A Semiphysiological Population Model for Prediction of the Pharmacokinetics of Drugs under Liver and Renal Disease Conditions

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ABSTRACT:
The application of model-based drug development in special populations becomes increasingly important for clinical trial optimization, mostly by providing a rationale for dose selection and thereby aiding risk-benefit assessment. In this article, a semiphysiological approach is presented, enabling the extrapolation of the pharmacokinetics from healthy subjects to patients with different disease conditions. This semiphysiological approach was applied to solifenacin, using clinical data on total and free plasma and urine concentrations in healthy subjects. The analysis was performed using nonlinear mixed-effects modeling and relied on the use of a general partitioning framework to account for binding to plasma proteins and to nonplasma tissues together with principles from physiology that apply to the main pharmacokinetic process, i.e., bioavailability, distribution, and elimination. Application of these physiology principles allowed quantification of the impact of key physiological parameters (i.e., body composition, glomerular function, liver enzyme capacity, and liver blood flow) on the pharmacokinetics of solifenacin. The prediction of the time course of the drug concentration in liver- and renal-impaired patients only required adjustment of the physiological parameters that are known to change upon liver and renal dysfunction without modifying the pharmacokinetic model structure and/or its respective parameter estimates. Visual predictive checks showed that the approach applied was able to adequately predict the pharmacokinetics of solifenacin in liver- and renal-impaired patients. In addition, better insight into the pharmacokinetic properties of solifenacin was obtained. In conclusion, the proposed semiphysiological approach is attractive for prediction of altered pharmacokinetics of compounds influenced by liver and renal disease conditions.

Introduction

Disease conditions can involve important alterations in drug disposition, metabolism, and/or absorption compared with the healthy condition. In liver and renal impairment, the main alterations are caused by changes in organ blood flow and plasma protein binding that affect the intrinsic capacity of the organ to metabolize/excrete drugs. Such physiological changes may affect the pharmacokinetics of drugs; therefore, in cases where the drug is likely to be administered under these pathological conditions, the pharmacokinetics should be assessed in clinical studies to provide alternative dosing recommendations. Model-based analysis and simulation is invaluable in optimization of these clinical studies mostly by providing a rationale for dose selection, thereby avoiding side effects due to unexpectedly high exposure of the drug. In this manner, this approach aids in risk-benefit assessments of dose selection.

The impact of altered liver function on the pharmacokinetics of a drug often depends on the stage of the disease, which occurs through different pathological mechanisms. Some of the known physiological changes that can affect pharmacokinetics are shunting of blood past the liver, impaired hepatocellular function, impaired biliary excretion, and decreased plasma protein binding (Schuppan and Afdhal, 2008). The impact of enzyme activities, plasma protein concentration, and hepatic blood flow (portal plus arterial) on the clearance (CL) of different pathological mechanisms. Some of the known physiological changes that can affect pharmacokinetics are shunting of blood past the liver, impaired hepatocellular function, impaired biliary excretion, and decreased plasma protein binding (Schuppan and Afdhal, 2008). The impact of enzyme activities, plasma protein concentration, and hepatic blood flow (portal plus arterial) on the clearance (CL) of different compounds has been characterized previously according to the Child-Pugh score classification and use of well stirred models (Edginton and Willmann, 2008; Johnson et al., 2010).

A reduction in liver function can also be caused by a reduction in renal function. To this end, the pharmacokinetics of drugs that are mainly metabolized by the liver can be markedly affected by renal impairment. Chronic renal disease not only influences glomerular filtration rate (GFR), tubular secretion, and protein binding but also has an impact on intestinal and hepatic uptake transporters (Nolin et al., 2008). In brief, a reduction in renal clearance leads to accumulation of uremic toxins and chronic inflammation, which then perturbs...
metabolic and transport processes in the liver and intestine (Dreisbach, 2009). In end-stage renal disease, dialysis removes uremic factors (Dreisbach, 2009), and consequently patients with severe renal impairment, who are not yet undergoing dialysis, in theory have the greatest risk of higher drug exposure.

