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Disclosure(s) Nothing to disclose

P91 REAL-TIME BREATH ANALYSIS OF ANTIEPILEPTIC DRUGS

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Background In the field of medicine, serum concentrations of drugs with a narrow therapeutic window, used to treat seizures, are measured to assure the most efficacious and safe way of treating every individual patient. This form of personalised medicine is called therapeutic drug monitoring (TDM). We have explored the possibility to measure and monitor drugs in exhaled breath (EB), to perform completely painless and non-invasive TDM for a future clinical application especially in pediatric patients.

Methods We employed secondary electrospray ionisation in combination with high resolution mass spectrometry to obtain highly resolved EB mass spectra. We then statistically compared these EB mass spectra between patients taking antiepileptic drugs against controls (no drugs), to find potential EB-based bio-markers for drugs. Suspected drug metabolites detected in breath will be compared with systemic blood concentrations. We will screen a total of 15 drugs requiring TDM.

Results So far we have successfully measured EB mass spectra of patients undergoing treatment with Valproic acid (VPA, n = 27), Lamotrigine (n = 19), Levetiracetam (n = 15) and Oxcarbazepine (n = 11). Exploratory data analyses are still ongoing for these drugs. However, for VPA we have identified few candidate ions which enables us to predict free VPA blood concentrations (RMSE 1.5 mg/L). Additionally, we have positively identify two molecules involved in free VPA prediction, based on LC-MS/MS of the exhaled breath condensate. In the near future we will continue to perform data analyses and LC-MS/MS on ions of interest to confirm their identity.

Conclusions This work is a part of an ongoing study and it is too early to come up with a definite conclusion. However, we observed several differentially abundant ions between controls and epileptic patients for various drugs, but the identity and clinical significance of these ions is yet to be determined.

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P92 METABOLOMICS IN CHILDREN WITH HEART FAILURE USING ACE-INHIBITORS, AN EXCITING OPPORTUNITY?

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Introduction ACE inhibitors (ACEi) have a prominent place in the treatment of heart failure in children. However, there is a significant interpatient variability in efficacy and safety in those children that is not completely understood. Metabolomics provides an interesting innovative approach to better understand underlying mechanisms for variation in disease and response to therapy. With this review, we aim to provide an overview of metabolomics in the field of heart failure therapy with or without ACEi in both adults and children and try to identify gaps in this field.

Methods The PubMed database was systematically searched using several search strategies. Articles were labelled as relevant when they included information on either metabolomics of adult patients with heart failure and/or ACEi-therapy or in children. This yielded 42 relevant articles

Results 24 articles were found describing metabolomics in adults with heart failure, either with or without ACEi-therapy. In addition, several metabolites were identified in adults correlating with either ACEi-efficacy or safety. No metabolomics articles were found in children with heart failure or in children on ACEi-therapy. Several papers (18) were found on metabolomics in children for other diseases and/or treatments.

Conclusion Metabolomics in adult heart failure patients has helped to unravel part of observed disease and therapy variability, and appears helpful in identifying patients at risk for therapy failure as well as detecting novel targets for heart failure therapy. In children, a significant information gap exists. This provides exciting opportunities for personalized treatment of heart failure.

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P93 SEMI-MECHANISTIC MODELLING OF HYDROCORTISONE PHARMACOKINETICS IN PAEDIATRIC PATIENTS WITH ADRENAL INSUFFICIENCY

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Background Patients with congenital adrenal hyperplasia (CAH) have low to no biosynthesis of cortisol and require lifelong cortisol replacement. Optimisation of hydrocortisone (HC, synthetic cortisol) therapy in this population is important, since too low or high cortisol concentrations increase the risk of adrenal crisis or Cushing's syndrome¹. HC has non-linear pharmacokinetics (PK) caused by saturable binding to corticosteroid binding globulin (CBG)². The objective of this analysis was to extend an established paediatric HC PK-model³ with dried blood spot (DBS) data in order to further characterise the binding behaviour of HC in children.

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.

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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

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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 (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.

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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 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 fetuses, 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