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. 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 ioxhol. PK modelling was performed with Phoenix
® WinNonlin®.

Results The clearance of ioxhol was 97.9 ± 16.1 ml/min/m² (mean ± 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. 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). 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.

REFERENCES

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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 potentialing to liver and renal dysfunction. Altogether, these 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).

Conclusion SCD alters drug disposition of commonly used drugs but data is scarce. A significant increase in clearance of 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).

REFERENCE

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A SMARTPHONE APPLICATION TO MONITOR NAUSEA IN PEDIATRIC CANCER PATIENTS DURING CHEMOTHERAPY

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Background Nausea is a common and distressing side effect for children in chemotherapy. Antiemetic recommendations are based on limited literature and prospective evaluation of antiepileptic efficacy is required. Smartphone applications (apps) may collect patient-reported outcomes with precision and effectiveness. We developed a smartphone app to track nausea in pediatric cancer patients during chemotherapy.

Methods Medical researchers, pediatric oncologists and software engineers worked synergistically in the development. We translated the validated Pediatric Nausea Assessment Tool to score nausea severity. We conducted three rounds of patient feedback and modification.

Results The app has a definition module where the child centers the concept of nausea. The child can then express nausea severity with four faces and the child’s own definition of nausea is incorporated in the question. The app includes a notification system to ensure high response rates. All participants felt that the app was user-friendly, intuitive and that time spent was acceptable.

Conclusions The app is a user-friendly tool to assess nausea in pediatric cancer patients that can ease future pediatric antiepileptic trials.

REFERENCES

Disclosure(s) Nothing to disclose

LIMITED SAMPLING STRATEGIES TO PREDICT VALGANCICLOVIR EXPOSURE IN KIDNEY TRANSPLANTED CHILDREN


Background Ganciclovir and its pro-drug, valganciclovir, are anti-viral drugs used in cytomegalovirus infections treatment in kidney transplanted children. Both present a high pharmacokinetic variability requiring dosage individualization and Therapeutic Drug Monitoring to ensure optimal therapeutic exposure. This retrospective monocentric study aimed to develop a Limited Sampling Strategy (LSS) predicting Area Under the Curve (AUC0-24h) reducing the number of blood samples to improve and facilitate kidney transplanted children medical care.

Methods Pediatric kidney transplanted children treated with valganciclovir were included. Rich pharmacokinetic data from ganciclovir plasmatic dosages (sampling times at 0h, 1h, 2h, 4h, 8h, 12 h and 24 h) were collected between February 2005 and November 2018. Ganciclovir exposures at steady-state (AUC0-24h) were calculated using the trapezoidal method. The LSS was developed using a multilinear regression approach to predict AUC0-24h. The overall patients population was divided into two groups for model development and validation purposes.

Results 129 patients were included: 46 girls and 83 boys, mean age at transplantation was 11.3 years ± 5.1. Multilinear regression models were developed on 85 pharmacokinetic profiles (85 patients, mean AUC0-24h=64 μg.h/mL ± 27, creatinine clearance=72.4 mL/min per 1.73 m2) and validated on an independent group of 73 pharmacokinetic profiles (44 patients). Regressions based on samples collected at 0, 2, 4 h (R=0.946) of 0, 2, 8 h (R=0.968) presented the best AUC0-24h predictive performances (RMSE=7.5 and 6.6, MAE=5.7 and 4.8 respectively) with an average difference between reference and predicted AUC0-24h of -0.52 and 0.67 μg.h/mL respectively.

Conclusions To date, this is the largest cohort of valganciclovir treated pediatric transplanted children used to develop a LSS. This LSS allows to accurately predict ganciclovir AUC0-24h in pediatric transplanted patients using 3 pharmacokinetic blood samples at 0h, 2h, and 4 h post-dose. Beside other Bayesian estimators developed in the literature, this multilinear regression can be easily implemented into daily practice facilitating patients care.

Disclosure(s) Nothing to disclose

NO INTERACTION BETWEEN DOXAPRAM AND CAFFEINE FOR THE TREATMENT OF PRETERM NEONATES WITH APNEA

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Background In preterm neonates with apneas, co-administration with doxapram is often initiated in case of inadequate response to caffeine alone. While doxapram is exclusively registered for adults, there is limited information on its use in preterm infants. To examine whether the observed effects of doxapram are actually due to doxapram itself, and not a pharmacokinetic interaction between both respiratory stimulants, we studied the pharmacokinetics (PK) of caffeine in a population of preterm neonates receiving both caffeine and doxapram.

Methods Caffeine concentrations from patients in the DINO study (NCT02421068) who received both caffeine and doxapram were analyzed using NONMEM V7.3. A PK model of caffeine in preterm neonates was used as a basis to estimate the PK parameters of caffeine when co-administered with doxapram with F fixed to 1 and ka fixed to 1.48 h⁻¹. The