available, together responsible for 36 area under the concentration time curves (AUCs) and trough concentrations. First, hematocrit-corrected concentrations were derived using a formula describing the relationship between whole blood concentrations, hematocrit, and plasma concentrations. Subsequently, target exposure was evaluated using the converted plasma target concentrations. Ultimately, differences in interpretation of target exposure were identified and evaluated.

Results In total, 92% of our patients had a lower hematocrit (median 0.29) than the reference value of adult renal transplant patients. A different evaluation of target exposure for either trough level, AUC or both, was defined in 42% of our patients, when applying hematocrit corrected concentrations.

Conclusion A critical role for hematocrit in therapeutic drug monitoring of tacrolimus in pediatric kidney transplant patients is suggested in this study. Therefore, we believe that hematocrit correction could be a step towards improvement of tacrolimus dose individualization.

Disclosure(s) All authors declare that they have no conflict of interest. This work was recently accepted for publication in Pediatric Nephrology. We are aware of the statement in the guideline about previously published work, however as we believe that this work suits the aim and topics of the congress very well, we chose to submit this work and will ofcourse leave the final decision to you.

P89 EMICIZUMAB DEVELOPMENT IN PAEDIATRIC PATIENTS WITH CONGENITAL HEMOPHILIA A AND INHIBITORS AGAINST FACTOR VIII

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Background Emicizumab, a bispecific monoclonal antibody, bridges activated factor (F) IX (FIXa) and FX, restoring missing FVIIIa function in patients with hemophilia A (PwHA). It has been recently approved for routine prophylaxis of bleeding episodes in PwHA with FVIII inhibitors in all age groups. We herein describe the paediatric development of emicizumab with a focus on dose selection, study design and extrapolation of efficacy.

Methods The dosing regimen for the HAVEN 1 study (adolescents/adults) was selected based on the exposure-response (annualized bleeding rate [ABR]) relationship derived from a phase I/II study in adolescent/adult PwHA. Pharmacokinetic (PK) simulations, with or without maturation of clearance (CL MAT), were performed to guide selection of the dosing regimen for the HAVEN 2 study (paediatrics) aiming to achieve the same target exposure as in HAVEN 1. HAVEN 2 employed a flexible design with possibility for individual- and population-level dose up-titration. Additional PK modeling and simulations together with exposure-response analyses were used to support full extrapolation of efficacy in any age category where no data was available.

Results 1.5 mg/kg/week in HAVEN 1 provided mean trough concentrations of ~50 µg/mL and was associated with a 87% reduction in ABR. Doses of ≥ 1.5 (with CL MAT) and ≥ 2.25 mg/kg/week (without CL MAT) were predicted to achieve this target exposure in children. HAVEN 2 began by investigating the same dose as HAVEN 1. Similar trough concentrations of ~ 50 µg/mL were achieved in children and were associated with low ABR. No patients < 1 year were enrolled in HAVEN 2. PK simulations and pharmacological rationale suggested that a different dose for these patients was not warranted.

Conclusions Efficacy of emicizumab in adolescents/adults was demonstrated in HAVEN 1, partially extrapolated to HAVEN 2 participants 1–11 year of age, and fully extrapolated in patients < 1 year.

Disclosure(s) Authors are Roche/Genentech employees

P90 NEUROPSYCHIATRIC DISORDER AND MONTELUKAST: A CASE REPORT AND VIGIBASE® ANALYSIS

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Learning objective Recognize neuropsychiatric symptoms as possible adverse drug reactions (ADR) associated with the leukotriene receptor antagonist Montelukast in children

Clinical Case An 11-year-old boy suffering from asthma presented to his pediatrician with an acute onset of nervousness, restlessness and irritability. The teacher noticed a decline in school performance with a reduced attention span. The patient had been treated with Salbutamol (Ventolin®) and Salmeterol/Fluticasone (Seretide®) for the last few years. A treatment with Montelukast chewable tablets was started four months ago. The ADR was reported to the Regional Pharmacovigilance Centre (RPVC) Bern. The termination of the therapy with Montelukast lead to an amelioration of the symptoms. According to the WHO-UMC Causality Categories,[1] the causality of Montelukast and the described symptoms was classified as 'probable'. The causality of the comedication was considered 'unlikely' as it had been used for several years without complications. After work-up at the RPVC, the case was reported anonymously to the National Pharmacovigilance Center of the Swiss Agency for Therapeutic Products Swissmedic.

Discussion Montelukast is a cysteinyl-leukotriene type 1-receptor antagonist used in the treatment of bronchial asthma in adults and children. Psychiatric disorders such as agitation, psychomotor hyperactivity (including irritability and restlessness), disorders of attention and memory impairment (and others) are listed as known ADRs of Montelukast.[2 3] The WHO pharmacovigilance database VigiBase® lists a total of 20'897 ADR reports for Montelukast, of which 4'705 (22.5%) refer to nervous system disorders and 6'828 (32.7%) to psychiatric disorders. Within the group of nervous system disorders 256 (5.4%) reports of psychomotor hyperactivity, 232 (4.9%) reports of disturbance in attention and 91 (1.9%) reports of memory impairment were recorded.[4] The most common symptoms in the group of psychiatric disorders are depression (1'311, 19.2%) and aggressive behavior (1'175, 17.2%). If psychiatric ADRs occur, the risks and benefits of Montelukast should be reassessed.

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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 syndrome[1]. HC has nonlinear 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-model[3] with dried blood spot (DBS) data in order to further characterise the binding behaviour of HC in children.