Model-based pharmacokinetic analysis can be used to gain more insights in how (patho-)physiological changes can affect the pharmacokinetics of a compound. To date, whole-body physiologically based pharmacokinetic (WB-PBPK) models have been proposed in two previously published reports for prediction of the pharmacokinetics in patients with liver impairment (Edginton and Willmann, 2008; Johnson et al., 2010). WB-PBPK requires a large number of physiological input parameters and a good understanding of all active processes affecting the pharmacokinetic properties of a drug. Thus, the lack of sufficient in vitro and in vivo data may hamper the use of this approach. In this investigation, we propose an approach that takes into account key principles from physiology in combination with the power of nonlinear mixed-effects modeling for estimation of population and random-effects parameters.

This semiphysiological population approach is proposed to predict the pharmacokinetics from healthy subjects to patients with two different disease conditions, i.e., renal and liver impairment. This approach combines an empirical compartmental model structure, a partitioning framework to describe protein binding in plasma, and the principles of the physiology that apply to volume of distribution (V<sub>eq</sub>) and CL to determine the impact of key physiological parameters [i.e., free fraction in plasma (f<sub>p</sub>)], total body water composition, liver weight, liver blood flow (Q<sub>L</sub>) and GFR] on the pharmacokinetic profiles.

The clinical utility of the proposed approach is illustrated with solifenacin ([+)-(15S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydrosoquinoline-2-carboxylate monosuccinate, YM905, Vesicare], which is a once-daily orally administered selective muscarinic (M<sub>1</sub> and M<sub>3</sub>) receptor antagonist for the treatment of overactive bladder (Simpson and Wagstaff, 2005; Payne, 2006). Solifenacin is primarily metabolized by the cytochrome P450 3A4 isozyme, leading to roughly 7% of the dose being excreted unchanged in the urine (Michel et al., 2004; Doroshenko and Fuhr, 2009). Furthermore, solifenacin exhibits a dose-proportional pharmacokinetics and extensively binds to a<sub>1</sub>-acid glycoprotein (AGP) and to a lesser extent to albumin, which makes it a suitable model compound to investigate the utility of the proposed semiphysiological approach.

### Materials and Methods

#### Clinical Studies

An overview of the clinical studies used for model development and comparison with model predictions is shown in Table 1. In total, the data of 59 subjects of three phase I clinical studies after administration of 5 and 10 mg of solifenacin were used for model development including data of young healthy male adults, young healthy female adults, elderly females, and elderly males. The data from 26 patients with liver and renal impairment were exclusively used to verify the model predictions. In total, data of approximately 8 patients with liver impairment and 6 patients with renal impairment were available for each group. Patients with liver impairment included in study 2 were classified as type B in the Child-Pugh category, and renal impairment in patients was classified as mild (GFR ≥50 and <80 ml/min), moderate (GFR ≥30 and <50 ml/min), or severe (GFR <30 ml/min). For the patient classification, GFR was calculated according to the Cockcroft-Gault equation (Cockcroft and Gault, 1976). In all studies, solifenacin concentrations were analyzed using liquid chromatography-mass spectrometry with a limit of quantification of 1.38 nmol/l for total solifenacin and 0.55 nmol/l for free solifenacin. A comprehensive description of these studies and results have been reported elsewhere (Krauwinkel et al., 2005; Kuipers et al., 2006; Smulders et al., 2007).

#### Structural Model

The structural model to describe the pharmacokinetics of solifenacin is shown in Fig. 1. In brief, the biphase pharmacokinetics of
total and free solifenacin in plasma was described by a two-compartment model with first-order absorption. The urine concentrations were described by linking the urinary excretion to the central compartment. To account for the effect of protein binding on the central volume of distribution \( (V_1) \), the central compartment of this system was assumed to have different components that are in instantaneous equilibrium: solifenacin-AGP, solifenacin-albumin, solifenacin-free, and solifenacin-nonspecific binding (NSB) (Fig. 1). NSB was assumed to be outside of the plasma so that variations in the concentration of plasma proteins would have an effect on the total solifenacin plasma concentrations. The higher the concentration of plasma proteins, the less solifenacin distributes from plasma to the NSB and consequently the higher are the total solifenacin plasma concentrations observed in plasma.

