Physiologically-based pharmacokinetic model to investigate the effect of pregnancy on risperidone and paliperidone pharmacokinetics: Application to a pregnant woman and her neonate

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学 位 論 文 の 内 容 要 旨

Physiologically-based pharmacokinetic model to investigate the effect of pregnancy on risperidone and paliperidone pharmacokinetics: Application to a pregnant woman and her neonate

リスペリドンおよびパリペリドン薬物動態に対する妊娠の影響を検討した

生理学的薬物動態モデル：妊婦とその出生児への適用

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Introduction

Risperidone (RIS) is one of the most commonly prescribed antipsychotic drugs for managing schizophrenia and bipolar disorder. The safety profile for RIS during pregnancy is still unknown. Although animal studies have demonstrated that RIS does not cause direct reproductive toxicity or teratogenic effects, human case studies have shown that RIS may cause significant unwanted effects, ranging from self-limiting side effects to newborns requiring intensive care and prolonged hospitalization. Therefore, RIS prescriptions for pregnant women are restricted to circumstances in which the benefits outweigh the risks to the fetus. Pregnant women and newborns are often excluded from scientific studies due to ethical and legal concerns. Consequently, current knowledge on optimal dosing regimens, pharmacokinetics, and safety characteristics of various drugs during pregnancy, fetal, and neonatal periods is inadequate. One possible solution is using physiologically-based pharmacokinetic (PBPK) modeling, which incorporates drug-specific parameters (e.g., physicochemical and disposition characteristics), physiological parameters relevant to pharmacokinetic processes, and clinical trial designs to generate a quantitative predictive model, might be a feasible approach for optimizing dosing regimens in pregnant and pediatric populations.

The objectives of this study were to develop, verify, and personalize pediatric and pregnant PBPK models for RIS and its active metabolite paliperidone (PAL). Consequently, we applied this personalized PBPK model to the assessment of RIS and PAL pharmacokinetics in a Japanese pregnant woman and her newborn by utilizing the "virtual twin" approach to estimate the risk of toxicity in pregnant and neonatal populations. Then, we investigated which physiological changes with pregnancy affects RIS and PAL pharmacokinetics by using a fixed-parameter approach.

Materials and Methods

PBPK models for RIS and PAL in adults, pediatric, and pregnant populations were developed and verified using the Simcyp simulator. The following criteria were predetermined to assess model performance. First, visual predictive check for predicted

(C_{pred}) and observed (C_{obs}) serum concentrations was used. The model was verified when the observed values were within the virtual population's 90% prediction interval (5th–95th percentile range), and the ratio of the predicted value to the observed value was within a two-fold difference. Moreover, the C_{pred} and the respective C_{obs} were compared in goodness-of-fit plots. Then, to assess the prediction bias and precision of each analyte concentration, the mean error percentage (ME) ± standard error (SE) and root mean square error (RMSE) of the C_{pred} compared with the C_{obs} were calculated.

RIS and PAL serum concentrations were determined in a pregnant woman and her newborn by liquid chromatography-tandem mass spectrometry. PBPK models were then applied to our two subjects, generating their "virtual twins." Effects of pregnancy on RIS and PAL were examined using models with fixed pharmacokinetic parameters. A fixed-parameter approach was used to assess the extent to which physiological changes associated with pregnancy affect RIS and PAL pharmacokinetics. In the neonatal PBPK simulation, ten methods, comprising four maturation-based models and six serum creatinine-based equations, were selected from glomerular filtration rate (GFR) estimates approaches published in the literature.

Results and Discussion

We developed a PBPK model using five previous studies in healthy adults (internal dataset), then we confirmed its accuracy by comparing its results to data from another seven studies (external dataset). The verified model was consequently extrapolated to pediatric population and validated by comparing the simulated pharmacokinetic data to the observed clinical data. Additionally, by parameterizing and expanding the model structure to pregnancy-induced physiological changes, the adult (non-pregnant) PBPK model for RIS and PAL was extrapolated to the pregnancy population. Then, it was utilized to estimate active moiety (RIS plus PAL) plasma concentrations at baseline (pregnancy week 0) and by trimester during pregnancy. The unique final step was to individualize the final pediatric and pregnant PBPK models and use them to predict the serum disposition of RIS and PAL in a Japanese woman and her newborn. The developed PBPK models accurately predicted PAL's

pharmacokinetics, as shown by minimal bias and acceptable precision across populations. The individualized maternal model predicted all observed PAL concentrations within the 90% prediction interval.

