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 being set up to quantify these findings and allow for further 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

1. Speiser PW, et al. *J Clin Endocrinol Metab* 2010;**95**(9):4133–4160.
2. Lentjes EG, WM, et al. *J Clin Endocrinol Metab*.1999;**84**(2):682–687.
3. Melin J:Dissertation 2017.
4. Melin J, et al:*Clin Pharmacokinet*.2018;**57**(4):515–527.
5. Neumann U. et al:*Clin Endocrinol*.2018;**88**(1):21–29.

Disclosure(s) Nothing to disclose

P94

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

FK Suessenbach*, M Feickert, J Tins, BB Burckhardt. *Institute of Clinical Pharmacy and Pharmacotherapy, Heinrich Heine University, Dusseldorf, Germany*

10.1136/archdischild-2019-esdppp.132

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 (EMA-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.

REFERENCES

1. Committee for Medicinal Products for Human Use (CHMP): EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** Guideline on bioanalytical method validation, June, 2015
2. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM): Bioanalytical Method Validation Guidance for Industry, May 2018

Disclosure(s) Fabian K. Suessenbach, Martin Feickert, Jutta Tins and Bjoern B. Burckhardt declare that there is no conflict of interest. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement n°602295 (LENA).

P95

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

FK Suessenbach*, T Gangnus, I Burdman, N Makowski, S Laeer, BB Burckhardt. *Institute of Clinical Pharmacy and Pharmacotherapy, Heinrich Heine University, Dusseldorf, Germany*

10.1136/archdischild-2019-esdppp.133

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 reevaluation 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 Adolescence' (LENA) project in the MEDLINE database via PubMed in January 2019. Key words: plasma renin activity and congenital heart disease/dilative 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, pre-term, 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