By applying the “law of mass action” to the plasma distribution component, the \( f_u \) could be defined as in eq. 1:

\[
f_u = \frac{1}{1 + \frac{C_{AGP}}{k_{AGP}} + \frac{C_{Alb}}{k_{Alb}}}
\]

in which \( C_{AGP} \) is the AGP plasma concentration, \( C_{Alb} \) is the albumin plasma concentration, \( k_{AGP} \) is the partition coefficient for AGP, and \( k_{Alb} \) is the partition coefficient for albumin.

To describe \( V_1 \) eq. 2 was derived:

\[
V_1 = V_{\text{plasma}} \cdot (1 + \beta \cdot f_u)
\]

where \( \beta \) represents a compilation of the concentration in the NSB divided by the partition coefficient for NSB, and \( V_{\text{plasma}} \) is the volume of plasma calculated as 5% of the lean body mass (Boer, 1984; Janmahasatian et al., 2005).

In addition, the effect of \( f_u \) on \( V_{ss} \) was included in the model by taking into account its physiological determinants (eq. 3) (Gibaldi and McNamara, 1978; Mehvar, 2005):

\[
V_{ss} = V_{\text{plasma}} + V_{\text{water}} \cdot \left(\frac{f_u}{f_{\text{tissue}}}\right)
\]

in which \( f_{\text{tissue}} \) is the free fraction in tissue and \( V_{\text{water}} \) is the aqueous volume outside of the plasma into which the drug distributes (Rowland and Tozer, 1995). Hence, \( V_{\text{water}} \) was assumed to be total body water composition minus plasma water volume, which is approximately 90% of \( V_{\text{plasma}} \). Total body water composition was calculated according to Watson et al. (1980).

The simultaneous analysis of the solifenacin plasma and urine concentrations enables the characterization of both renal clearance (CLR) and hepatic clearance (CLH) as illustrated in eq. 4:

\[
CL = CLR + CLH
\]

Renal clearance has been characterized as a fraction of the clearance due to the glomerular filtration (CLGFR) as displayed in eq. 5:

\[
CL_{GFR} = \frac{\alpha \cdot CL_{GFR}}{CL_{GFR} + f_u}
\]

where \( \alpha \) is a fraction of CL_{GFR}. If \( \alpha > 1 \), tubular active secretion is mainly involved in renal clearance, if \( \alpha < 1 \) reabsorption is mainly involved in renal clearance, and if \( \alpha = 1 \), GFR is sufficient to explain all renal clearance. GFR was calculated according to the modification of diet in renal disease equation (Levey et al., 1999) and corrected for body surface area (Haycock et al., 1978).

To characterize the CLH, the well-stirred model concept was included in the model according to eq. 6 (Yang et al., 2007):

\[
CLH = CL_{H, F}, F, V_{SS}, V_{1}, Q
\]

### TABLE 2

Overview of the demographic covariates, physiological parameters, and estimated and derived model parameters

<table>
<thead>
<tr>
<th>Demographic Covariates</th>
<th>Physiological Parameters</th>
<th>Estimated Parameters</th>
<th>Derived Parameter (Primary)</th>
<th>Derived Parameter (Secondary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td>( C_{Alb}, C_{AGP} )</td>
<td>( k_{Alb}, k_{AGP} )</td>
<td>( f_u )</td>
</tr>
<tr>
<td>Gender, age, and weight</td>
<td>Liver weight</td>
<td>( Q_{H} )</td>
<td>( CL_{H, invivo} )</td>
<td>( CL_{H} )</td>
</tr>
<tr>
<td>Race, gender, age, and creatinine</td>
<td>GFR</td>
<td>( \alpha )</td>
<td>( \beta )</td>
<td>V_{R}</td>
</tr>
<tr>
<td>Gender, weight, and height</td>
<td>( V_{\text{plasma}} )</td>
<td>( V_{\text{plasma}} )</td>
<td>( f_{\text{tissue}} )</td>
<td>V_{SS}</td>
</tr>
<tr>
<td>Gender, age, weight, and height</td>
<td>( V_{\text{water}} )</td>
<td>( V_{\text{water}} )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
where CLin vivo is the in vivo clearance, liver weight was calculated according to Chouker et al. (2004), and MPPGL is the milligrams of microsomal protein per gram of liver, adult levels of which were reported to be 35 mg/g (Johnson et al., 1999).

