Methods Observational study of 64 preterm neonates during their first five days of life with gestational age (GA) < 32 weeks or very low birth weight of < 1500 g. Total of 52 patients treated with caffeine and 12 controls without caffeine were included. Sleep-wake behavior was scored in wakefulness (W), active sleep (AS), and quiet sleep (QS) associated with physical and cerebral regeneration. Individual caffeine concentration of every neonate was simulated with a pharmacokinetic model.

Results For increasing caffeine concentration, W increased, AS decreased, and QS was unchanged for GA > or = 28 weeks. No caffeine effect for GA < 28 weeks could be demonstrated. Maturation effects could be seen when comparing preterm neonates of GA > 32 weeks with a birth weight of < 1500 g with very preterm neonates born of GA < 32: Neonates born > 32 weeks had a significantly higher amount of W and lower percentage of AS.

Conclusions Treatment of apnea and bradycardia as well as stabilization of respiration with standard caffeine treatment is not at cost of QS, i.e. time for physical and cerebral regeneration during sleep remains unchanged. There is an increased fraction of W, alertness and most probably also arousability.

Disclosure(s) Nothing to disclose

P25 COMPARISON OF RENAL FUNCTION ESTIMATION METHODS IN CRITICALLY ILL CHILDREN: A PILOT STUDY

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Background Accurate assessment of renal function is crucial in intensive care to guide therapy. Both acute kidney injury and augmented renal clearance (ARC) may compromise outcome. Common formulas to estimate glomerular filtration rate (GFR) are unreliable in critically ill adults.¹ A comparison of a gold standard technique to assess GFR with these formula-based estimations has never been reported in pediatric intensive care (PICU) patients. Our aim was to evaluate the feasibility of measuring plasma iothexol clearance (CL_{IOHEX}) for GFR assessment in critically ill children and to compare CL_{IOHEX} with estimated GFR using the modified Schwartz formula (eGFR_{Schwartz}).

Methods A prospective, interventional study was conducted at the PICU of the Ghent University Hospital, Belgium. Critically ill children without chronic kidney disease were included. After injection of a weight-dependent bolus of iothexol, serial blood samples (n=6) were taken over a 6-hours interval. CL_{IOHEX} was compared to eGFR_{Schwartz}. Correlation between both methods was assessed by a Pearson's correlation coefficient (r). Bland-Altman plots were evaluated to assess bias and limits of agreement (LOA). ARC was defined as a GFR exceeding normal values for age plus two standard deviations.

Results 40 patients, median age 16 months (range 15 days - 13,6 years), 72,5% males, were included. No adverse effects related to iothexol were observed. Median CL_{IOHEX} was 121 ml/min/1.73m² (range: 43–221 ml/min/1.73m²). ARC was present in 20 patients based on CL_{IOHEX}. Median

eGFR_{Schwartz} was 81 ml/min/1.73m² (range: 31–131 ml/min/1.73m²). Only 1 patient was identified with ARC by eGFR_{Schwartz}. eGFR_{Schwartz} was systematically lower than CL_{IOHEX}. There was a good correlation between CL_{IOHEX} and eGFR_{Schwartz} (r = 0,69; p < 0,01). Bias was 34 ml/min/1.73m² with LOA (-24,5; 93 ml/min/1.73m²).

Conclusion CL_{IOHEX} was safely used to measure true GFR in critically ill children. eGFR_{Schwartz} systematically underestimates GFR, especially in patients with ARC and seems not reliable in this patient population.

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Disclosure(s) Nothing to disclose

P26 PILOT ON HARMONISING DOSING RECOMMENDATION FOR TERM AND PRETERM NEONATES IN THE NETHERLANDS (NEODOSE PROJECT)

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Background Many drugs are used off-label in term and pre-term neonates, and dosing recommendations for many drugs are lacking in the Dutch Paediatric Formulary (DPF). This results in widely varying dosing regimens used across neonatal intensive care units (NICUs) in the Netherlands. The Neodose pilot project aimed to develop best-evidence national dosing recommendations for (pre)term neonates. Because scientific evidence is scarce, a consensus-based approach was used.

Methods A priority drug list, containing the most frequently used drugs for neonates, was drafted. From this list 22 drugs were selected for further research within the Neodose pilot project. The pilot utilized a two-step approach: First, consensus was established with all Dutch NICUs for neonatal dosing recommendations. Local treatment protocols were retrieved, compared and discussed, leading to consensus-based dosing recommendations. Secondly, we aimed to develop best-evidence dosing recommendations for the following five drugs: acyclovir, ganciclovir, ibuprofen, hydrocortisone and dexamethasone.

