P72

MATURATION OF SILDENAFIL CLEARANCE IN PREMATURELY BORN INFANTS WITH BPD ASSOCIATED PULMONARY HYPERTENSION

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Background Sildenafil is used as an off-label treatment for bronchopulmonary dysplasia (BPD) associated pulmonary hypertension in prematurely born infants. As there is only limited information on the pharmacokinetics (PK) of sildenafil in this population, the aim of this study is to investigate the PK of sildenafil in prematurely born infants with BPD associated pulmonary hypertension.

Method In this multicentre study, a population PK model for sildenafil in prematurely born infants was developed based on samples obtained using opportunistic sampling during clinical use of sildenafil. Data of seven subjects (42 plasma samples) were analysed by nonlinear mixed-effect modelling (NONMEM[®]7.3). Median (range) gestational age (GA) was 26.1 (24.1–27.6) weeks, current bodyweight 1960 (632–3157) grams, birthweight 635 (465–1125) grams and postnatal age (PNA) at start of therapy 64.9 (10.9–89) days. The median (range) treatment duration was 4.9 (1.6–13.1) weeks, with six subjects receiving oral doses of median 2.6 mg/kg/day (1.5–5.3) in three doses and one subject receiving oral and intravenous doses of 6.7 mg/kg/day in two doses.

Results The plasma concentration time profiles of sildenafil were best described by a one compartment model. Clearance (CL) and volume of distribution (Vd) for a child with a PNA of 64.9 days and bodyweight of 1.96 kg was 4.42 L/h (RSE) 11%) and 29.5 L (32%), respectively. PNA was found to significantly influence CL, resulting in an increase of 10.7% in a week, and 43% in a month for a 65-day old infant. No other covariates (i.e. bodyweight, birthweight, GA, postmenstrual age and sex) were identified for CL or Vd.

Conclusion In this PK study, we characterised the pharmacokinetics of sildenafil in prematurely born infants and found that clearance increases with PNA. Due to the limited sample size in this study, further research in a larger population is needed to extend these findings.

Disclosure(s) Nothing to disclose

P73

PAEDIATRIC POPULATION PHARMACOKINETIC MODELING FOR GENTAMICIN – IS THE CURRENT DOSE RECOMMENDATION JUSTIFIED?

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Background Monitoring of gentamicin serum trough level (Cmin) is standard practice in children to prevent toxicity by accumulation¹. Cmin < 2 mg/L are recommended. Peak serum concentration (Cmax) is not routinely measured although

Cmax between 10 and 12 mg/L have been recommended balancing efficacy and toxicity^{2,3}. We aimed to develop a population pharmacokinetic (PK) model for gentamicin in children to optimise current dosing regimens.

Methods All patients receiving once daily intravenous gentamicin (5 mg/kg in children < 7 days and 7.5 mg/kg in children > 7 days of age) at the University Children's Hospital Zurich between 10/2017 and 01/2019 were eligible for this study. Children with cystic fibrosis and renal replacement procedures were excluded. Routine Cmin were measured in all patients before administration of the second or third dose. Additional gentamicin serum levels were measured 30 min (C30) and 4 h after the second dose in patients giving written informed consent. Data were analysed by non-linear mixed-effects modeling.

Results 165 patients (median age 34 days; IQR 15–56 days) were included in the study. A total number of 103 C30 and 166 Cmin measurements were available, respectively. C30 (mean 19.7 mg/L, SD ±6.1 mg/L) was >12 mg/L in 94/103 (91%) and Cmin > 2 mg/mL in 3/166 (1.8%) measurements. The PK model successfully predicted most C30 >12 mg/L but performed poorly at the trough levels.

Conclusions Our current gentamicin dosing regimen rarely leads to accumulation but most Cmax are above optimal range. The latter was successfully modelled. Although no evidence for a Cmax upper limit exists, toxicity has been associated with high drug exposure³. This calls for an adjustment of our dosing regimen using our PK model based on body height or weight in order to lower exposure. Further studies investigating the relationship between Cmax levels and clinical outcome and additional data for PK model testing are needed for validation.

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P74

RITUXIMAB EFFECT ON B CELL DEPLETION IN PAEDIATRIC PATIENTS WITH AUTOIMMUNE DISEASES: A RETROSPECTIVE DOSE-RESPONSE ANALYSIS OF AN OBSERVATIONAL STUDY

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Background Rituximab is a chimeric IgG1 monoclonal antibody that depletes B cells for the treatment of several conditions including autoimmune diseases. It is not licensed for use in children but administered off-label. This study aimed to quantify the effect of rituximab on B cell depletion in children with autoimmune diseases and to optimise the dosing regimen.