CLint was calculated according to Wynne et al. (1989), \( C_{\text{blood}}/C_{\text{plasma}} \) is the total blood plasma concentration ratio, which was fixed at 0.89 as established in vitro (T. Minematsu and T. Hashimoto, unpublished results), and CLint is intrinsic clearance, which was calculated as in eq. 7:

\[
CL_{\text{int}} = CL_{\text{micro}} \cdot \text{weight} \cdot \text{MPPGL}
\]

where \( CL_{\text{micro}} \) is the in vivo clearance, liver weight was calculated according to Chouker et al. (2004), and MPPGL is the milligrams of microsomal protein per gram of liver, adult levels of which were reported to be 35 mg/g (Johnson et al., 1999).

Intercompartamental clearance (\( Q \)) of solifenacin was assumed to be dependent on \( f_u \) (eq. 8):

\[
Q = Q^* \cdot f_u
\]

where \( Q^* \) was a model constant.

Maximal oral bioavailability (\( F_{\text{max}} \)) was physiologically characterized in this model as described in eq. 9:

\[
F_{\text{max}} = \frac{Q_{H}}{Q_{H} + CL_{\text{int}} \cdot f_u (C_{\text{blood}}/C_{\text{plasma}})}
\]

Table 2 shows an overview of the demographic covariates necessary to calculate the physiological parameters and consequently to derive model parameters.

**Random Effects.** Random interindividual variability for each pharmacokinetic parameter was perceived as a log-normal distribution (eq. 10):

\[
P_i = P_{\text{typical}} \cdot \exp(\eta_i)
\]

where \( P_i \) represents the parameter value for the \( i \)th individual, \( P_{\text{typical}} \) is the parameter for a typical group value and \( \eta_i \) is the interindividual random effect with \( \eta_i \sim N(0, \sigma^2) \).

The residual errors were separately defined for total and free solifenacin concentrations in plasma and solifenacin concentrations in urine:

\[
C_{\text{obs},u} = C_{\text{pred},u} \cdot (1 + \epsilon_u)
\]

where \( C_{\text{obs},u} \) and \( C_{\text{pred},u} \) are, respectively, the observed concentration and the predicted concentration in individual \( i \) at time \( j \) and \( \epsilon_u \) is the residual error with \( \epsilon_u \sim N(0, \sigma^2) \).

**Model Performance.** Throughout model development, NONMEM subroutine ADVAN16 and first-order conditional estimation with interaction was used. Samples below the limit of quantification were considered as missing values. Model performance was evaluated by both visual inspection and the likelihood ratio test. Physiological considerations and the conventional critical values for the likelihood ratio test (\( p < 0.001 \)) were used for model development. Precision of parameter estimates was evaluated as the coefficient of variation (CV) calculated by the ratio of the estimated S.E. and its respective parameter estimate multiplied by 100.

**Model Evaluation.** Internal model validation was performed by means of a visual predictive check, which evaluates whether the identified model is able to predict the observed total plasma concentrations, urine excretion rates, and \( f_u \) (Post et al., 2008). Plasma concentration-time, urine excretion rate-time, and \( f_u \) plasma protein curves were simulated for 1000 hypothetical subjects. In all simulations, the correlation matrix for \( \theta \) estimates was considered to account for parameter uncertainty.

For the simulation of plasma concentration and urine excretion rate curves, the physiological parameters (i.e., \( V_{\text{plasma}} \), \( V_{\text{urine}} \), \( Q_{H} \), liver weight, and GFR) were calculated by sampling the required demographic covariates and the plasma protein concentrations (i.e., AGP plasma concentration and albumin plasma concentration) from the data set used for model development. For simulations of the \( f_u \) AGP curve, the albumin plasma concentration was fixed to the average value observed in the data set and the AGP plasma concentration was allowed to vary within the observed range. The opposite was applied for the simulations of the \( f_u \) albumin curve.

Graphical representation of total plasma and urine data shows 90% predicted population variability explained by the differences in the physiological parameters alone and combined with the estimated interindividual variability. For graphical representation of urine data, the urine excretion rate was calculated by dividing the simulated amount of total solifenacin excreted in the urine during a certain time interval by the time interval. The graphical display of \( f_u \) shows the 95% confidence interval of the population median. The observed \( f_u \) was calculated by dividing free solifenacin by total solifenacin plasma concentrations per time point.

