treatment of apnoea in premature infants,[1] its disposition varies with postnatal age[2] and can differ markedly between premature and term neonates.
Methods The Preterm population within the Simcyp Simulator V18R1 population library was used to replicate clinical studies to predict caffeine exposure after single[3] and multiple[4] intravenous administration to preterm neonates of gestational weeks 28.5 and 29 (28–33) respectively, ranging in postnatal age of 3–30 days and 0–3 days respectively. Predictive performance of the Physiologically Based Pharmacokinetic Model (PBPK) was evaluated by comparing the simulated to the clinical results. A population simulation was performed for the single dose study as only pharmacokinetic parameters were available. However, for multiple doses study, where individual plasma concentration-time profile data were available, simulations were performed for each individual.
Results PBPK model predictions for caffeine in preterm neonates were in good agreement with the clinical observations. In the case of single dose administration, the ratios of predicted vs observed mean Volume of distribution (Vss), peak plasma concentration (Cmax), Clearance (CL) and Half-life ($t_{1/2}$) were 1, 1.2, 1 and 1.1, respectively. Individual predicted concentration-time profiles following multiple dose administration were in close agreement with the observed data for all 16 subjects, overall 95% of individual observed data points were within the 5th and 95th percentile of predicted plasma concentration-time profile.
Conclusions The predictive performance of preterm PBPK models for caffeine was found to be appropriate. A similar PBPK approach can be utilized in the clinics for the accurate prediction of pharmacokinetic parameters and plasma concentrations and for dosage adjustment to attain specific plasma concentrations of drugs in premature population.

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