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ORAL PRESENTATIONS

001 DRUG-RELATED HOSPITAL ADMISSIONS IN PAEDIATRICS – WHAT IS PREVENTABLE?

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Background Safety of paediatric pharmacotherapy is of major concern. Due to high off-label use (about 46–64% of patients in primary care are affected), missing paediatric dosage forms and complex dosage calculations, adverse drug reactions (ADR) and medication errors (ME) occur more often in children.^{1–3} Moreover, it is estimated that 3 to 5% of paediatric hospital admissions are drug-related.^{3–7}

The aim of the present study was to systematically investigate the nature and preventability of drug-related hospital admissions in paediatrics.

Methods An observational study was carried out for 10 months at the Department of Paediatrics and Adolescent Medicine Erlangen, Germany. All patients aged 0 to <18 years, admitted during the study period and treated for at least 24 hours at the general paediatric ward were assessed and analysed with regard to ADR and ME requiring hospitalisation. The identification of these was based on intensive chart review. Seriousness was assessed using the ICH E2A criteria.⁸

Results 741 patients fulfilled the inclusion criteria and were screened for ADR and ME leading to hospital admission. Median age of patients was 7 years (IQR 1 – 13) while duration of stay was 2 days (IQR 2 – 4) at median level. In total 50 events were discovered in relationship to drug intake before hospitalisation; 41 (82.0%) of these were assessed with the seriousness criterion 'requires inpatient hospitalisation', while 23 (56.1%) events were preventable and therefore considered as ME. The incidence of drug-related hospital admissions was 5.5%.

Conclusions This study confirms that drug-related hospital admissions pose a significant problem in children and adolescents, however more than 50% of them were considered preventable. Increasing awareness towards paediatric pharmacotherapy and providing standardised guidance may help to reduce the risk for drug-related hospital admissions.

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Disclosure(s) Nothing to disclose.

002 DEVELOPMENTAL PHARMACOGENETICS OF SLCO2B1 ON MONTELUKAST PHARMACOKINETICS IN CHINESE CHILDREN

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Background Montelukast, a potent orally selective leukotriene-receptor antagonist, inhibits the action of cysteinyl-leukotriene in patients with asthma. Although pharmacokinetic studies of montelukast have been reported in Caucasian adults and children, and showed significant inter-individual variability on pharmacokinetics. None of pharmacokinetic study has been explored in Chinese children. Given the potential inter-ethnic difference, the purpose of this study was to evaluate the effects of developmental factors and pharmacogenetics of CYP2C8 and SLCO2B1 on Montelukast pharmacokinetics in Chinese paediatric patients.

Methods After oral administration with montelukast, opportunistic samples were collected from asthma children and plasma concentrations were determined by high performance liquid chromatography coupled with fluorescence detector (HPLC-FLD) method. Population pharmacokinetic analysis was performed using a nonlinear mixed-effects model approach (NONMEM V 7.2.0) and variants of CYP2C8 and SLCO2B1 were genotyped.

Results Fifty patients (age range 0.7–10.0 years) with asthma were enrolled in this study. The clearance of montelukast was significantly higher in subjects with SLCO2B1 c.935GA and c.935AA genotype compared with SLCO2B1 c.935GG subjects (0.94 ± 0.26 versus 0.77 ± 0.21 , $p = 0.020$). Weight was also found to be significantly corrected with montelukast clearance ($p = 0.0001$).

Conclusions The developmental pharmacogenetics of montelukast in Chinese children was evaluated. Weight and SLCO2B1 genotype showed independently significant impacts on the clearance of montelukast.

Disclosure(s) Nothing to disclose.

003 ALLERGY TO PENICILLINS IN A PEDIATRIC POPULATION: REPORTED VS TRUE

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Background Reported allergy to penicillins is a major clinical problem. Over 10% of parents report drug allergy resulting in

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 (iPTA) 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

004 FETAL OUTCOME FOLLOWING DYDROGESTERONE EXPOSURE IN PREGNANCY

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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 utero* 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

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

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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