**Extrapolations.** The model developed for the healthy subjects was subsequently used to extrapolate the pharmacokinetics in plasma and urine to patients with liver and renal impairment. For the extrapolations, the data in patients was compared with the model predictions, which were exclusively based on the alterations of the physiological parameters. To evaluate what

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**Table 3**

Overview of the expected changes in the physiological parameters in liver- and renal-impaired patients as a fraction of the values in healthy subjects

<table>
<thead>
<tr>
<th>Physiological Parameter</th>
<th>Liver-Impaired (Edgin and Willmann, 2008)</th>
<th>Renal-Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{AGP}} ) (mg/dl)</td>
<td>0.56 (severe) ( V_{\text{plasma}} ) (Boer, 1984; Janmahasatian et al., 2005)</td>
<td>1.4 (severe) ( V_{\text{plasma}} ) (Boer, 1984)</td>
</tr>
<tr>
<td>( C_{\text{AGP}} ) (g/dl)</td>
<td>0.68</td>
<td>1.0</td>
</tr>
<tr>
<td>( Q_{H} ) (liters)</td>
<td>0.85</td>
<td>1.0</td>
</tr>
<tr>
<td>( CL_{\text{int}} ) (liters)</td>
<td>0.40</td>
<td>0.66 (severe) ( V_{\text{plasma}} ) (Boer, 1984; Janmahasatian et al., 2005)</td>
</tr>
<tr>
<td>( GFR ) (ml/min)</td>
<td>0.70</td>
<td>Uniform distribution according to classification as specified in the protocol (see clinical studies)</td>
</tr>
</tbody>
</table>

**Table 4**

Summary statistics of the physiological parameters in various pathological conditions

<table>
<thead>
<tr>
<th>Physiological Parameter</th>
<th>Control ( n = 6 )</th>
<th>Liver-Impaired ( n = 8 )</th>
<th>Renal-Impaired ( n = 6 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{AGP}} ) (mg/dl)</td>
<td>79.5 (54–138)</td>
<td>43.5 (30–70)</td>
<td>81 (74–126)</td>
</tr>
<tr>
<td>( C_{\text{AGP}} ) (g/dl)</td>
<td>4.17 (3.6–4.95)</td>
<td>4.14 (2.5–4.23)</td>
<td>4.40 (3.7–4.6)</td>
</tr>
<tr>
<td>( V_{\text{plasma}} ) (liters)</td>
<td>3.43 (2.21–4.4)</td>
<td>3.51 (2.18–3.74)</td>
<td>3.52 (3.02–4.12)</td>
</tr>
<tr>
<td>( V_{\text{urine}} ) (liters)</td>
<td>41.1 (28.4–52.4)</td>
<td>41.3 (28.1–45)</td>
<td>39 (36.5–48)</td>
</tr>
<tr>
<td>Liver weight (g) (Chouker et al., 2004)</td>
<td>2070 (1690–2550)</td>
<td>1990 (1830–2420)</td>
<td>1800 (1550–2060)</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²) (Levey et al., 1999)</td>
<td>87.8 (66.1–124)</td>
<td>78.8 (64.9–85)</td>
<td>57.4 (37.1–79.5)</td>
</tr>
</tbody>
</table>

\* GFR classification based on the Cockcroft-Gault equation: mild (GFR >50 and <80 ml/min), moderate (GFR >30 and <50 ml/min), or severe (GFR <30 ml/min).
extent the identified model is able to predict the plasma and urine data in these pathological conditions, a visual predictive check of the full pharmacokinetic profiles was performed. A posterior predictive check of $V_{SS}$, $CL$, and renal clearance was performed to characterize the possibility that the pharmacokinetic parameter predictions are in accordance with the limited amount of patients recruited for the clinical studies.

The visual predictive check was performed similarly to the model evaluation. The physiological alterations were considered by using literature reported values (Table 3) and by using the observed physiological parameters (Table 4). Alterations in $Q_{HI}$ and intrinsic clearance were in both cases assumed to be as reported in the literature. Graphical representation of plasma and urine data shows 90% predicted population variability explained by alterations in the physiological parameters combined with the estimated random interindividual variability in healthy subjects.

