論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Name	島本　裕子
論文題名 Title	Model-Informed Vancomycin Dosing Optimization to Address Delayed Renal Maturation in Infants and Young Children with Critical Congenital Heart Disease （低年齢の先天性心疾患小児における腎臓機能発達遅延を考慮したバンコマイシン投与量適正化）

論文内容の要旨

〔目　的(Purpose)〕

Ensuring safe and effective drug therapy in infants and young children often requires accounting for growth and organ development; however, data on organ function maturation are scarce for special populations, such as infants with congenital diseases. Children with critical congenital heart disease (CCHD) often require multiple staged surgeries depending on their age and disease severity. Vancomycin (VCM) is used to treat postoperative infections; however, the standard pediatric dose (60–80 mg/kg/day) frequently results in overexposure in children with CCHD. In this study, we characterized the maturation of VCM clearance in infants and young children with CCHD and determined an age-appropriate dosing regimen for this special population using population PK modeling and simulations.

〔方法 (Methods)〕

Population PK modeling and simulation were performed using a nonlinear mixed effect modeling software, Phoenix NLME 8.4 (Certara, Princeton, NJ). To account for the effect of body size differences, the allometrically scaled body weight was applied to volumes of distribution and clearances in the base model with power coefficients of 1.0 and 0.75, respectively. Patient demographics and laboratory parameters were evaluated as candidate covariates on PK parameters using an exponential model. GFR increases rapidly during the first days of life and then steadily increases until adult values are reached at 8–12 months of age. To explain the developmental change, the maturation function described by postmenstrual age (PMA) was evaluated as a covariate on CL. TM50 is the PMA at which 50% of the maturation effect is reached and Hill is a slope of the maturation profile. Univariate analysis was conducted by individually incorporating each candidate covariate into the base model. To obtain the target attainment rate in the dosing simulation, a realistic virtual CCHD pediatric population was generated based on the age versus BW distribution observed in CCHD patients. The observed age-matched BW was modeled with a Box-Cox power exponential distribution using generalized additive modeling for location, scale, and shape (GAMLSS) strategy as implemented in the R software package library GAMLSS (version 4.3-8 under R.4.0). The virtual age-matched BW dataset (e.g., virtual CCHD pediatric population) was generated by the fitted model at five patients per 0.01 month up to 36 months (18,000 patients in total). The VCM CL in the virtual CCHD pediatric population was estimated by the developed population PK model at any given eGFR value. The daily steady-state AUC for a given daily VCM dose was then calculated by dividing the daily dose by CL. A target AUC/MIC ratios of 400 and 600 were used for the efficacy and safety target, respectively and the target attainment rate was calculated at a given eGFR and a given daily VCM dose. An MIC of 1 mg/L was used for the simulation because it is the most frequently reported MIC for MRSA in the European Committee on Antibacterial Susceptibility Testing (EUCAST) database.

〔成績(Results)〕

The PK model was developed using a two-compartment model with allometrically scaled body weight, estimated glomerular filtration rate (eGFR), and PMA as covariates. The observed clearances in patients aged ≤ 1 year and 1–2 years were 33% and 40% lower compared with that of non-CCHD patients, respectively, indicating delayed renal maturation in CCHD patients. Simulation analyses suggested VCM doses of 25 mg/kg/day (age ≤ 3 months, eGFR 40 mL/min/1.73 m^2) and 35 mg/kg/day (3 months < age ≤ 3 years, eGFR 60 mL/min/1.73 m^2).

〔総　括(Conclusion)〕

This study revealed delayed renal maturation in children with CCHD, could be due to cyanosis and low cardiac output. Model-informed simulations identified the lower VCM doses for children with CCHD compared with standard pediatric guidelines.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

抗MRSA薬バンコマイシン(VCM)は術後感染症の治療に使用されるが、標準的な小児用量では、過剰曝露が散見される。本研究では母集団薬物動態モデリングとシミュレーションを駆使し、重篤な先天性心疾患(CCHD)の乳児および幼児におけるVCMの体内動態特性を解明した。薬物動態モデル解析では、共変量として相対的成長率に基づく体重、推算糸球体濾過率および月経後週齢を組み込んだ2コンパートメントモデルを用いた。結果、1歳以下および1～2歳の患児におけるクリアランスは、非CCHD患児のクリアランスに比べそれぞれ33%および40%低く、CCHD患児における腎成熟遅延が示唆された。シミュレーションの結果、CCHD患児におけるVCM推奨投与量を月齢3か月以下及び3か月超え3歳以下に分けて設定することに成功した。本研究はCCHD患児における腎成熟の遅れを明らかにするとともに、VCM投与設計に有用な情報を提供しており、学位に値するものと認める。