Background The broad-spectrum antiparasitic drug ivermectin is widely used in children, and its use in children weighing < 15 kg is off-label, as little data is available to inform the use of ivermectin in this young age group. Pediatric doses associated with consistent exposure across age are still unknown. Therefore, we aim to identify a dosing strategy for ivermectin treatment in both pre-school-aged children (2–5 years of age) and school-aged children (6–12 years of age) that achieves equivalent exposure coverage in children and adults.
Methods A population pharmacokinetic model for ivermectin was developed based on data collected in 80 pre-school-aged children (2–5 years), 120 school-aged children (6–12 years),[1] and eleven adults,[2] receiving an oral dose of 100–600 µg/kg ivermectin. Model-based simulations were performed to optimize pediatric dosing to achieve consistent exposure across various age groups.
Results Clearance per kilogram was higher in children than in adults, with a median (90% confidence interval) of 0.35 (0.12–0.73) L/h/kg in children compared to 0.20 (0.10–0.31) L/h/kg in adults. As a result, ivermectin exposure in children following a 200 µg/kg dose is ~30% lower than in adults. An increased dose of 250 and 300 µg/kg would be needed in school-aged children (6–12 years) and pre-school-aged children (2–5 years), respectively, to achieve equivalent exposure coverage in children and adults. Alternatively, we propose a height-based dosing schedule with a stepwise increase in number of administered 3-mg-tablets from 1 to 5 for children in sub-Saharan Africa with a height of 75–90 cm, 90–130 cm, 130–150 cm, 150–165 cm, and 165–175 cm.
Conclusion We report the first dosing strategy for the widely-used drug ivermectin that is associated with equivalent exposure coverage in children and adults. Further studies are necessary to establish the safety and efficacy of appropriate doses in the pediatric population.

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025 CLAVULANATE STABILITY IN CHILD-APPROPRIATE FORMULATIONS IS INADEQUATE FOR USE IN TREATING YOUNG CHILDREN IN ASIA

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Background Amoxicillin-clavulanate (AMC) is among the most frequently used antibiotic for paediatric infections globally. AMC child-appropriate formulations are largely limited to dry powder suspensions, which have to be stored refrigerated once reconstituted due to stability limitations of clavulanate.
Methods Oral Amoxicillin (AMX) and AMC formulations were identified from IQVIA-MIDAS wholesale data, and 2015 antibiotic consumption in courses/1000 child-years was estimated in Bangladesh, India, Indonesia, Pakistan, Philippines and Vietnam with an assumed average treatment of 7 days. Costs per course in US-$ standardised to 2015 were estimated from the same dataset. Nationally representative data on access to a refrigerator was extracted from the Demographic & Health Surveys Program. Degradation under different temperature conditions of two different AMC suspensions commercially available in Switzerland was tested. Average degradation (three bottles of each product) was measured during 8 days with ambient temperatures of 8°C versus 28°C.
Results In India and Pakistan more AMC than AMX courses were sold. In all countries AMC was at least twice and up to 10 times as expensive as AMX. Access to refrigeration was below 45%, even in countries with a high number of sold AMC courses (compared with AMX). In the evaluated co-formulated products, clavulanate showed a maximum degradation of 34% at 8°C, and 73% at 28°C after 8 days. AMX was largely stable at 8°C but 13% degraded at 28°C after 8 days.
Conclusions Oral amoxicillin-clavulanate suspensions are widely used in six Asian countries classified as middle-income countries by the World Bank. In reconstituted liquid AMC formulations, neither component is satisfactorily stable at room temperature. Storage conditions for stability are likely inadequate for AMC in many households in the six Asian countries of interest.
Disclosure(s) Nothing to disclose

026 POPULATION PHARMACOKINETIC META-ANALYSIS OF INDIVIDUAL DATA TO DESIGN THE FIRST RANDOMIZED EFFICACY TRIAL OF VANCOMYCIN IN NEONATES AND YOUNG INFANTS

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Background In the absence of consensus, the present meta-analysis was performed to determine an optimal dosing regimen of vancomycin for neonates.
Methods A 'meta-model' using NONMEM with 4894 concentrations from 1631 neonates was built and Monte Carlo simulations were performed to design an optimal intermittent infusion, aiming at reaching a target AUC0-24 of 400 mg*h/L at steady state in at least 80% of neonates.

Results A two-compartment model best fitted the data. Current weight, post-menstrual age (PMA) and serum creatinine were the significant covariates for clearance (CL). After model validation, simulations showed that a loading dose (25 mg/kg) and a maintenance dose (15 mg/kg twice daily if < 35 weeks PMA and 15 mg/kg three times daily if ≥ 35 weeks PMA) achieved the AUC0-24 target earlier than a standard 'Blue Book' dosage regimen in more than 89% of the treated patients.