For the posterior predictive check, only the observed alterations in the physiological parameters (Table 4) were used to predict $V_{SS}$, $CL$, and renal clearance. In total, 1000 data sets for each pathological condition were simulated, containing the same number of patients/samples as observed in the original data set. The 1000 simulated data sets each provided a value for the median and hence an estimate of the posterior predictive distribution. The simulated median and its 95% confidence interval were compared with the median of the observed pharmacokinetic parameters originating from a post hoc analysis. If the medians of the post hoc values were within the 95% confidence interval of the posterior predictive distribution, then the prediction was deemed plausible.

For the renal-impaired patients, the fraction 0.6 used in the extrapolations to reflect the change in intrinsic clearance is the average change in hepatic clearance between healthy subjects and severe renal-impaired patients for cyclophosphamide (0.69), felbamate (0.65), roboxetine (0.44), and telithromycin (0.68) reported by Nolin et al. (2008). Compounds for which dialysis-dependent patients were included were not considered. In this publication, severe renal-impaired patients were often considered as the patients with a GFR within the range of 10 and 40 ml/min/1.73 m$^2$.

Software. Nonlinear mixed-effects modeling was implemented using NONMEM version 7 (GloboMax, Ellicott City, MD). Data management and simulations were performed using R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Data. Table 4 compares the physiological parameters of the control group of studies 1 and 2 (Table 1) with the physiological parameters of the liver-impaired patients and mild, moderate, and severe renal-impaired patients. The median AGP plasma concentration in the liver-impaired patients was 1.6 times lower and in the severe renal-impaired patients was 1.4 times higher than that in the control group. Mild and moderate renal-impaired patients did not show marked differences in AGP plasma concentration. The albumin plasma concentration was not markedly changed in liver- and mild renal-impaired patients and was reduced in moderate and severe renal-impaired patients. GFR was shown to decrease by a factor of 0.89 in the liver-impaired patients compared with that in the control groups.

In renal-impaired patients, GFR calculated using the modification of diet in renal disease equation resulted in lower GFR values than those using the Cockcroft-Gault equation, which were the base for the classification of the patients as mild, moderate, or severe renal-impaired. For all other physiological parameters, no clear differences were observed between the control groups and the liver and (mild, moderate, and severe) renal-impaired patients.

Structural Model. The semiphysiological model to describe the effect of protein binding and key physiological parameters on the pharmacokinetics of solifenacin is illustrated in Fig. 1. During model development, eq. 9 was used to calculate the bioavailability, which was found to be comparable to the bioavailability obtained in a clinical study (Kuipers et al., 2004). Similarity of the results allowed inclusion of $F_{\text{max}}$ as $F$ in the model.

Table 5 displays the pharmacokinetic parameters that were estimated and derived by the final model in healthy subjects. All structural parameters were estimated with good precision (CV <20%). The

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### Table 5

**Population parameter estimates including CV percentage and median of the derived structural parameters including range, if applicable**