Methods Electronic health record data were collected from a retrospective and anonymised study at Great Ormond Street

Hospital in London. Dosing protocols of rituximab were two 750 mg/m² intravenous infusions or four weekly 375 mg/m² infusions. Serum concentrations of rituximab were not measured. CD19+ lymphocyte counts were taken before and after rituximab treatment. A turnover mechanism described the life cycle of CD19+ lymphocytes with rituximab increasing the death rate of CD19+ lymphocytes; a negative feedback was added on the production rate to examine the rebound effect. Rituximab was assumed to decay by first-order kinetics.

Results 258 measurements of CD19+ lymphocyte counts were collected from 39 children with 8 autoimmune diseases. The dose-response model well described the time course of CD19+ lymphocytes following rituximab administration. The elimination half-lives of rituximab and CD19+ lymphocytes were estimated to be 19 and 35 days, respectively, consistent with findings from other studies [1–5]. The rebound increase in CD19+ lymphocytes was found negligible. Methotrexate and cyclophosphamide increased the maximum death rate by 66% and 38% respectively. Age and gender were not significant covariates.

Simulations from the model suggested that a single infusion of rituximab of 375 mg/m² can provide similar six-month suppression of CD19+ lymphocytes to the higher doses currently used. Methotrexate or cyclophosphamide added minimal suppression effect on CD19+ lymphocytes when taken concurrently with rituximab.

Conclusions Our results could be used in future to assess the effect of rituximab biosimilars and to inform biosimilar dosing in paediatric populations.

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P75 RELATION BETWEEN POLYMORPHISM OF FOLIC ACID CYCLE GENES AND EFFECTIVENESS OF METHOTREXATE IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background Methotrexate (MTX) is the basic treatment of patient with Juvenile Idiopathic Arthritis (JIA), but effectiveness of this therapy is different. We aimed to study effectiveness of MTX in children with JIA with different genotypes of folic acid cycle genes.

Methods The study included 8 patients with JIA. For determination of MTX effectiveness the American College of Rheumatology pediatric criteria (ACR-pedi) was used. Patients were divided into 2 groups according the effectiveness of MTX treatment. Group I included 4 patients, who were non-responders because ACR-pedi was less than 10%. Second group contained 4 patients, who had ACR-pedi more than 10%. The megerment of genotypes of genes of folate cycle, such as 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR), 5,10methylenetetrahydrofolate reductase C677T

and A1298C variants (MTHFR-677 and MTHFR129) by polymerase chain reaction (PCR) was performed for all patients.

Results In II group effectiveness of therapy according ACR-pedi was from 30% to 70% in 75% of children and more then 70% - in 25% of patients. In general, MTR gene indicated AA-genotype in 50% of patients, AG and GG-genotypes - in 25%; MTRR gene was performed with AA-genotype in 25%, AC-genotype in 12.5% and CC-genotype in 62.5%. MTHFR1298 gene was presented in 50% of patients with AA-alleles, in 25% - with AC and CC-genotypes. 50% of children had CC-genotype of MTHFR677 gene and other 50% - AC-genotype of MTHFR677 gene. CC-genotype of MTHFR1298 gene more frequently was determined in II group ($p < 0.01$). In group of non-responders AA-genotype of MTR gene was found more frequent in comparison with patients from group II ($p < 0.01$).

Conclusion Response to standard therapy in patients with JIA depends on time of prescription of MTX and genotype of MTHFR1298 and MTR genes.

Disclosure(s) Nothing to disclose

P76

THE EFFECT OF THE PREGNANCY AND LACTATION LABELING RULE ON PRESCRIBING INFORMATION OF FDA-APPROVED DRUGS

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Background The U.S. Food and Drug Administration implemented the new Pregnancy and Lactation Labeling Rule (PLLR) in June 2015. Under PLLR, all new drug applications were to present a narrative risk assessment (as opposed to letter category), while drug approvals after June 2001, were required to phase in by June 2020. The purpose of this study was to assess the quality of presented pregnancy and lactation data in the drug labeling and degree of adherence to the PLLR.

Design/Methods We reviewed the labeling data of all new molecular entities (NMEs) approved from 1999–2017. The pregnancy and lactation information was classified as: 1. Harmful to use 2. Safe to use 3. Consideration of safety and efficacy. For drugs approvals after June 2001, presence of pregnancy letter category system was noted.

Results Of the 456 NMEs, 131 (29%) were classified as harmful to use in pregnancy and 207 (45%) as harmful to use during lactation. This number did not follow any specific pattern over the course of 19 years. Less than 1% of drugs were deemed to be safe during pregnancy or lactation. Human data was the source of pregnancy or lactation information for only 2% of drugs. Up to 70% of drugs belonged to each implementation schedule has yet to meet the PLLR compliance requirement.

Conclusion(s) Pregnant and lactating women are mostly advised against use of medications that might be needed for their health and health of their infants based on very limited data. Pharmaceutical companies lagged behind the required adherence rule for labeling updates on pregnancy and lactation information.

Disclosure(s) Nothing to disclose