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PHARMACOKINETICS OF PROPHYLACTIC AND THERAPEUTIC FLUCONAZOLE IN PRETERM NEONATES

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Introduction Fluconazole is a first choice drug for neonatal cerebral candidiasis and for prevention of candidemia/invasive candidiasis in neonates. Selection of the optimal neonatal dose is difficult and requires solid multiple dose pharmacokinetic (PK) research to guide dosing decisions. We performed a pharmacokinetic study in preterm neonates who received fluconazole prophylactically or as treatment.

Methods Preterm neonates received fluconazole according to local protocol for either prophylaxis or treatment in 5 different hospitals. Samples were collected on multiple occasions with an opportunistic sampling scheme. Patient characteristics were bodyweight, birthweight, postnatal age (PNA), gestational age (GA), postmenstrual age, gender and weight for age. Population PK modelling was performed using NONMEM V.7.3.

Results In 44 preterm neonates (median (range) GA 25.3 (24.0–31.3) weeks), 153 plasma samples were collected. Median PNA at treatment initiation was 1 (0–59) day, treatment duration 11 (2–67) days and median PNA during treatment 15 (4–60) days. A one-compartment model described the data best, with an estimated clearance (CL) for a neonate of 0.84 kg and PNA of 15 days of 0.0147 L/h (RSE 4.3%, interindividual variability 21.4%) and volume of distribution (V_d) of 0.815 L (RSE 5.9%). Bodyweight was found to influence both CL and V_d , with exponents of 1.05 (RSE 13.4%) and 1.19 (RSE 22.4%), respectively. Maturation of CL was best described by an exponent of 0.184 on PNA (RSE 34.3%).

Conclusion In this pharmacokinetic study on fluconazole in preterm neonates, CL was influenced by both bodyweight and PNA while V_d was influenced by bodyweight only. These findings imply that initial dosing of fluconazole in preterm neonates should be based on bodyweight and that an increase of the dose with 32% during the first week and with 47% during the first month of life could be necessary because of increasing clearance with PNA.

Disclosure(s) Nothing to disclose

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DRUG DELIVERY KINETICS OF INTRAVENOUS GENTAMICIN IN A POPULATION OF NEONATES

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Background Gentamicin is commonly used in the NICU setting and is often administered via long lines, which increases variability in the rate of administration. We aimed to model

drug delivery pharmacokinetic parameters for intravenous gentamicin administered via umbilical venous catheters (UVCs).

Methods Data was modelled from infusion simulations of gentamicin delivery using UVCs with a background flow rate of 0.5 ml/h.¹ Different combinations of dose (2 mg, 5 mg) were given by bolus injection over 3–5 minutes, followed by a normal saline flush (1 ml, 2 ml). Gentamicin levels were measured at 5 minute intervals over an hour via high pressure liquid chromatography.

Phoenix Certara (version 8.1) was used for modelling. An extravascular model with clearance removed was used to predict parameters: absorption constant (K_a), time lag (Tlag), and bioavailability (F). F was used to enable an estimate of the variability in dose administered. Different error models were tested to ascertain which best described the data.

Results An extravascular one compartment model with first order absorption and additive error best described the data. Estimates for the model with a 2 mg dose and 1 ml flush were K_a 0.341/min, Tlag 1.28min, F 0.97, standard deviation (stdev) 0.14. For 2 mg, 2 ml flush, estimates were K_a 0.861/min, Tlag 3.01min, F 0.87, stdev 0.01. For 5 mg, 1 ml flush, estimates were K_a 0.481/min, Tlag 3.13min, F 1.03, stdev 0.12. For 5 mg, 2 ml flush, estimates were K_a 0.831/min, Tlag 3.29min, F 1.09, stdev 0.02. For each model $epsshrinkage$ and $nshrinkage$ for Tlag and F were low, however $nshrinkage$ for k_a was 0.9999.

Conclusion This is the first known modelling of gentamicin delivery kinetics. The studies all had high $nshrinkage$ for K_a , therefore the individual estimates of k_a may be unreliable. Further studies with a higher number of replicates would provide more favourable data for estimating K_a .

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EFFECT OF HEMODIALYSIS DOSE (SPKT/V) ON SURVIVAL IN PATIENTS ON MAINTENANCE HEMODIALYSIS SINCE CHILDHOOD – A RETROSPECTIVE ANALYSIS

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Background Hemodialysis (HD) prescription significantly differs between pediatric and adult patients on maintenance HD, resulting in greater difference between prescribed and delivered HD dose.^{1,2} HD dose targets have formally not been evaluated for children, hence targets are mainly derived from adults ($spKt/V > 1.4$; sp : single-pool model of urea distribution, K : urea clearance, t : duration of HD session, V : urea distribution volume). This analysis aimed to evaluate the relationship between delivered dialysis dose and survival in a large cohort of patients having started HD therapy in childhood.

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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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