

Methods This retrospective analysis included a cohort of patients < 30 years (y) on chronic HD treatment since childhood, having received thrice-weekly HD between 2004 and 2016 in outpatient DaVita dialysis centers. Survival while on HD (death from any cause) was investigated using Kaplan-Meier analysis stratified by age at start of HD (0–2, >2–6, >6–12, and >12–18 y), and three mean delivered dialysis dose levels (spKt/V < 1.4, 1.4–1.6, >1.6). Survival curves between subgroups were compared using the Log-rank test.

Results 1773 patients were included in the analysis, among n=34 having started HD at age of 0–2y, n=57 at >2–6y, n=244 at >6–12y, and n=1438 at >12–18y. Median follow-up on HD ranged between 1.5 (>2–6y) to 4.7 years (>6–12y) with maximal follow-up of 23 years. Death while on HD occurred in 1/34, 6/57, 26/244, and 101/1438 patients during recorded follow-up (p=0.075, n.s.). Patients with mean spKt/V < 1.4 had lower survival on HD than those with spKt/V >1.4–1.6 (p=0.019) and those with spKt/V >1.6 (p=0.035), with 10-year survival estimated to 75% (65.2–86.2%) versus 84.5% (78.5–90.9%) and 85.0% (80.8–89.5%), respectively.

Conclusions This is the first study to report long term survival and its relationship with delivered HD dose in patients starting HD in childhood. Our results support targeting spKt/V (urea)>1.4 in children on chronic HD treatment.

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CHARACTERISING THE PHARMACOKINETICS OF PHENOBARBITONE IN NEONATES TO FACILITATE FUTURE INDIVIDUALISED DOSING

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Background Phenobarbitone is commonly used as a first-line drug in the treatment of neonatal seizures. Previous studies, with small subject numbers, have identified covariates that may influence the pharmacokinetics of phenobarbitone but results have been inconsistent. In particular, oral bioavailability is poorly described with doses reported as being identical for intravenous and oral administration, however, 2 recent studies have reported oral bioavailability of 49% and 59% respectively.^{1,2}

Methods A population pharmacokinetic model was built based on routine therapeutic drug monitoring data from 112 infants at the Royal Brisbane and Women's Hospital Neonatal Intensive Care Unit. Population modelling was performed using NONMEM 7.3 and PsN 4.7 with assistance from R studio and the packages Xpose and VPC. Body weight with

allometric scaling on Clearance (CL) and Volume of Distribution (V) were included *a priori* in the structural model. Covariates tested included age (post-menstrual, gestational and post-natal), Apgar scores, concomitant phenytoin treatment, infection and method of nutrition.

Results A one-compartment model provided an adequate fit to the data. Typical clearance increased with patient post-natal age (PNA) and was best modelled using the equation $CL = 5.1 * WT^{0.75} * (PNA/6.25)^{0.43}$ (mL/h) where weight is in kg, PNA in days and 6.25 is the median post-natal age. Volume of distribution (V) was best modelled using the equation $V = 799 * WT^{1.0}$ (mL). Oral bioavailability (F) was 85%. Between-subject variability was 25% and 30% respectively for CL and V.

Conclusion This study describes the largest population pharmacokinetic model of phenobarbitone developed to date with estimates of CL and V similar to previously published models. Estimated F is higher than previously reported but still lower than the implied F of 100% in most recommended dosing regimens. The model could be used to assist with future individualisation of dosing in this cohort.

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012

CIRCULATING CONCENTRATIONS OF BROAD-SPECTRUM BETA-LACTAMS IN CHILDREN WITH CANCER: BEWARE OF GLOMERULAR HYPERFILTRATION!

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Background Broad-spectrum beta-lactams such as meropenem (MER) and piperacillin-tazobactam (PIP) are commonly prescribed in children with cancer having febrile neutropenia. They are introduced at intensive dosage, unless decreased renal function calls for dose reduction. Recently, glomerular hyperfiltration (HF) was recognized to be frequent among children with cancer during initial cycles of chemotherapy.¹ We evaluated the impact of HF on therapeutic exposure to MER and PIP.

Methods We retrieved retrospectively all MER and PIP plasma levels measured in children with cancer in our hospital between 2012 and 2018. We compared trough levels with usual therapeutic ranges (derived from reference values of minimum inhibitory concentrations). We classified the children according to plasma creatinine and estimated glomerular filtration rate (Schwartz formula) as either altered-normal (< 160 mL/min/1.73 m²) or increased (i.e. HF, ≥160). Neutropenia was defined as absolute neutrophil count < 500 cells/μL.

