Methods A semi-mechanistic adult PK model for a novel HC formulation4 has previously been reduced to a paediatric model using sparse plasma samples from a phase III study in 24 patients with adrenal insufficiency5. Plasma and DBS concentrations of cortisol were collected and additional DBS HC concentrations were obtained from a follow-up study. The relation between plasma and DBS samples was characterised by a graphical evaluation, after which nonlinear mixed-effects modelling was applied using NONMEM 7.4.

Results Plasma concentrations of cortisol were substantially higher than the corresponding DBS concentrations. The plasma/DBS ratio ranged between 2 to 8 within and between children, while the relation between the cortisol DBS concentrations and cortisol plasma concentrations showed nonlinear behaviour mirroring the nonlinear binding kinetics to CBG.

Conclusions Our graphical analysis identified substantial differences and high inter- and intraindividual variabilities between plasma and DBS samples. A nonlinear mixed-effects model is needed to evaluate cortisol replacement therapy prediction of HC exposure. Afterwards, effect biomarkers can be included in order to evaluate cortisol replacement therapy and to optimise the HC treatment in paediatric patients.

REFERENCES

Disclosure(s) Nothing to disclose

P94 RELIABLE ACQUISITION OF PLASMA RENIN ACTIVITY IN THE MATURATION OF RENIN-ANGIOTENSIN-ALDOSTERONE-SYSTEM BY A VALIDATED SMALL-VOLUME ASSAY IN CONTEXT OF THE LENA PROJECT

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Background Physiological and pathophysiological circumstances of the paediatric renin-angiotensin-aldosterone-system (RAAS) are still inadequately understood. Due to the limited paediatric data available, the LENA (Labeling of Enalapril from Neonates up to Adolescents) project aimed to comprehensively investigate the drug enalapril and its effect on humoral parameters of the RAAS. Examination of four humoral parameters, including plasma renin activity (PRA), was conducted regarding cardiac diseased paediatric population receiving enalapril, of which 60% were below 1 year of age. To fully address the agreed Paediatric Investigation Plan (EMEA-001706-PiP) of the LENA project, reliable small-volume assays for pharmacodynamics determination were mandatory to ensure the reliable data sets.

Materials and methods A commercial PRA enzyme linked immunosorbent assay (ELISA) was tailored for paediatric application and validated according to European Medicine Agency (EMA) and U.S. Food and Drug Administration (FDA) bioanalytical guidelines.1 2 In this context, accuracy, precision, total error, linearity, parallelism, matrix effects and stability were investigated.

Results The adopted bioanalytical PRA-assay was successfully validated. Between-run precision (CV) and accuracy (relative error) ranged from 1.6% to 19.6% and -13.0% to +11.2% respectively. Samples of five different human sources showed no substantial matrix effect and facilitated the assay’s application to heterogeneous populations. The obtained precision of parallelism of five dilution steps ranged from 7.7% to 8.3% allowing to dilute high samples within the calibration range. Stability measurements proved four freeze and thaw cycles plus short-term and long-term (37 weeks) stability. Overall, all results were complied with guideline requirements.

Conclusion The FDA/EMA-compliant PRA assay is able to accurately and precisely quantify PRA values in 50 µL plasma and is applicable for GCLP-compliant clinical studies enabling sophisticated investigations in children within the LENA project.

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P95 COMPILATION OF AVAILABLE PLASMA RENIN ACTIVITY LEVELS IN THE HEALTHY AND CARDIAC DISEASED PAEDIATRIC POPULATION

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Background The physiological and pathophysiological characteristics regarding plasma renin activity (PRA) in the context of the renin-angiotensin-aldosterone-system (RAAS) are well investigated in adults, whereas less is known in paediatric population suffering from heart failure. Challenges in the conduct of paediatric investigations limit the enrolled children often to specific age groups allowing only a partial revaluation of the maturing RAAS. To constitute the comprehensive picture of the paediatric RAAS from 0–18 years, a compilation of available PRA data was conducted via literature search.

Methods A systematic literature search was accomplished in the context of the ‘Labeling of Enalapril from Neonates up to Adolescents’ (LENA) project in the MEDLINE database via PubMed in January 2019. Key words: plasma renin activity and congenital heart disease/dilatative cardiomyopathy/heart failure/congenital heart defect and child/neonate/infant/toddler/paediatric. Eligible records included PRA values in children of 0–18 years of age. Exclusion criteria comprised foetuses, preterm, cord blood, urine, adults, < 2500 g birthweight, ex vivo studies and deviant diseases.

Results Literature search resulted in 167 findings of which 58 full-text articles were assessed for eligibility. Finally, 33 publications were classified as relevant. Of these, 21 and 12 records were assigned for healthy and cardiac diseased population respectively, leading to PRA data sets of 2000 healthy and 254 diseased children. Visual check of data revealed an
age dependent decrease of PRA, in particular in the early childhood, and a substantial elevation of PRA in heart failure patients.