Conclusions The results of a population meta-analysis of vancomycin data have been used to develop a new dosing regimen for neonatal use and assist in the design of the model-based, multinational European trial, NeoVanc.

Disclosure(s) Nothing to disclose

027 PROSPECTIVE EVALUATION OF A POPULATION PHARMACOKINETIC MODEL OF PANTOPRAZOLE FOR OBESE CHILDREN

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Background Pharmacokinetic (PK) data for proton pump inhibitors, acid suppressive medications commonly prescribed to children, are lacking for obese children who are at greatest risk for acid related disease. Our aim was to evaluate the performance of the only published population PK model of pantoprazole for obese children, in an independent cohort of obese and non-obese children.

Methods A published 2-compartment structural model,[1] modified to exclude transit compartments for delayed absorption, was used to predict the PK of pantoprazole (PAN) oral suspension, immediate release (k_a=7.3 hr^{-1}). Calculated population parameters and covariate relationships (e.g., weight, CYP2C19 genotype) were extracted. Predictions were based on dose, sampling times, and covariates from 57 children (6–17 years; 21% obese, 28% overweight) who received a single dose PAN and had plasma PAN concentrations collected at 10 time-points over 8 hours. Model predictive performance was assessed visually and by relative root mean squared error (RMSE), with mean ratio of predicted-to-observed area under the concentration time curve (AUC) compared via one-way ANOVA across weight groups, defined by body mass index for age (10–84th percentile normal-weight, 85–94th percentile overweight, >95th percentile obese; α=0.05, R).

Results The model generally over-predicted observed PAN concentrations (RMSE 194%). Ratios of predicted versus observed AUC were not significantly different among obese, overweight and normal-weight children (1.5 vs. 1.7 vs. 2.2, p=0.06); however, a trend toward better model prediction was observed in the subset of obese children.

Conclusion Observed PAN PK deviated from model predictions, which may be due to differences in patient demographics or PAN formulation. A validation study using a delayed release PAN formulation is in progress, with the overarching goal of understanding PAN disposition, and appropriate dose selection, for obese children, who are at potential risk for drug over- or under-dosing using commonly employed dosing strategies in pediatrics (e.g., mg/kg, weight-tiered).

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028 VARIABILITY IN LIVER ANATOMY AND PHYSIOLOGY IN CHILDREN PARTICIPATING IN PHARMACOKINETIC STUDIES

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Background Obesity-related changes in liver anatomy and physiology (e.g., hepatic fat infiltration) may be important sources of interindivdual variability in hepatic drug metabolism and relevant covariates for physiologically-based pharmacokinetic (PBPK) models. The aim of this investigation was to quantify variability in hepatic fat fraction (HFF) and hepatic volume in children participating in PK studies, utilizing a novel, non-invasive, magnetic resonance imaging (MRI) sequence.[1]

Methods Children, without a known diagnosis of fatty liver disease, enrolled in a PK study for hepatic CYP2C19 and CYP3A4 substrates, had hepatic volume and total HFF estimated using MRI proton density fat fraction (PDFF) and HFF assessed via conventional MRI spectroscopy (MRSFF) using a region of interest in the right upper hepatic lobe (LiverLab, Siemens Healthcare). Patient anthropometrics, laboratories and LiverLab outcomes were compared between obese and non-obese children, using independent student t-test, and associations explored via Spearman's correlation (ρ); SPSSv24, α=0.05. Obesity was defined by body mass index (BMI)≥ 95th percentile for age; clinically significant liver adiposity defined as HFF>5%.

Results 25 children (7–20 years; 56% obese) had evaluable MRI data. Liver volume ranged 911–2227cm^3, MRSFF 1.6–34.8% and PDFF 2.1–31.1%. Liver volume and HFF significantly correlated with BMI (both ρ=0.6, p< 0.01), but not age (both ρ=0.3, p>0.11). Liver volume (1574.5±367.1 vs 1284.8±216.3, p=0.04), MRSFF (8.9±8.4 vs 2.8±1.2, p=0.02), PDFF (8.9±7.0 vs 3.4±1.3, p=0.07) and alanine aminotransferase (ALT; 37.7±15.8 vs 26.8±3.6 IU/L, p=0.02) were higher in obese vs non-obese children. HFF>5% and ALT> 40 were only observed in obese children.

Conclusion Liver volume and adiposity varied substantially among children and may be important covariates for pediatric PBPK models, especially for obese children. HFF> 5% and ALT> 40 were only observed in obese children. Recently, 24% reduction in clearance of azithromycin, a CYP3A4 substrate, was reported for children with ALT> 40.[2] Our PK analyses are in progress.

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