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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.