

IV-31: Ferran Gonzalez Pharmacokinetic model development for total and free vancomycin in critically ill children

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Objectives: Vancomycin is an antibiotic agent used against Gram-positive bacterial infections. In order to achieve optimal target concentrations, it is essential to develop pharmacokinetic (PK) models. Specifically, determining the PK properties in paediatric populations is of clinical importance, since these are at high risk of inadequate concentrations. A number of vancomycin PK studies have already been performed in children, in which PK models were fitted to total vancomycin plasma concentration. However, to improve vancomycin dosages, unbound concentration needs to be considered, since this matrix is driving antimicrobial efficacy [1]. Therefore, the aim of this study was to develop a PK model of vancomycin considering total and unbound plasma concentration.

Methods: Data from a multicentric clinical trial were used, in which intermittent and continuous intravenous doses were administered to a cohort of 76 subjects aged between 0 and 14 years. A total of 395 samples were collected, measuring plasma concentrations of total and unbound vancomycin, albumin, creatinine and C-reactive Protein. Population PK models were developed using NONMEM VII. Initially, one and two-compartment models with first-order elimination rates were fitted to the total plasma concentration of vancomycin. A priori allometric weight scaling on clearance ($wt^{0.75}$) and volume (wt) was added, and a sigmoid maturation function driven by postmenstrual age was included for clearance. Finally, a two-compartment model using the same scaling, covariates and elimination rate was accounted for plasma protein binding to fit total and unbound vancomycin simultaneously, assuming linear protein binding.

Results: A two-compartment model with first-order elimination rate and maturation function described the PK of total vancomycin significantly better than the one-compartment model ($\Delta obj = 275.6$). The final parameter estimates, standardised to a 70kg mature individual, were 6.7 L/h for clearance (CL), 12.3 L for the central volume of distribution, 11.6 L/h for the inter-compartmental CL, 15.8 L for the peripheral volume of distribution, 60.5 weeks for PMA₅₀ and 1.9 for the Hill coefficient.

The two-compartment model fitted to the unbound and total vancomycin together resulted in the following estimated parameters for free vancomycin: 9.3 L/h CL, 15.6 L for the central volume of distribution, 11.7 L/h for the inter-compartmental CL and 21.1 L for the peripheral volume of distribution. Fraction unbound was estimated to be 0.7 and the estimated maturation parameters resulted in 59.3 weeks for PMA₅₀ and a Hill coefficient of 2.0.

Conclusions: In conclusion, PK models to estimate population parameters of vancomycin when using unbound and total plasma concentrations were developed. The estimated pharmacokinetic parameters were consistent with previous studies [2, 3]. Finally, the two-compartment model fitted to the unbound

and total concentration together exhibited a good distribution of the residuals. Future work will include a more exhaustive covariate analysis, and secondary structural and covariate model building by means of a genetic algorithm.

References:

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