P111 DEVELOPMENTAL PHARMACOGENETICS OF CYP2D6 IN CHINESE CHILDREN: LORATADINE AS A PROBE DRUG

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Background Although the understanding of CYP2D6 developmental pharmacogenetics in children has made great progress, the current findings are mainly focused on Caucasian children. Given the clear ethnicity difference of CYP2D6 pharmacogenetic profile, there are still unmet needs in understanding developmental pharmacogenetics in inter-ethnic population. We sought to use loratadine as a probe drug to evaluate the effects of ontogeny and pharmacogenetics on the developmental pattern of CYP2D6 in Chinese paediatric patients.
Methods Chinese children receiving loratadine treatment were enrolled in the present study. The metabolic ratio (MR) of loratadine converted to desloratadine [desloratadine concentrations/loratadine concentrations] of trough concentrations samples at steady-state condition was used as a surrogate of CYP2D6 activity. Loratadine and desloratadine were determined by LC/MS/MS method and variants of CYP2D6 were genotyped.
Results A total of 40 patients were available for final analysis. The mean age was 4.6 (range 0.5–9.0) years and the mean weight was 19.9 (range 9.0- 42.0) kg. The MR was significantly higher in homozygous wild-type subjects compared with CYP2D6*10 subjects (16.94±14.12 versus 9.37±7.54, p = 0.028). Weight was also found to be significantly corrected with MR (p = 0.030).
Conclusions The developmental pharmacogenetics of CYP2D6 in Chinese children was evaluated using loratadine as a probe drug. Weight and CYP2D6 genotype showed independently significant impacts on MR.
Disclosure(s) Nothing to disclose.

P112 PREDICTION OF FREE CEFTRIAXONE CONCENTRATION IN CHILDREN: DISEASE AND MATURATION DO MATTER

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Background To evaluate the predictive ability of the existing formula to measure free ceftriaxone levels in children, and optimize the formula by adding disease and maturation factors.
Methods Fifty children receiving ceftriaxone were evaluated, and the predictive performance of the different equations were assessed by mean absolute error (MAE), mean prediction error (MPE) and linear regression of predicted vs. actual free levels.
Results The average free ceftriaxone concentration was 2.11 ± 9.51μg/ml. The predicted free concentration was 1.15 ± 4.39μg/ml with the in vivo binding equation, which increased to 1.58 ± 7.73μg/ml and 2.01 ± 9.53μg/ml when adjusted for age (disease adapted equation), and age and albumin (disease-maturation equation) respectively. The average MAE values were 0.48 (in vivo banding equation), 0.34 (disease adapted equation) and 0.41 (disease maturation equation). The average MPE values were -0.41 (in vivo binding equation), 0.14 (disease adapted equation) and 0.09 (disease maturation equation). The respective linear regression equations and coefficients were $y=1.8647x+1.0731(R2=0.7398)$, $y=1.1455x+0.8414(R2=0.8674)$, and $y=0.9664x(R2=0.8641)$ for the in vivo binding, disease adapted and disease maturation equations respectively.
Conclusion Compared to the in vivo binding equation, the disease adapted and disease maturation equations showed lower MAE and MPE values, and the latter showed the lowest MPE value. In addition, the slope of the disease maturation equation was closer to 1 compared to the other two. Therefore, the optimized disease maturation equation should be used to measure free ceftriaxone levels in children.
Disclosure(s) Nothing to disclose.

P113 POPULATION PHARMACOKINETICS AND DOSING OPTIMIZATION OF AZLOCILLIN IN NEONATES

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Background Azlocillin is prescribed for the treatment of infections in neonatal clinical practice, however, the optimized dose is still questionable due to the lack of pharmacokinetic study Thus, we aim to evaluate the population pharmacokinetics of azlocillin and optimize dosing regimen in order to improve azlocillin treatment in neonates.
Methods This is a prospective, open label pharmacokinetic study of azlocillin. Blood samples were collected using an opportunistic sampling design. Theplasma concentrations ofazlocillinwere determined by high performance liquid chromatography method with UV detection. Population pharmacokinetic-pharmacodynamic analysis was performed using NONMEM software.
Results Ninety-five neonates (postmenstrual age (PMA) range 32.1–42.0 weeks) were included in this study. A total of 167 azlocillin concentrations were available for the final analysis. A one-compartment model with first-order elimination best fitted the data. Covariate analysis demonstrated that current weight, birth weight and postnatal age had significant effect on azlocillin pharmacokinetics. MonteCarlo simulation demonstrated that for the common pathogens with MIC of 8 mg/liter, the currently used dosage regimen (100 mg/kg, q12h) resulted in 61.2% of newborns achieved the pharmacodynamic target (drug concentrations above MIC during 70% of the dosing interval) with a potential risk of underdosing. When shortening the dosing interval to 8 hours, the target could be achieved in 89.3% of patients, using the MIC break point of 8 mg/liter.
Conclusion The population pharmacokinetics characteristics of azlocillin were assessed in neonates. An optimal dosage regimen of azlocillin was established based on developmental pharmacokinetics-pharmacodynamics in this vulnerable population.