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural estimated parameters</strong></td>
</tr>
<tr>
<td>$k_i$ (l/h)</td>
</tr>
<tr>
<td>0.304 (12)</td>
</tr>
<tr>
<td>$\alpha$ (l/h)</td>
</tr>
<tr>
<td>5.56 (8.1)</td>
</tr>
<tr>
<td>$Q^*$ (l/h)</td>
</tr>
<tr>
<td>1120 (20)</td>
</tr>
<tr>
<td>$\beta$</td>
</tr>
<tr>
<td>5810 (11)</td>
</tr>
<tr>
<td>$f_{\text{in}}$ (nmol/l)</td>
</tr>
<tr>
<td>0.00142 (4.6)</td>
</tr>
<tr>
<td>$\lambda_{\text{AGP}}$ (nmol/l)</td>
</tr>
<tr>
<td>659 (18)</td>
</tr>
<tr>
<td>$\lambda_{\text{ALB}}$ (nmol/l)</td>
</tr>
<tr>
<td>293000 (22)</td>
</tr>
<tr>
<td><strong>Derived structural parameters</strong></td>
</tr>
<tr>
<td>$F$</td>
</tr>
<tr>
<td>0.93 (0.891–0.954)</td>
</tr>
<tr>
<td>$V_1$ (liters)</td>
</tr>
<tr>
<td>331 (165–982)</td>
</tr>
<tr>
<td>$V_2$ (liters)</td>
</tr>
<tr>
<td>161 (89.2–264)</td>
</tr>
<tr>
<td>$V_{SS}$ (liters)</td>
</tr>
<tr>
<td>484 (303–1150)</td>
</tr>
<tr>
<td>$CL$ (l/h)</td>
</tr>
<tr>
<td>6.15 (2.41–18.7)</td>
</tr>
<tr>
<td>$CL_H$ (l/h)</td>
</tr>
<tr>
<td>5.62 (2.11–16.3)</td>
</tr>
<tr>
<td>$CL_L$ (l/h)</td>
</tr>
<tr>
<td>0.587 (0.247–2.36)</td>
</tr>
<tr>
<td>$Q$ (l/h)</td>
</tr>
<tr>
<td>23.1 (15.6–26.7)</td>
</tr>
<tr>
<td>$f_{o}$</td>
</tr>
<tr>
<td>0.0205 (0.0139–0.0264)</td>
</tr>
<tr>
<td><strong>Random interindividual variability</strong></td>
</tr>
<tr>
<td>$\sigma^2$ total</td>
</tr>
<tr>
<td>0.0181 (12)</td>
</tr>
<tr>
<td>$\sigma^2$ free</td>
</tr>
<tr>
<td>0.186 (83)</td>
</tr>
<tr>
<td>$\sigma^2$ urine</td>
</tr>
<tr>
<td>0.176 (30)</td>
</tr>
</tbody>
</table>

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![Figure 2](https://example.com/fig2.png)

**Fig. 2.** Relationship between $fu$ ($f_{\text{plasma}}$) and AGP (A) and fu and albumin (B). ▲, observed data used for model development (control group study 1 and 2 and study 3); ◯, observed data used for extrapolation (liver- and renal-impaired groups in study 1 and 2); line, population prediction (median); shaded area, 95% confidence interval of the predicted median.
value of \(f_u\) was 0.0205 (range, 0.0139–0.0264), \(V_{SS}\) was 484 (range, 303–1150 liters), CL was 6.15 (range, 2.41–18.7 l/h), and renal clearance was 0.587 (range, 0.247–2.36). Interindividual variability was estimated for \(V_1\) and hepatic and renal clearance. The correlation between interindividual variability of \(V_1\) and hepatic and renal clearance was accounted for using an omega matrix. No relevant shrinkage in the omega distribution was observed (1.1% for \(V_1\), 0.3% for hepatic clearance, and 9.6% for renal clearance).

**Model Validation.** The adequacy of the approach to describe the effect of changes in protein plasma concentration on the free fraction of solifenacin is shown in Fig. 2. The AGP plasma concentration was demonstrated to have a strong effect on \(f_u\), whereas the effect of albumin was shown to be negligible. This observation is in agreement with the roughly 1000 times lower partition coefficient observed for AGP (Table 5), which overcomes the greater molar plasma concentration of albumin. As a consequence, the variation in AGP ends up playing a main role in the plasma binding of solifenacin.

An adequate description of the plasma and urine data by the model is illustrated by the internal visual predictive check (Fig. 3). Slight model overprediction of the plasma concentrations is observed only for the control group of study 2 (Fig. 3A). The internal visual predictive check also illustrates that part of the interindividual variability can be explained by considering only the variability in the physiological parameters, i.e., without random effects (inner shaded area). For the urine data, the variability in the physiological parameters (inner shaded area) can explain most of the interindividual variability observed.

