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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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 is 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 trial¹ 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

identify the relation between midazolam concentrations and level of sedation in mechanically ventilated P-ICU patients.

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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).