Our patient gave birth vaginally to a male child after 40 weeks and five days of gestation. At birth, there were no signs of toxicity related to the use of RIS, and the baby was born healthy without any congenital malformations or neonatal abstinence syndrome. In our case, the maternal RIS concentrations were not detected in all samples (below 0.5 ng/mL), and the serum PAL concentrations were between 2.05−3.80 ng/mL before childbirth and 3.80–9.90 ng/mL postpartum. The PAL concentrations seemed to increase after birth, although the dosage of RIS was only changed from 0.5 mg twice a day to 1 mg once a day.

During pregnancy, changes in oral bioavailability, tissue volumes, blood protein bindings, enzyme activity, and cardiac output can theoretically cause this observed decrease in the AM concentration throughout pregnancy. In our PBPK analysis, at the end of pregnancy, simulated intrinsic clearance (CL) of RIS and PAL mediated by CYP2D6 were three times higher than in the nonpregnant state, and simulated total CL of RIS and PAL were increased 1.61 and 1.95-times, respectively. Although hepatic CYP2D6 induction during pregnancy promotes PAL production through RIS 9-hydroxylation, the increased total CL of PAL nullified the increase in PAL concentrations. Actually, in the fixed-parameter combined model, where all the parameters of interest were held constant, the predicted PAL maximum concentration as well as RIS total CL were almost equal to the values observed in the non-pregnant state. Namely, the decreased serum albumin and the increased fetoplacental volume, GFR, and CYP2D6 activity, with a concomitant increase in PAL production from RIS hepatic metabolism, influenced RIS and PAL pharmacokinetics during pregnancy.

The RIS concentrations in the umbilical artery and vein were undetectable, whereas the PAL concentrations were 1.10 and 1.05 ng/mL in the umbilical artery and vein, respectively. This assessment of the fetal drug exposure may aid in directing treatment selection and providing a greater insight into the extent to which intrauterine drug exposure is primarily responsible for neonatal potential toxicity. The median PAL maternal-to-cord concentration ratio was determined to be 2.83 at steady-state (typically after 4-5 days for PAL), which

corresponds reasonably well with previous findings. In another previous study, the maternal-to-cord plasma ratio for AM was determined to be 2.44 ± 2.80 [standard deviation], which coincides to the ratio for PAL alone.

RIS was not detected in the neonatal serum samples (below 0.5 ng/mL). The neonate serum PAL concentrations were 0.99, 1.03, 0.83, and 0.82 ng/mL on 0, 1, 2, and 3 days after birth, respectively, and became undetectable afterward. Due to the expected poor clearance in neonates, we evaluated numerous GFR estimating approaches to identify the optimal ontogeny model for this vulnerable population using our personalized PBPK model. The Flanders metadata equation consisting of serum creatinine, body height, and age showed the lowest absolute bias (ME: 22.3% ± 6.0%) and the greatest precision (RMSE: 23.8%) in predicting PAL plasma concentration in the neonatal population.

Conclusion

Our PBPK model elucidated the mechanisms underlying the observed variations in RIS and PAL serum concentrations and clearances in pregnant women and newborns. Our study has three main implications: (1) laying out a strategy for using PBPK to predict drug disposition in an individual patient with limited serum samples; (2) identifying key parameters that influence drug pharmacokinetic parameters in pregnant women; and (3) comparing various maturation models and formulas for calculating eGFR in our newborn. As part of model-informed precision dosage, this model may help optimize RIS dosing regimens across populations, moving away from a "one-size-fits-all" approach and avoiding subtherapeutic or toxic doses that could expose the mother and fetus to both the medicine and the disease.

