treatment interruptions and/or reduced dose were at risk of relapse.

Disclosure(s) Nothing to disclose

P04

NON-COMPARTMENTAL ANALYSIS OF VANCOMYCIN PHARMACOKINETICS IN CRITICALLY ILL CHILDREN

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Background Vancomycin is often used as the drug of choice in the treatment of bacteria that are methicillin resistant or in patients sensitive to penicillin. This study describes the pharmacokinetics of vancomycin in critically ill children.

Methods Children aged 1 month to 16 years admitted to the paediatric intensive care unit of the Red Cross War Memorial Hospital and on vancomycin treatment for ≥ 24 hours and ≤ 72 hours were prospectively recruited. Blood samples were collected around predetermined optimal sampling times. A minimum of three samples per patients was analysed. Non-compartmental analysis was used to determine the volume of distribution (V), clearance (CL), half-life ($t_{1/2}$), area under the concentration-time curve (AUC), elimination constant (Ke) and Mean residence time (MRT). The minimum concentration (Cmin) and maximum concentration (Cmax) of vancomycin were measured directly as trough and peak plasma concentration respectively. Analysis of data was performed using PKNCA version 0.8.5 in R.

Results Forty-nine serum concentrations from 10 patients were included in the analysis. The ratio of male to female was 1:1. Median age (Range) was 1.6 (0.2–15) years, weight = 10.6 (3.1–31.3) kg, baseline serum creatinine (Scr) = 0.31 (0.15–0.78) mg/dL. Patients received daily vancomycin doses ranging from 56 to 78 mg/kg. Mean PK parameters (range) were as follows: CL = 0.12 ± 0.15 (0.018–0.52) L/h/kg, V = 0.68 ± 0.47 (0.15–1.57) L/kg, Ke = 0.147 ± 0.073 (0.07–0.33) h⁻¹, $t_{1/2}$ = 5.54 ± 2.03 (2.11–9.62) h, MRT = 8.02 ± 2.92 (3.04–13.88) h, AUC = 322.07 ± 245.65 (31.6–850.4) mg/L.h, Cmin = 6.21 ± 3.66 (2.0–14.5) mg, Cmax = 38.91 ± 31.92 (10.4–97.2) mg. Trough concentration and AUC were not met in $>80\%$ and $>75\%$ of the patients.

Conclusion Variability in vancomycin pharmacokinetics was observed in patients. At current doses, target trough concentrations and AUC were not met.

Disclosure(s) Nothing to disclose

P05

ESTABLISHING THE INTEGRITY OF THE CONTINUALLY PAEDIATRIC PHARMACOKINETIC BIOANALYSIS FOR CLINICAL TRIAL WITHIN AN ACADEMIA ENVIRONMENT USING QUALITY ASSESSMENT PROCESS

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Background European Medicines Agency (EMA) outlines criterion for validation of bioanalytical assay applied under Good Clinical Laboratory Practice (GCLP) within clinical studies. The validation is performed once and does not inevitably ensures comparable reliability over long duration of assay's

applicability. To address this hurdle, the investigator-driven 'Labelling of Enalapril from Neonates up to Adolescents' project (LENA) adapted quality system comparable to industry. A comprehensive set of quality measures was applied to ensure reliability of monthly quantified paediatric samples over duration of 31 months.

Methods A 3-step quality approach analysing the calibration standards (CS), quality controls (QCs) and incurred sample reanalysis (ISR) was used to established reliability of unknown samples. Unknown concentrations were reported only if results of known CS (11 levels) and QCs were within the predefined limits. A maximum deviation of $\pm 15\%$ was acceptable at all five QCs level. ISR was conducted for randomly selected paediatric samples to monitor the assay's performance over time. The acceptable difference was $\pm 20\%$ for at least 67% of the ISR according to international guidelines.^{1,2}

Results 38 analytical runs were conducted for two drugs (enalapril/enalaprilat) from February 2016 to August 2018. Calibration curve evaluation accounted for exclusion of four enalapril and five enalaprilat runs. Additional investigation of QCs resulted in further exclusion of two enalapril and one enalaprilat runs. Within 32 valid runs 820, QCs were measured for enalapril and enalaprilat. 94% enalapril and 89% enalaprilat QCs were within limits ($\pm 15\%$). This set ensured reliable determination of 1262 LENA paediatric study samples. 93 and 104 incurred samples for enalapril and enalaprilat were reanalysed. ISR for enalapril (70%) and enalaprilat (67%) was also within guidelines.^{1,2}

Conclusion The analysis of bioanalytical data ensured the reliability of reported unknown concentrations. It ensured consistent and reliable pharmacokinetic data from first to the last LENA study patient.

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P06

PATERNAL EXPOSURE TO METHOTREXATE AND THE RISK OF MISCARRIAGE – A REGISTER BASED NATIONWIDE COHORT STUDY

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Objective To study the association between paternal exposure to methotrexate within three month before conception and during the first trimester of pregnancy and the risk of miscarriage.