Conclusion The conducted literature search allowed a systematic description of PRA values in healthy and cardiac diseased pediatrics, which facilitates a classification of reference ranges of the maturing RAAS for LENa and future paediatric trials.

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P96 PRELIMINARY RESULTS ON THE STUDY TO IDENTIFY THE RELATION BETWEEN MIDAZOLAM CONCENTRATIONS AND LEVEL OF SEDATION IN CRITICALLY MECHANICALLY VENTILATED CHILDREN

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Introduction While evidence on the pharmacokinetics of midazolam in children in increasing, there is only limited information on the pharmacokinetic-pharmacodynamic relation of midazolam in critically ill children. In this study, we explored the relation between midazolam concentrations and level of sedation using data from a multi-institutional clinical trial comparing Daily Sedation Interruption (DSI) with protocolised sedation versus protocolised sedation alone (i.e DSI + PS vs. PS) in critically-ill, mechanically ventilated paediatric ICU (P-ICU) patients.

Methods Pharmacokinetic information on midazolam use along with COMFORT and NISS scores from 113 mechanically ventilated P-ICU patients (median age 3 months, range: 0 to 17 years) admitted between 2010 and 2014 were used from the original study.1 Midazolam plasma concentrations at the time of each COMFORT score were calculated using a pharmacokinetic model published on the same dataset.2 Sedation scores were categorised into under-, adequate- and over-sedated categories according to the study protocol.3

Results In total, 6662 COMFORT scores were elicited (3112 and 3550 scores for DSI+PS and PS arms, respectively). Patients were observed to be adequately sedated in 4232 (64%) scores, and under- and over-sedated in 720 scores (10%) and 1710 (26%) scores, respectively. For all three sedation categories, median midazolam concentrations were significantly lower in the DSI+PS arm compared to PS (P < 0.001). Generalized multivariate linear mixed-effects modelling identified previously reported over-sedation scores (P < 0.001) in combination with high log-transformed midazolam concentrations (P < 0.001) as predictors of over-sedation in patients. Prior under-sedation, but not individual predicted midazolam concentration, predicted current under-sedation (P < 0.001).

Conclusion These preliminary results suggest a role of previous sedation scores in subsequent sedation scores. Further exploration of these data using Markov modelling seems required to identity the relation between midazolam concentrations and level of sedation in mechanically ventilated P-ICU patients.

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P97 BUSULFAN/SULFOLANE METABOLIC RATIO ON THE THIRD DAY OF CONDITIONING MAY PREDICT THE EVENT-FREE SURVIVAL IN CHILDREN RECEIVING BUSULFAN BASED CONDITIONING PRIOR TO HEMATOPOIETIC STEM-CELL TRANSPLANTATION

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Introduction Busulfan (Bu) is widely used as a component of myeloablative conditioning regimen before hematopoietic stem cell transplantation (HSCT) in children. Obtaining the ratio of Bu to its metabolite sulfolane i.e. metabolic ratio (MR) may serve as an indicator of Bu GSH conjugating capacity of an individual.

Objective To evaluate the utility of Bu MR to predict EFS in children undergoing allogeneic HSCT.

Methods Two different cohorts with children receiving Bu in four times daily (QID, n=44) and once daily doses (QD, n=13) at St. Justine’s Hospital, Montreal were studied. Bu and S levels were measured on day 3 of the conditioning regimen at the end of infusion (dose 9 in QID or dose 3 in QD dosing). EFS was defined from the time of transplant until death, relapse, or rejection, whichever occurred first. A receiver-operator characteristic curve (ROC) of Bu MRs was analyzed in relation to EFS. Cutoff values were defined based on the Youden’s J statistic.

Results Twenty-two males and 22 females aged from 0.1 to 19.9 years (mean±SD: 7.2 ± 5.7) from Bu QID cohort had the mean MR of 29.3 (SD: 16.6). In ROC analysis, a cut off value of 25.06 was chosen with better sensitivity (71%) and specificity (70%) for EFS prediction (p=0.003; AUC=1.0).

Background Busulfan (Bu) is widely used as a component of myeloablative conditioning regimen before hematopoietic stem cell transplantation (HSCT) in children. Obtaining the ratio of Bu to its metabolite sulfolane i.e. metabolic ratio (MR) may serve as an indicator of Bu GSH conjugating capacity of an individual.

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Results Twenty-two males and 22 females aged from 0.1 to 19.9 years (mean±SD: 7.2 ± 5.7) from Bu QID cohort had the mean MR of 5.9 (SD: 3.2). A cut off value of 4.9 in MR was chosen in ROC analysis in this cohort, with better sensitivity (71%) and specificity (70%) for EFS prediction (p=0.01, AUC= 0.7 (95% CI= 0.6–0.8)). In QD cohort nine females, and four males aged between 0.4 and 15.8 years (6.7 ±5.1) had the mean MR of 29.3 (SD: 16.6). In ROC analysis, a cut off value of 25.06 was chosen with better sensitivity (100%) and specificity (100%) for EFS prediction (p=0.003; AUC=1.0).