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Active metabolites formed during hepatic first-pass: simulations featuring their contribution to the overall effect in altered liver clearance and drug-drug interactions

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Background

Phase I and – occasionally – also phase II metabolites may contribute to the overall effect of a drug. This is not always apparent or revealed, since total concentrations of metabolites may be low in relation to parent drug concentrations. In the case of carvedilol, using a comparison of HPLC and β_1 -specific radioligand receptor binding assay (RRA), it was possible to demonstrate that regarding β -adrenoceptor blockade the effect appears directly linked to the serum compartment, which indicates instantaneous equilibrium between the blood compartment and the biophase, and that oxidative metabolites significantly contribute to the effect, particularly after oral administration. This drug serves as model compound in different approaches for evaluating the role of formation of active metabolites during first-pass when hepatic clearance varies.

Methods

A kinetic model, which includes the immediate transformation of a fraction of the dose into active metabolites during first-pass through the liver, i.e., before it reaches the systemic circulation (AM-FP model), was found superior to standard models.

Results

Overall, both systemic and oral clearance values were different for the two carvedilol enantiomers: 27.5 L/h (*R*) and 49.6 L/h (*S*) for i.v. administration, and 11.3 L/h (*R*) and 21.6 L/h (*S*) for p.o. administration. The hepatic extraction ratio was estimated to approximately 0.76 and 0.77 for the (*R*)- and (*S*)-enantiomer, respectively.

Conclusions

For carvedilol, the hepatic extraction ratio is considerable, and the oral availability (calculated assuming complete absorption and no intestinal elimination) amounts to 25–35% for the parent drug due to extensive first-pass metabolism. In spite of their low serum levels, the contribution of the metabolites must not be neglected, especially for oral dosing. Elimination of the parent drug was found to be rate-limiting, i.e., the kinetics of the metabolites is formation-rate-limited, at least in healthy volunteers. The AM-FP model was most suitable, since parent drug and metabolites appear to enter the systemic circulation simultaneously. The new compartmental model is applicable for PK/PD simulation studies including situations where hepatic clearance is affected. It was used to simulate the contribution of active metabolites formed during first-pass to the overall effect, also under conditions of impaired liver function leading to reduced metabolic clearance and in case of drug-drug interactions that are hypothesized to induce absorption.