Results For 21 of 22 drugs, local dosing guidelines differed significantly. Mostly concerning total daily dose, dosing frequency and route of administration. Little or no distinction is made between treatment of preterm and term neonates. Approximately half of the consensus-based dosing recommendations (45%) differ in some degree from all local protocols. Comparing the consensus-based dosing recommendations with the available evidence, almost half of the consensus doses were adjusted. The grounds on which dosing recommendations were adjusted differed. Acyclovir-dosing adjustment was based on pharmacokinetics. Hydrocortisone-dosing was adjusted due to new insights after the evidence has been put together. For dexamethasone-dosing, the consensus dose was eventually chosen, because every available trial used a different dosing regimen.

Conclusion This pilot showed that, when evidence is inconclusive, consensus on dosing regimens in neonates can be obtained by comparing local regimens and analysing the available evidence. For more uniform use, these new recommendations will be published in the DPF.

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P27

THE JUVENILE PIG AS ANIMAL MODEL FOR UNRAVELING RENAL DRUG ELIMINATION PROCESSES IN CHILDREN

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Background Over the years pigs were promoted as potential animal model for humans due to their high degree of anatomical and physiological similarities with humans. Gasthuys et al. demonstrated that the maturation of the kidney function in terms of the glomerular filtration rate (GFR) in growing pigs was comparable to humans, but no data are currently available on renal plasma flow, renal tubular secretion and reabsorption.¹ The aim of this pilot study was to unravel the contribution of distinct renal elimination processes in juvenile pigs and to compare with reported human values.

Methods Eight seven-week-old pigs were intravenously administered a single bolus of a cocktail of following renal markers: iohexol (64.7 mg/kg body weight (BW), GFR), para-aminohippuric acid (PAH, 10 mg/kg BW, effective renal plasma flow (ERPF) and anion secretion), pindolol (0.05 mg/kg BW, cation secretion) and fluconazole (0.5 mg/kg, tubular reabsorption). Plasma and urinary concentrations were determined for PAH, pindolol and fluconazole at several time points. Only plasma concentrations were assessed for iohexol. PK modelling was performed with Phoenix® WinNonlin®.

Results The clearance of iohexol was 97.9 ± 16.1 ml/min/m² (mean $\pm$ SD). The ERPF, calculated as the renal clearance of PAH, was 9.5 ± 2.1 ml/min/kg. These GFR and ERPF values are approximately a factor 1.3 higher than the values observed in humans, namely 63.5–75.0 mL/min/m² and 6.5 ± 2.0 mL/min/kg.^{2,3} The net tubular secretion of PAH was 5.4 ± 1.8 mL/min/kg, which was comparable with the values obtained in humans (5.0 ± 1.8 mL/min/kg).³ Results for cation secretion and tubular reabsorption are not yet available (to be presented at the congress).

Conclusion The net tubular secretion of PAH was comparable between the juvenile pigs and humans. The GFR and ERPF were generally a factor 1.3 higher in juvenile pigs compared to humans.

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P28

PHARMACOKINETICS AND IMPLICATIONS FOR DRUG DOSING IN CHILDREN WITH SICKLE CELL DISEASE: A SYSTEMATIC REVIEW

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Background Children with sickle cell disease (SCD) are at high risk of intractable pain and severe infections despite early and aggressive drug treatment. SCD is a multisystemic disease potentially leading to liver and renal dysfunction. Altogether, those may lead to pharmacokinetic (PK) alterations, which may contribute to therapeutic failure or drug toxicity. We performed a systematic literature review to describe the current evidence on the effect of SCD on drug disposition in children.

Methods A systematic literature search was conducted by a librarian on 5 databases until 08.2018 and independently assessed by two reviewers. All full-text articles, containing PK data in children, were included. The reported differences in PK parameters between SCD and non-SCD children were examined.

Results Among 4213 retrieved abstracts, 50 full-text articles were assessed and 27 studies were included (13 exclusively children). Data on 15 drugs was available from which 5 were exclusively developed for SCD (impeding any comparison). From the remaining 10 drugs, a comparison of PK parameters was available in 8. Six were investigated in adults and children. Three (37.5%) showed significant PK alterations (morphine, cefotaxime, lidocaine) while 5 did not (hydroxyurea, sulfadoxine-pyrimethamine, methadone, rofecoxib, arginine butyrate). In children with SCD, clearance was higher by 42–61% for IV morphine, and by 24–62% for cefotaxime, compared with non-SCD controls. This difference led to a new dosing recommendation only for cefotaxime (400 mg/kg/day). Hepatic drug metabolism assessed by lidocaine was impaired in children with SCD compared to healthy controls.

Conclusion SCD alters drug disposition of commonly used drugs but data is scarce. A significant increase in clearance of morphine and cefotaxime, two commonly used drugs in patients with SCD, suggests that recommended doses may not be sufficient to provide adequate analgesia and antimicrobial control. PK data is urgently needed to ensure adequate drug efficacy and safety in this high-risk population.

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