Results We collected 120 concentration values (53 MER, 67 PIP) measured in 50 children with cancer. Among them, 74 (62%) had concomitant creatinine values suggestive of HF, and 80 (67%) were neutropenic. Overall, 67% of trough

levels were below usual therapeutic ranges (MER: 2–8 mg/L, PIP 8–30 mg/L). This was more often the case in presence of concomitant HF (MER: 92%, PIP: 83%), often associated with neutropenia. Low exposure was observed not only at initial intensive dosage (MER: 120 mg/kg/day, PIP: 400 mg/kg/day)² but tended to persist despite dosage readjustment based on concentration monitoring. Moreover, bacteremia was diagnosed in 38 cases.

Conclusion Current recommended doses of MER and PIP do not provide optimal concentration coverage throughout the dosing interval in a large fraction of children with cancer and febrile neutropenia as a result of HF. Monitoring of beta-lactams should be offered to all children with cancer to ensure best therapeutic success and avoid the development of resistance.

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013

IMPROVED EARLY VANCOMYCIN EXPOSURE IN NEONATES USING A POPULATION PHARMACOKINETIC MODEL-BASED VANCOMYCIN DOSING REGIMEN

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Background We previously documented that 2 published vancomycin dosing regimens resulted in subtherapeutic exposure in 66.3 and 76.2% of neonates.¹ A new dosing regimen derived from a population pharmacokinetic (PK) analysis and using a loading dose, was implemented in our unit.² We aimed to investigate if the new regimen results in improved vancomycin exposure (target trough 10–15 mg/L).

Methods Clinical data and early (24 h after start) vancomycin therapeutic drug monitoring (TDM) in neonates receiving vancomycin for medical reasons, were retrospectively collected and pooled with 2 historical cohorts [cohort 1 (2011, n=193 observations), dosing based on postmenstrual age (PMA) and creatininemia and cohort 2 (2012, n=101 observations), dosing based on PMA and postnatal age (PNA)]. The new regimen [cohort 3 (2018, n=71 observations)] consists of a loading dose, followed by dosing based on birthweight, PNA and ibuprofen co-treatment [2]. Clinical characteristics and early TDM were compared across the cohorts using the Kruskal-Wallis Test. Results were significant if $p < 0.05$.

Results Clinical characteristics (cohort 1, 2 and 3 respectively) did not differ significantly across the cohorts. Median (IQ range) GA was 32.8 (28.4–37.6), 32.1 (28.5–37.5), 28 (26–38) weeks with $p=0.097$; PNA 13 (6–26), 12 (7–23), 14 (10–25) days with $p=0.15$ and creatininemia 0.43 (0.33–0.55), 0.49 (0.33–0.65), 0.45 (0.32–0.57) mg/dL with $p=0.15$. Median vancomycin trough level was 7.8 (5.1–11.3), 5.8 (4.1–8.7), 13.3 (9.9–17.3) mg/L with $p < 0.0001$. With the new

regimen, 25.4% of trough levels was < 10 mg/L, 40.8% > 15 mg/L, and 33.8% was on target, versus 23.3 and 19.8% on target in cohort 1 and 2 respectively.

Conclusion A population PK model-based vancomycin dosing regimen using a loading dose, resulted in improved neonatal vancomycin exposure. Although only 25% of trough levels was subtherapeutic, dosing optimisation for cases with supra-therapeutic exposure is also needed, as well as further prospective validation.

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PATERNAL ACITRETIN EXPOSURE AND PREGNANCY RISKS

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Background In the literature it is well known that acitretin is highly teratogen when used in pregnant women. Therefore, several restrictions to all fertile women prior, during and up to three years after ended treatment are recommended. However, as for paternal acitretin exposure data is very limited leading to worries and anxiety among couples planning or already pregnant.

Methods We conducted a nationwide cohort study during the period between 1996–2016 investigating paternal acitretin exposure and the risk of spontaneous abortions and the association to major malformation. Data were obtained from the Medical Birth Registry and the National Hospital Registry. All fathers exposed to acitretin were identified by the Danish National Prescription Registry.

Results We identified in total 1.477.252 registered pregnancies with known father identity. Of these 244 pregnancies and 205 children were exposed to paternal acitretin treatment between one year prior to conception to the end of first trimester. The adjusted hazard risk (HR) of spontaneous abortion was 0.71 (95% CI: 0.43–1.17). When analysing exposure three months prior to conception and during first trimester only, the adjusted HR was 0.76 (95% CI: 0.38–1.51) and 1.06 (95% CI: 0.55–2.04), respectively. As for the association between major malformation and paternal acitretin exposure between one year prior to conception to the end of first trimester the adjusted odds ratio (OR) was 1.15 (95% CI: 0.57–2.34). When stratifying for the period of acitretin exposure the same insignificant trend was detected. In addition, both spontaneous abortions and major malformation were independent of dosage.

Conclusion We found no increased risk of spontaneous abortions or major malformation in pregnancies exposed to paternal acitretin one year before to three months after conception. This was persistent when sub-analysing exposure period and dosage. These data are an important contribute to the sparse evidence suggesting that paternal acitretin exposure during fertility is safe.

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