P62 POPULATION PHARMACOKINETIC STUDY OF AMINOPHYLLINE IN INDIAN PRETERM NEONATES (≤34WEEKS) WITH APNOEA; A LONGITUDINAL OBSERVATIONAL STUDY

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Background Current dosage regimen of aminophylline is similar in both Appropriate for Gestational Age (AGA) and Small for Gestational Age (SGA) preterm neonates.[1] In contrast with AGA babies, SGA babies handle drugs in different way. However, developing countries like India has significant proportion of Growth Restricted/SGA babies. Hence, there is a need to develop appropriate dosage regimen in this population. Objective of the current study was set to develop and qualify the Population-Pharmacokinetic (PPK) model for aminophylline in premature neonates in Indian population.[2]

Methods Aminophylline-treated neonates with IV loading dose of 5 mg/kg followed by maintenance dose of 1.5 or 2 mg/kg 8th hourly for Apnoea of Prematurity (AOP) were included. Any other conditions for secondary causes were excluded. Blood samples were collected by adopting sparse sample scheme and estimated by LCMS-MS. PPK model was developed with appropriate covariates.[3] Data was analysed by NONMEM vesion 7.3. Non-parametric bootstrap procedure and Visual Predictive Check (VPC) was used to qualify the developed model.

Results One compartment, first-order structured model was fitted to the dataset containing 454 observations from 107 neonates. PPK parameters were represented as model estimated values and variability was depicted as% Co-efficient of variation (%CV). Typical population value of CL was 0.011 L/hour with inter-individual variability (IIV) of 59% and V was 0.332 (L/kg) with 31% IIV. Residual error was found to be 19%. Only postnatal age (PNA) had significant effect on V which was assessed by forward addition and backword elimination regression model.

Conclusion AGA and SGA had no influence on PK parameters. However, PNA showed to have significant influence on V. Developed nomogram based on the qualified model may be effective and safe for aminophylline therapy in preterm neonates with apnoea.

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P63 UPLC/MS/MS ASSAY FOR THE SIMULTANEOUS DETERMINATION OF SEVEN ANTIBIOTICS IN HUMAN SERUM – APPLICATION TO PEDIATRIC STUDIES

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Background Antimicrobials are widely used in children but pediatric dose regimens are not always validated, and PK studies, required to validate dosage, are difficult to conduct in children. Low sampling volume limits the number of PK samples drawn per patient and analytical methods adapted to small volumes are not always available. Due to the wide inter-patient pharmacokinetic (PK) variability in children, particularly neonates, therapeutic drug monitoring is required to adapt dosage to individual patients. In such clinical and analytical context, our aim was to develop a unique, rapid and highly sensitive ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) assay to quantify 7 antibiotics (amoxicillin, azithromycin, cefotaxime, ciprofloxacin, meropenem, metronidazole and piperacillin) in low sample volumes (50 µL) for both routine monitoring and pharmacokinetic studies.

Methods After protein precipitation by acetonitrile, the antibiotics and their associated deuterated internal standard were separated on a Waters Acquity UPLC HSS T3 (100 mm x 2.1 mm; 1.8 µm). The mobile phases consisted of a gradient of ammonium acetate (pH 2.4; 5mM) and acetonitrile acidified with 0.1% (v/v) formic acid (started ratio of 93:7, v/v), run at 0.5 mL/min flow rate (total run time: 2.75 min). Ions were detected in the turbo-ion-spray-positive and multiple-reaction-monitoring modes.

Results This method was linear from 0.1–50 µg/mL. Accuracy and precision were evaluated using Quality Control (2, 10, 35 µg/mL). Validation of the method proved that precision, selectivity and stability were all within the recommended limits.

Conclusion This method has the advantage of a unique, efficient and standardized analytical tool for rapid measurement of 7 antibiotics in low blood volume. It has been successfully applied for routine activity and pharmacokinetic studies in children and neonates.

