SUMMARY

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The comprehensive analysis of the pharmacokinetics of a drug in the early phase of clinical development (phase I) in a data-rich situation forms the basis of subsequent pharmacokinetic and pharmacodynamic analyses in the target population, thus enabling the development of rational dose regimens, especially for the efficient planning and execution of phase II and III trials. Pharmacokinetic analysis using the population approach includes the characterization of the quantitative relations between dosing regimen, drug concentration and time course, as well as the pharmacokinetic variability of the drug within a population. In addition, covariates (e.g. demographic and laboratory values) may be identified and quantified that account at least in part for the variability observed.

In this thesis a population pharmacokinetic analysis of the I_f channel blocker cilobradine, that was investigated in phase I clinical trials, was performed. Inhibition of the I_f channel specifically reduces heart rate and thus myocardial oxygen demand, with little if any effect on myocardial contractility, left-ventricular function and blood pressure. Thus, I_f channel blockers represent a promising new therapy option for the treatment of myocardial ischemia. A population pharmacokinetic model for cilobradine was developed using the software NONMEM®. Data from six phase I trials were analyzed that included 2733 plasma concentrations with a variety of dosing regimens: 9 dose groups over a range of 0.6 – 40 mg cilobradine, three different formulations (p.o. solution, p.o. capsule, i.v. infusion), as well as single and multiple dosing. Due to the strongly unbalanced design of the entire data set, the non-linear mixed-effects modeling approach was applied.

The developed population pharmacokinetic structural sub-model was characterized by an open three-compartment structure, describing p.o. drug invasion by first-order kinetics, and i.v. short infusion (20 min) by zero-order kinetics. For the characterization of the absorption process of the p.o. capsule, a lag time was incorporated which was estimated to be 0.154 h, ameliorating the precision of the model. Absolute bioavailability F1 for p.o. solution or p.o. capsule was estimated to 34 % or 43 %, respectively, suggesting a high presystemic elimination of cilobradine. Distribution between central and shallow compartment (first distribution process) displayed administration route-dependent characteristics in the three compartment model, resulting in separate estimation of distribution volumes V2, V3, and the inter-compartmental clearance Q3 for i.v. or p.o. data. The first distribution phase was faster and more pronounced after i.v. than p.o. administration. After p.o., the first distribution phase

was probably masked by dominating slower processes (e.g. absorption) and thus not detectable as fast distribution phase. Typical steady state volumes, calculated from estimated population values of V2, V3, V4 for p.o. or i.v., were large (95.8 or 130 L), suggesting an extensive tissue distribution of cilobradine. Total clearance CL was estimated to 21.5 L/h (= 358 mL/min), indicating a high elimination capacity for cilobradine.

In the pharmacostatistical sub-model, two hierarchical levels were identified for the variability by random effects. The inter-individual variability ω^2 was modeled with an exponential random effects term. Residual variability σ^2 as the second level was established using a proportional error model. Inter-individual variability estimated for CL, F1, central volume of distribution for i.v. ($V2_{iv}$) and absorption rate constant (KA) was moderate (15 % to 46 %), residual variability was low (26 %).

After a GAM analysis, the preselected covariates were further tested for significance using the forward inclusion and backward exclusion techniques in NONMEM®. Only the parameter covariate relation between KA and dose was statistically significant. The relation was best described by a positive saturation function with a KA_{max} of 0.43 h^{-1} and a dose of 0.99 mg at $0.5 \cdot KA_{max}$, indicating that the relation was primarily acting in the low dose range. The incorporation of the parameter covariate relation mainly improved the model fit to the observed trough concentrations of the 0.6 mg and 1.25 mg dose groups from one study. However, there were neither reports on such a covariate influence, nor was there successful confirmation by external study data. This suggested that this finding did not represent typical characteristics of cilobradine and may thus be of minor relevance. The other demographic, laboratory or study-specific parameters did not show any statistically significant influence on the pharmacokinetics of cilobradine. The covariates dose, age, and alkaline phosphatase each graphically suggested a relation to the structural parameter CL, which finally did not prove to be statistically significant. This finding requires verification of the respective relations in a population with a larger range of covariate values and in the patient target population.

Simulations of the data set that had been used for model development based on the final model showed sufficient predictability for the concentrations measured. The simulated median concentration-time profile reflects a slight underpredictive tendency of the model which was confirmed by the value of the median prediction error of -4 %. Beyond this internal evaluation the final model was successfully applied to external phase I data of cilobradine with a different population of volunteers and partially different dose groups. This

result documented the robustness and general applicability of the developed model for the prediction of cilobradine concentrations of different origin. The estimates of the final population pharmacokinetic model based on the external data set were rather similar to those obtained by the development data set except for the covariate relation. Furthermore, all observations were well predicted with most of them being within the 90 % prediction interval when excluding the covariate relation.

In summary, in this thesis a reliable population pharmacokinetic model was developed for the I_f channel blocker cilobradine based on complex phase I data. Its general applicability for cilobradine was confirmed by external evaluation using phase I data. This model may form the basis for following pharmacokinetic and pharmacodynamic investigations and for the development of rational dosing regimens for further clinical trials, e.g. with patients suffering from ischemia. Moreover, most of the pharmacokinetic properties of cilobradine revealed in this thesis were similar to other known I_f channel blockers. Thus, the results of the present thesis may be used for future pharmacokinetic analyses with new structural analogues displaying physicochemical properties similar to cilobradine.