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Investigating the role of altered organ blood flows on enantiomeric disposition of carvedilol in adult and pediatric chronic heart failure patients by using a physiologically based pharmacokinetic approach

Rasool M.F.(1, 2), Khalil.F.(1), Läer.S.(1)
Institute of Clinical Pharmacy and Pharmacotherapy, Heinrich-Heine University of Düsseldorf, 40225, Germany (1); Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan (2)

Introduction: Chronic heart failure (CHF) is associated with reduction in blood flow to different organs and has the potential to alter the pharmacokinetics (PK) of the drugs being administered. Carvedilol is a racemic mixture of R and S-enantiomers and shows extensive stereoselective first pass metabolism. The organ blood flow changes occurring in CHF can affect the stereo-selective disposition of carvedilol and may lead to increased incidence of adverse drug reactions.
Methods: Previously quantified organ blood flow reductions (liver, kidney, bone, skin, muscle and adipose) with respect to severity of CHF were incorporated into a whole body physiologically based pharmacokinetic (PBPK) model using population based PBPK simulator, Simcyp®. The developed model was used to predict carvedilol PK in adult CHF patients and after evaluation in adults, it was scaled to pediatric population on physiological basis using pediatric module of the program. The visual predictive checks and ratios(observed/predicted) for the PK parameters with a 2-fold error range were used for model evaluation.
Results: The predictions in healthy adults after intravenous and oral administration of carvedilol were comparable with the observed data. The predictions after incorporation of reduced organ blood flows in adult CHF patients categorized according to New York Heart Association (NYHA) functional classification of heart failure were in close agreement with the observed data and the ratios(observed/predicted) for the PK-parameters were within the 2-fold error range. The predictions in pediatric patients between the age range of 1 month and 14 years, who were classified according to Ross score, showed no improvement with incorporation of reductions in organ blood flows. While, amongst the adolescents above 17 years of age who were classified as adults, according to NYHA system, two out of three patients were better described with incorporation of reduction in organ blood flows.
Conclusion: The incorporation of reduced organ blood flows in the adult CHF patients resulted in significant improvement of the predictions but for the pediatric patients included in model evaluation, improvements were seen only in the adolescent age group and the infants and young children were better described without incorporating organ blood flow reductions.