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 paediatrics, 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[1] 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 records 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.

REFERENCES

1. Vet NJ, de Wildt SN, Verlaat CW, *et al*. A randomized controlled trial of daily sedation interruption in critically ill children. *Intensive care medicine* 2016;**42**(2):233–44. doi: 10.1007/s00134-015-4136-z [published Online First: 2015/11/26]
2. Vet NJ, Brussee JM, de Hoog M, *et al*. Inflammation and organ failure severely affect midazolam clearance in critically ill children. *American journal of respiratory and critical care medicine* 2016;**194**(1):58–66. doi: 10.1164/rccm.201510-2114OC [published Online First: 2016/01/23]
3. Vet NJ, de Wildt SN, Verlaat CW, *et al*. Daily interruption of sedation in critically ill children: study protocol for a randomized controlled trial. *Trials* 2014;**15**:55. doi: 10.1186/1745-6215-15-55 [published Online First: 2014/02/15]

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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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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.

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 Su 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 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).

Conclusion The Bu MR on day 3 above 4.973 and 25.06 were associated with worse EFS in children undergoing HSCT and received Bu in QID and QD dosing schedules, respectively.

Disclosure(s) Nothing to disclose

P98 SEMI-QUANTIFICATION AND LOCALIZATION OF MEMBRANE TRANSPORTERS IN PAEDIATRIC KIDNEY TISSUE

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Background The kidney has a critical role in disposition, efficacy and toxicity of drugs and xenobiotics. Developmental changes of renal membrane transporters have the potential to explain population variability in paediatric pharmacokinetics and -dynamics of drugs but data are missing. We aimed to further delineate the expression of human renal tubular transporters multidrug resistance-associated protein (MRP) 4 and MRP2 and study localization in paediatric kidney samples.

Methods We planned to semi-quantify expression levels and to study the age-specific localization of the transporters MRP4 and MRP2 with immunohistochemistry on 44 human neonatal and paediatric kidney samples with age range of 24,00 - 40,00 weeks gestational age (GA) and 0,29 - 744 weeks post-natal age (PNA). The staining intensity was semi-quantitatively scored by two independent observers (MB and BG).

Results MRP4 is found to be localized at the apical membrane of the renal proximal tubules at 27 weeks of GA (n=3, 1,29- 4 weeks PNA) and no age-related changes of expression levels were detected. In a premature neonate of 24 weeks GA (n=1), no MRP4 was detected. The MRP2 staining did not meet the requirements to be scored and was rejected.

Conclusion MRP4 is expressed from at least 27 weeks GA onwards and does not show developmental changes. The localization was similar as in adults (Ritter et al., 2005). The half-life of the MRP4 substrate furosemide was found to be 6 to 20-fold longer in neonates than in adults (Pacifici, G.M., 2013). This could potentially be linked with the absence of MRP4 in a premature neonate with GA 24 weeks. However, these data should be confirmed as we only had 1 sample of ±24 weeks GA available. Moreover, our data help us in understanding altered disposition of transporter substrates in paediatrics.

REFERENCES

1. Pacifici, G. M. (2013). Clinical pharmacology of furosemide in neonates: a review. *Pharmaceuticals*;**6**(9):1094–1129.
2. Ritter CA, Jedlitschky G, Meyer zu Schwabedissen H, Grube M, Köck K, & Kroemer HK. (2005). Cellular export of drugs and signaling molecules by the ATP-binding cassette transporters MRP4 (ABCC4) and MRP5 (ABCC5). *Drug metabolism reviews*;**37**(1):253–278.

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P99 CLINICAL VALIDATION OF PUBLISHED VANCOMYCIN POPULATION PK MODELS IN CRITICALLY ILL NEONATES

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Background Vancomycin is commonly used for treatment of severe Gram+ neonatal infections. Currently, even with the use of optimized dosing regimens and therapeutic drug monitoring (TDM), target attainment rates are abominable, leaving patients at risk for therapeutic failure and toxicity. Model-informed precision dosing (MIPD) offers a large potential to improve therapy in the individual patient.

The aim of this study was to identify a suitable model for bedside MIPD by assessing the predictive performance of published population pharmacokinetic (popPK) models.

Methods A literature search was conducted to identify parametric popPK models. PK vancomycin data were retrospectively collected from NICU patients at the Radboud University Hospital, Nijmegen, The Netherlands. The model predictive performance was assessed by comparison of predictions to observations, calculation of bias (Mean Percentage Errors, MPE) and imprecision (Normalized Root Mean Squared Errors, NRMSE). Evaluations included both *a priori* (model covariate input) and *a posteriori* (model covariate and TDM concentration input) scenarios.

Results 265 TDM measurements from 65 neonates (median postmenstrual age:32 weeks [range:25–45 weeks]; median weight:1281g [range:597–5360g]; median serum creatinine:0,48 mg/dL [range:0,15–1,28 mg/dL]) were used for model evaluation. Six popPK models were evaluated[1–6]. *A posteriori* predictions of all models were consistently more accurate and precise compared to the *a priori* (starting dose) predictions. PopPK models of Frymoyer *et al.* and Capparelli *et al.* consistently performed best through all evaluations in both the *a priori* and *a posteriori* scenario (MPE ranging from -18 to 6,4% in *a priori* scenario and -6,5 to -3,8% in *a posteriori* scenario; NRMSE ranging from 34 to 40% in *a priori* scenario and 23 to 24% in *a posteriori* scenario).

Conclusion Large differences in predictive performance of popPK models were observed. Repeated therapeutic drug monitoring remains necessary to increase target attainment rate. Best performing models for bedside MIPD were identified in our patient population.

REFERENCES

1. Zhao W, Lopez E, Biran V, *et al*. (2013). Vancomycin continuous infusion in neonates: Dosing optimisation and therapeutic drug monitoring. *Arch Dis Child*;**98**(6):449–453.
2. Capparelli EV, Lane JR, Romanowski GL, *et al*. (2001). The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol*, **41**:927–934.
3. De Cock RFW, Allegaert K, Brussee JM, *et al*. (2014). Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm Res*;**31**(10):2642–2654.
4. Frymoyer A, Hersh AL, El-Komy MH, *et al*. (2014). Association between vancomycin trough concentration and area under the concentration-time curve in neonates. *Antimicrob Agents Chemother*, **58**(11):6454–6461.