Predicting morphine drug exposure in elderly using an age-informed physiologically based pharmacokinetic approach

Jan-Frederik Schlender¹², Michaela Meyer², Kirstin Thelen², Markus Krauss², Michael Block², Stefan Willmann², Thomas Eissing², Ulrich Jaehde¹

¹Institute of Pharmacy, Clinical Pharmacy, University of Bonn, 53121 Bonn, Germany; ²Bayer Technology Services GmbH, Computational Systems Biology, 51368 Leverkusen, Germany

Objectives: Elderly patients are often underrepresented in clinical trials, yet receive the majority of the prescribed drugs. The resulting knowledge gap regarding the pharmacokinetic (PK) drug exposure of elderly subjects may jeopardize their pharmacotherapy. The goal of this study was to apply a recently developed age-informed physiologically based pharmacokinetic (PBPK) approach to encompass the full course of healthy aging supporting dose selection of the test compound morphine. The results in this abstract have been published in part [DOI: 10.1007/s40262-016-0422-3].

Methods: The capability of the age-informed PBPK database to predict PK of drugs was verified using the software PK-Sim®, using intravenously administered Morphine as test compound. Morphine is mainly cleared by phase II metabolism. Literature information about plasma concentration time profiles and major PK parameters for morphine was compared to those predicted by PBPK simulations, for both younger and older adults.

Results: Based on the age-informed physiology, the predicted PK parameters described age-associated trends well. Using the age-informed physiology, the root mean squared prediction error was reduced by 49% for the simulations of plasma concentrations in elderly subjects. Individual Vss and t1/2 values were mostly within the two-fold range for the elderly population simulations.

Conclusions: The results of this study support the feasibility of using a knowledge-driven PBPK model to predict PK alterations throughout the entire course of aging, and thus to optimize drug therapy also in elderly individuals. These results indicate that pharmacotherapy and safety-related control of geriatric drug therapy regimens may be greatly facilitated by the information gained from PBPK predictions.