神戸大学大学院医学(系)研究科（博士課程）

論文審査の結果の要旨

受付番号	甲 第3280号	氏　名	Walaa Yousef Bassyouni Mahdy
論文題目 Title of Dissertation	Physiologically-based pharmacokinetic model to investigate the effect of pregnancy on risperidone and paliperidone pharmacokinetics: Application to a pregnant woman and her neonate リスペリドンおよびパリペリドン薬物動態に対する妊娠の影響を検討した生理学的薬物動態モデル：妊婦とその出生児への適用		
審査委員 Examiner	主　査 Chief Examiner 古屋敷智之 副　査 Vice-examiner 野津寛大 副　査 Vice-examiner 矢口純一		

（要旨は１，０００字～２，０００字程度）

Introduction

Risperidone is one of the most commonly prescribed antipsychotic drugs for managing schizophrenia and bipolar disorder. In the Australian classification system for prescribing medications during pregnancy, risperidone is categorized as a category C drug, and risperidone prescriptions for pregnant women are restricted to circumstances in which the benefits outweigh the risks to the fetus. Consequently, current knowledge on optimal dosing regimens, pharmacokinetics, and safety characteristics of various drugs during pregnancy, fetal, and neonatal periods is inadequate.

The objectives of this study were to develop pediatric and pregnant physiologically-based pharmacokinetic (PBPK) models for risperidone and its active metabolite paliperidone. The developed PBPK model was applied to evaluate risperidone and paliperidone pharmacokinetics in a Japanese pregnant woman and her newborn, and clarified physiological changes with pregnancy and maturation affecting risperidone and paliperidone pharmacokinetics.

Methods

A PBPK model using the Simcyp simulator was developed using five previous studies in healthy adults, and its accuracy was confirmed by comparing its results with data from another seven studies. The model was then extrapolated to pediatric population and verified by comparing the simulated pharmacokinetic data to the reported clinical data. By parameterizing and expanding the model structure to pregnancy-induced physiological changes, the adult (non-pregnant) PBPK model for risperidone and paliperidone was extrapolated to the pregnancy population.

Risperidone and paliperidone serum concentrations were determined in a pregnant woman and her newborn by liquid chromatography-tandem mass spectrometry. Developed PBPK models were applied to these subjects, generating their "virtual twins." Effects of pregnancy on risperidone and paliperidone pharmacokinetics were examined using a fixed-parameter approach to assess the extent to which physiological changes in the pregnancy were associated with their pharmacokinetics. In the neonatal PBPK simulation, ten methods, comprising four maturation-based models and six serum creatinine-based equations, were selected from glomerular filtration rate (GFR) estimates approaches published in the literature.

Results and Discussion

Developed PBPK models accurately predicted risperidone as well as paliperidone pharmacokinetics, as shown by minimal bias and acceptable precision across reported populations (healthy adults, pediatrics, and pregnant women). The patient gave birth to a male child after 40 weeks and five days of gestation. The maternal risperidone concentrations were not detected in all samples (below 0.5 ng/mL), and the serum paliperidone concentrations were between 2.05−3.80 ng/mL before childbirth and 3.80–9.90 ng/mL postpartum. The paliperidone concentrations seemed to increase after birth. The individualized maternal model predicted all observed paliperidone concentrations within the 90% prediction interval.

The study revealed that changes in oral bioavailability, tissue volumes, blood protein bindings, enzyme activity, and cardiac output during pregnancy can affect the pharmacokinetics of drugs and this should be considered when prescribing drugs during pregnancy. Fixed-parameter simulations showed that CYP2D6 activity largely affects risperidone and paliperidone pharmacokinetics during pregnancy.

In the newborn, risperidone was not detected in the serum samples (below 0.5 ng/mL).

The neonate serum paliperidone concentrations ranged between 0.82 ng/mL in the last day and 0.99 ng/mL in the first day. The Flanders metadata equation consisting of serum creatinine, body height, and age showed the lowest absolute bias (mean error: 22.3% ± 6.0%) and the greatest precision (root mean square error: 23.8%) in predicting paliperidone plasma concentration in the neonatal population.

Conclusion

Developed PBPK model elucidated the mechanisms underlying the observed variations in risperidone and paliperidone serum concentrations and clearances in pregnant women and newborns. This study has three main implications: (1) laying out a strategy for using PBPK to predict drug disposition in an individual patient with limited serum samples; (2) identifying key parameters that influence drug pharmacokinetic parameters in pregnant women; and (3) comparing various maturation models and formulas for calculating eGFR in the newborn.

The candidate, having completed studies on physiologically-based pharmacokinetic model analysis of risperidone and paliperidone in pregnancy, with a specialty in pharmacokinetic changes in the pregnant women and neonates, and having advanced the field of knowledge in the area of personalizing antipsychotic drug dosage regimens in the special populations, is hereby recognized as having qualified for the degree of Ph.D. (Medicine).