

variability. The model was validated for paracetamol, ibuprofen, flurbiprofen and naproxen, and for a paediatric meningitis population by estimating meropenem blood-brain barrier penetration using sensitivity analysis. Plasma and CSF drug concentrations derived from literature were used to perform visual predictive checks and to calculate ratios between simulated and observed AUCs in order to evaluate model performance.

Results Simulated data were comparable to observed over a broad age range (1 day - 15 y postnatal age), for all drugs investigated. The ratios between observed and simulated AUCs were within 2-fold difference both in plasma and in CSF, indicating acceptable model performance. Disposition of meropenem into the brain was slow and CSF concentrations were lower compared to plasma concentrations. In addition, several days were needed to achieve CSF steady-state concentration.

Conclusions Our paediatric brain PBPK model provides a new tool to predict CSF concentrations in children with and without meningitis and can be used as a template model for other drugs acting in the CNS.

Disclosure(s) Nothing to disclose

020

DOSE-LINEARITY OF THE PHARMACOKINETICS OF AN INTRAVENOUS [¹⁴C]MIDAZOLAM MICRODOSE IN CHILDREN

¹BD van Groen*, ²WHJ Vaes, ³BK Park, ⁴EJH Krekels, ²E van Duijn, ⁵L-T Kõrgvee, ⁶W Maruszak, ⁶G Grynkiewicz, ⁷RC Garner, ^{4,8}C Knibbe, ¹D Tibboel, ^{1,9}SN de Wildt*, ³MA Turner*. ¹Erasmus MC – Sophia Children's Hospital, Rotterdam; ²TNO, Zeist, The Netherlands; ³University of Liverpool, Liverpool, UK; ⁴Leiden University, Leiden, The Netherlands; ⁵University of Tartu, Tartu, Estonia; ⁶Pharmaceutical Research Institute, Warsaw, Poland; ⁷Garner Consulting, York, UK; ⁸St. Antonius Hospital, Nieuwegein; ⁹Radboudumc, Nijmegen, The Netherlands

10.1136/archdischild-2019-esdppp.21

Background Drug disposition in children may vary from adults due to age-related variation in drug metabolism, but paediatric pharmacokinetic (PK) studies are challenging. Microdose studies present an innovation to study PK in paediatrics, and can only be used when the PK of a microdose are dose-linear to a therapeutic dose. We aimed to assess dose-linearity of [¹⁴C]midazolam (MDZ), a marker for the activity of the developmentally regulated CYP3A enzyme, by comparing the PK of an intravenous (IV) [¹⁴C]MDZ microtracer given simultaneously with therapeutic MDZ, with the PK of a single IV [¹⁴C]MDZ microdose.

Methods Preterm to 2-year-old infants admitted to the intensive care unit received [¹⁴C]MDZ IV either as a microtracer during therapeutic MDZ infusion or as an isolated microdose. Dense blood sampling was done up to 36 hours after dosing. Plasma concentrations of [¹⁴C]MDZ and [¹⁴C]1-OH-MDZ were determined by accelerator mass spectrometry. A population PK model was developed with NONMEM 7.4 to study whether there was a difference in the PK of the microtracer versus those of a microdose [¹⁴C]MDZ.

Results Of fifteen children (median gestational age 39.4 [range 23.9–41.4] weeks, postnatal age 11.4 [0.6–49.1] weeks), nine received a microdose and six a microtracer [¹⁴C]MDZ (111 Bq/kg; 37.6 ng/kg). In a two-compartment PK model, body-weight was the most significant covariate for volume of distribution. There was no statistically significant difference in any PK parameter between the [¹⁴C]MDZ microdose or

microtracer, suggesting the PK of MDZ to be linear within the range of the therapeutic doses and microdoses.

Conclusion Our data supports the dose-linearity of an IV [¹⁴C]MDZ microdose in children, thus a [¹⁴C]MDZ microdosing approach can be used to study developmental changes in hepatic CYP3A activity.

Disclosure(s) This project was funded by the ZonMw ERA-NET PRIOMEDCHILD programme (projectnumber 113205022). * both authors contributed equally

021

PROGRESS TOWARDS THERAPEUTIC DRUG MONITORING VIA BREATH ANALYSIS

KD Singh, V Ziesenitz, J Usemann, J Van Den Anker, U Frey, N von der Weid, A Datta, P Sinues*. *University Children's Hospital Basel (UKBB), University of Basel, Basel, Switzerland*

10.1136/archdischild-2019-esdppp.21

Background Therapeutic Drug Monitoring (TDM) is essential aspect for the clinical management of patients. However, despite the clear advantages of TDM, it faces several challenges to being more widely used in the clinic. Specially challenging is the case of TDM in children, as they experience rapid physiologic developments, leading to great pharmacokinetic and pharmacodynamic variability. Breath analysis provides a patient-friendly approach to support TDM. To explore this possibility, we are currently running a pilot study, whereby we analyze the exhaled breath of pediatric patients receiving anti-seizure or chemotherapy drugs requiring TDM.

Methods We analyzed by secondary electrospray ionization-high resolution mass spectrometry (SESI-HRMS) exhaled breath of pediatric patients under therapy for Valproic acid (VPA; n = 27), Lamotrigine (n = 19), Levetiracetam (n = 15), Oxcarbazepine (n = 11) and Methotrexate (n = 4). Systemic blood concentrations were measured simultaneously to the breath test. In the case of VPA, we constructed a regression model to predict systemic blood concentrations based on the signal intensity of breath mass spectral features. For the rest of the drugs listed, due to its current limited size, we conducted preliminary data visualization approaches.

Results We found that exhaled metabolites of VPA allow to predict free VPA blood concentrations with a root-mean-square error of 1.5 mg/L for concentrations in the range 0–12 mg/L. This prediction is accomplished within 20 minutes, comprising the breath test and data analysis. For Levetiracetam, Lamotrigine and Oxcarbazepine the data analysis is still ongoing. For MTX we found breath metabolites clearly altered as a result of the drug administration. However, a great inter-individual variability was also observed.

Conclusion We conclude that breath analysis may support current TDM approaches. This will lead to new opportunities to guide the dose of drugs with a high level of accuracy, in real-time and non-invasively.

Disclosure(s) PS gratefully acknowledges the financial support of the Fondation Botnar (Switzerland) and the Swiss National Science Foundation (320030_173168 and PCEGP3_181300). PS is part of the board of directors of Deep Breath Initiative AG. JU was supported by research fellowship of the University Children's Hospital Basel. VS and JVDA were supported by the Eckenstein-Geigy Foundation. *AD and PS: shared senior authorship