Methods We conducted a nationwide cohort study identifying all registered pregnancies in Denmark from 1997 to 2015. All births were identified using the Medical Birth Registry, and all records of induced abortion and miscarriage were from the National Hospital Register. Data on drug use were from the

National Prescription Register. Cox proportional hazard regression models were used to calculate the hazard of miscarriage in women with a partner exposed to methotrexate. The study was approved by the Danish Data Protection Agency (2015-41-4309). **Results** We identified 1,364,063 registered pregnancies with known paternity, of whom 520 fathers were exposure to methotrexate within the three months before conception to the end of the first trimester. Among these, 46 (8.9%) experienced a miscarriage compared to 122,926 (9.0%) among the unexposed.

There was no increased risk of experiencing a miscarriage in pregnancies to men exposed to methotrexate before pregnancy compared to unexposed (adjusted hazard ratio 0.99 (CI95% 0.67- 1.46)). Furthermore, we found no increased risk of experiencing a miscarriage in pregnancies to men exposed to methotrexate during first trimester compared to unexposed (adjusted hazard ratio 0.90 (CI95% 0.61-1.32)).

Conclusion We found no association between paternal exposure to methotrexate before and during early pregnancy and miscarriage. Available data suggest that paternal methotrexate exposure should not be of major concern. Multinational recommendations could be changed accordingly.

Disclosure(s) Nothing to disclose

P07

ROXITHROMYCIN IN EARLY PREGNANCY AND THE RISK OF MAJOR CONGENITAL MALFORMATION: A REGISTER BASED NATIONWIDE COHORT STUDY

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Background Medicine use during pregnancy often causes concern for fetal harm. Roxithromycin, a macrolide antibiotic, is regarded as inadvisable to use during pregnancy due to lack of safety data. However, alternative macrolides have been associated with adverse outcomes in pregnancy. We conducted a register-based nationwide cohort study testing the hypothesis that use of roxithromycin in the first trimester is associated with major congenital malformations.

Methods We included all Danish women giving live birth from 1997 to 2012. Women with at least one redeemed receipt of roxithromycin during first trimester were regarded as exposed. Multivariable logistic regression adjusting for maternal age, multiple birth, parity, year of conception, smoking, educational length, and household income was performed, supplemented by sensitivity analyses comparing unexposed with exposure to increasing accumulated doses of roxithromycin.

Results The study included 966,372 pregnancies of which 2,430 children were born to an exposed mother, 78 (3.34%) of the exposed children were diagnosed with a major congenital malformation compared with 33,609 (3.49%) among children born to unexposed mothers. The odds ratio for the occurrence of a major congenital malformation after exposure to roxithromycin was 0.96 (95% CI 0.76-1.20) and multivariationally adjusted 0.94 (0.74-1.18). Sensitivity analyses comparing unexposed with exposure to increasing accumulated doses of roxithromycin showed no dose response relationship. Further, no differences in the type of major malformation according to the EUROCAT subgrouping system were seen.

Conclusions We found no association between exposure to roxithromycin in the first trimester of pregnancy and major congenital malformations.

Disclosure(s) Nothing to disclose

P08

IS THERE A DIFFERENCE IN THE FREQUENCY OF MANIPULATED ORALLY AND RECTALLY ADMINISTERED MEDICINES TO PAEDIATRIC IN-PATIENTS IN SWEDEN IN THE YEAR 2009 AND 2018 RESPECTIVELY? A REGISTER STUDY

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Background Since there is a lack of drugs in suitable strengths and child-friendly dosage forms, manipulation is sometimes necessary in paediatrics. A manipulation is the physical alteration of a drug dosage form with the purpose to extract and administer the prescribed proportion of a drug dose.

The purpose of this study was to calculate the frequency of manipulated medicines administered to paediatric in-patients at a large Children's Hospital for two separate years and compare whether there has been a change in practice.

Material and Methods Data were collected for all administered doses during 2 separate years (2009 and 2018) at the paediatric wards at our Children's Hospital, from a hospital-based electronic register. All administered doses where the number of tablets or suppositories were decimal were added and calculated as a percentage of the total number of oral and rectal administrations. Data are anonymous but information regarding gender, age, hospital ward and number of drugs per patient were available and were analysed.

Results In one year, approximately 450 000 doses of medicine are administered to paediatric patients in our Children's hospital.

The results will be analysed with regards to differences between patient age, gender, prescribing year and drug substance. A pilot study showed that 10% of all solid oral administrations to patients 6 - 12 years old, were part of a tablet. For patients 0 - 2 years over 20% of all solid rectal administrations were part of a suppository.

The extent of manipulation is affected by a lot of factors, where the most prominent is whether there are strengths suitable for that age-group available on the market or not.

Conclusion Most often there is a lack of knowledge how manipulation of medicines influences the dosing accuracy and often we do this to our most vulnerable patients.

Disclosure(s) Nothing to disclose

P09

SERUM NEUROFILAMENT LIGHT CHAIN LEVELS ARE AN INDEPENDENT PREDICTOR OF NEURODEVELOPMENTAL OUTCOME IN PRETERM INFANTS

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