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Individualizing simvastatin dose with respect to CYP3A4 activity

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The study presented examined whether the dose adaptation of a CYP3A substrate to the enzyme's activity was feasible. Dose adaptation is a desirable approach to avoid adverse events from over-dosing, while guaranteeing sufficient therapeutic effect.

The example chosen for this study was simvastatin, a CYP3A4 substrate that is one of the most often administered drugs worldwide and usually prescribed with a combination of other medication. Topicality of the example was given by the Food and Drug Administration (FDA) restricting the use of simvastatin due to the risk of the adverse event of myopathy in summer 2011.

The starting point of the study was the question whether a CYP3A4 substrate, the example being simvastatin, could be individually adapted to CYP3A4 activity. This was researched in an open-label, randomized, three-arm, two-period, single-centre phase 1 study with 18 healthy volunteers. Partial oral midazolam metabolic clearance was determined in a limited sampling strategy, considering clinical practicability, and it represented the surrogate for CYP3A4 activity.

In preparation of the clinical study, a preliminary retrospective analysis of previous data on inter- and intra-individual variability of oral midazolam metabolic clearance was performed. It showed oral midazolam metabolic clearance, representing CYP3A4 activity, to be sufficiently stable for dose adaptation, while intra-individual variability was also smaller than inter-individual variability. An observed range in inter-individual variability of about 5 was in accordance with literature. On the basis of the results from the

retrospective analysis, a simvastatin dosing scheme for individual dose adaptation could be developed in preparation of this study.

Midazolam partial metabolic clearance and simvastatin exposure could be shown to correlate when a standard dose of 40 mg simvastatin was administered. Linearity of dose adaptation could be assumed. When individually adapted simvastatin doses were administered, correlation diminished and variability of simvastatin exposure decreased. While variability diminished, too, after co-medication with ritonavir, geometric mean simvastatin exposure increased, indicating most likely an interaction with p-glycoprotein and OATP1B1.

Overall, the concept of dose adaptation to CYP3A4 activity proved successful, indicating a possible way to safer and more effective drug therapy.