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P64 QUALITY ASSESSMENT FOR THE CONTINUOUS BIOANALYSIS OF ALDOSTERONE: APPLICATION IN AN EUROPEAN PAEDIATRIC STUDY

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Background A validation is crucial to ensure the quality of an analytical method and its results. However, the validation is only a first step, further quality assessment has to be utilised

to ensure high quality research. Specifications for the validation process, but also for the assessment of data, acquired in a study setting, are given by the EMA and FDA to ensure highest quality of the data.[1 2]

Methods A multi-level analytical quality system was established. Data of the calibration standards (CSs), quality control samples (QCs), and incurred sample reanalysis (ISR) were evaluated according to the specifications given by the EMA and FDA guidelines.[1,2] For a run to be considered valid ≥6 levels or 75% of the CSs and 67% of the QCs (≥50% per level) had to vary ≤±20% (LLOQ ≤±25%) from their nominal concentration.[1,2] For the ISR analysis at least 67% of the ISR samples have to lay in ±30% to the nominal concentration of the mean of the original and reanalysed value.[1]

Results Seventy analytical runs were conducted, applying the quality measures, 79% runs were classified as valid and were used to determine unknown samples in a paediatric study. The high quality of the acquired data is reflected in the high conformity of the CSs and QCs to the EMA and FDA guidelines, 99% of the CSs and 95% of the QCs were accepted. Further underlining the high quality of the acquired data, 85% of the IRS have also been accepted. The assay was successfully used over a time period of 29 months.

Conclusion The results of the quality assessment confirmed the robustness of the aldosterone assay throughout the whole study duration. Thus, the samples measured by this assay are reliable and facilitate the high quality research in the paediatric population.

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P65 DIFFERENTIATING ALPROSTADIL ASSOCIATED FEVER FROM INFECTIOUS FEVER: A RETROSPECTIVE CASE-CONTROL STUDY OF NEONATES WITH DUCTUS DEPENDENT CONGENITAL HEART DISEASE IN A TERTIARY CARE CENTER

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Background Alprostadil is used to maintain ductus patency in neonates with ductus dependent congenital heart disease (CHD), until corrective surgery. Fever is a common side effect of alprostadil and may also be a sign of infectious disease. We aimed to identify potential parameters that may differentiate infectious from alprostadil fever.

Methods Retrospective case-control study included all neonates with ductus dependent CHD, who were admitted at the Children´s Hospital in Ramat-Gan, Israel, from August 2003 to August 2017 and developed fever on alprostadil. Cases were defined as neonates with a positive bacterial culture and controls were defined as neonates with a negative culture. Multivariate cox-regression was conducted to identify potential parameters that may differentiate alprostadil from infectious fever.

Results Three hundred and four neonates developed fever under alprostadil. Fifty five (18%) had a positive bacterial culture and 249 (82%) had a negative culture. In univariate analysis, the duration of alprostadil infusion was 95 hours (IQR 45–116) in the case group and 72 hours (IQR 49–215) in the control group (p=0.011). The time between alprostadil initiation and fever was longer for the case group: 14.13 hours (IQR 6.5–47.5) versus 12.96 (IQR 5–30.51), (p=0.039). In multivariate cox-regression, a more than 10% increase in neutrophil count before fever was significantly associated with an increased risk for infection (HR 6.14, 95% CI 1.94–19.42). A trend towards an association was observed with CRP ≥ 10 mg/dl before fever (HR 2.5, 95% CI 0.66–9.47) and in an increase ≥ 1000 micromol/L in WBC before fever (HR 1.74, 95% CI 0.58–5.21).

Conclusions In neonates with CHD on alprostadil therapy, an increase in neutrophil count before the appearance of fever is associated with infection. Full sepsis work-up and is still warranted in neonates who develop fever under alprostadil. Further larger studies are needed to fully establish these results.

Disclosure(s) The authors have no conflict of interests to disclose.

P66 CHARACTERIZATION OF THE PHARMACOKINETICS OF ACETAMINOPHEN AND ITS METABOLITES IN THE FETUS THROUGH INTEGRATION OF PLACENTAL TRANSFER IN A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL

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Background Little is known about fetal acetaminophen (paracetamol) pharmacokinetics and its potential for toxicity, despite the frequent use of acetaminophen during pregnancy. The aim of this study was to develop a feto-maternal physiologically based pharmacokinetic model (f-m PBPK) to predict placental transfer and PK of acetaminophen and its metabolites in fetus at term pregnancy.

Methods Previously, a pregnancy PBPK model was developed for prediction of maternal PK of acetaminophen and its metabolites. This model was structurally extended with the fetal liver, and quantitative information on the maturation of relevant enzymes was integrated. Three different approaches (ex vivo placenta perfusion experiments, scaling of passive diffusion transfer rates, and the Mobi® default method) to describe placental drug transfer were tested. Predicted