**Extrapolations.** Figures 4 and 5 illustrate the results of the visual predictive check performed to evaluate the predictive power of the semiphysiological approach for liver- and renal-impaired patients, respectively. In the liver-impaired patients, the approach slightly overpredicts the terminal half-life of the observed total plasma concentrations, whereas in renal-impaired patients, the observed total plasma concentrations are underpredicted, especially in the patients classified as having severe impairment and to a lesser extent in the patients classified as having moderate impairment (Fig. 6, A–C). Predictions substantially improved when the potential involvement of hepatic uptake transporters was taken into account by increasing the intrinsic clearance by a factor of 0.6 in patients with a GFR lower than 40 ml/min/1.73 m² (Fig. 6, D–F). The population prediction and the interindividual variability did not markedly change when the model predictions were based on either the observed or literature-reported alterations (Table 3) of the physiological parameters (Figs. 4 and 5).

Table 6 illustrates the posterior predictive check results for \(V_{SS}\), CL, and renal clearance for liver-impaired patients and mild, moderate, and severe renal-impaired patients. The medians of the post hoc estimates were inside the 95% confidence interval of the posterior predictive distribution. For severe renal-impaired patients, the predictive check results confirmed the improvements in the predictions observed after consideration of the potential involvement of hepatic uptake transporters.

**Discussion**

The application of model-based drug development in special populations becomes increasingly important for clinical trial optimization, mostly by providing a rationale for dose selection and thereby aiding the risk-benefit assessment. At present, WB-PBPK models have been used for prediction of the pharmacokinetics in patients with liver impairment (Edginton and Willmann, 2008; Johnson et al., 2010). However, attempts to use this approach sometimes fail because WB-PBPK models require extensive knowledge of all active processes affecting the pharmacokinetics of the drug. As an alternative, a semiphysiological approach is proposed for pharmacokinetic extrapolations. This concept takes into account key principles from physiology in combination with the nonlinear mixed-effects modeling approach for estimation of population and random-effect parameters.

In this article, the semiphysiological concept is presented, enabling...
prediction of the pharmacokinetics from healthy subjects to patients under two different disease conditions, i.e., liver and renal impairment.

The uniqueness of this approach relies on the use of a general partitioning framework to account for binding to plasma proteins and to nonplasma tissues together with principles from physiology that apply to the main pharmacokinetic process (i.e., bioavailability, distribution, and elimination). In combination with compartmental modeling, the proposed semiphysiological approach can be used to investigate the impact of (patho-)physiological alterations on the time course of drug concentration. An important feature of the proposed semiphysiological approach is that the model captures physiological parameters that are believed to change under pathophysiological conditions. To this end, extrapolation of the pharmacokinetics from healthy volunteers to liver- and renal-impaired patients relies on the

![Fig. 4. Plasma (A and B) and urine (C and D) extrapolation results to patients with liver impairment. A and C, extrapolations based on expected changes in the physiological parameters (Table 3); B and D, extrapolations based on observed physiological parameters (Table 4). △, observed data study 2; line, population prediction (median); shaded area, 90% including differences in the physiological parameters and random effects.]

![Fig. 5. Plasma (A and B) and urine (C and D) extrapolation results for patients with renal impairment. A and C, extrapolations based on expected changes in the physiological parameters; B and D, extrapolations based on observed physiological parameters. ○, observed data mild impaired group; ◼, observed data moderate group; △, observed data severe group; line, population prediction (median); shaded area, 90% including differences in the physiological parameters and random effects.]

key principle that only the physiological parameters change without
the need for adjustment of the model structure and/or pharmacokinetic
parameter estimates.

In this investigation, solifenacin served as a model compound to
show the validity of the concept. Rich clinical pharmacokinetic data
for total solifenacin were available from healthy subjects and patients
with impaired liver and/or renal function. In addition, free solifenacin
in plasma and solifenacin in urine were included in the analysis.
Because solifenacin extensively binds to AGP, which is known to
widely vary under impaired liver and renal conditions, it was antici-
pated that protein binding would be a physiological parameter of key
relevance. Accordingly, solifenacin was considered a suitable model
compound to investigate the utility of the proposed semiphysiological
approach.

First, the semiphysiological approach was applied to character-
ize the pharmacokinetics of solifenacin in healthy subjects (Fig. 1).
Characterization of the binding of solifenacin to plasma proteins in
the model was a key step for the inclusion of the physiological
principles, which allowed investigation of the impact of key phys-
iological parameters on the time course of solifenacin concentra-
tion. These key physiological parameters represented body com-
position, glomerular function, liver enzyme capacity, and liver
blood flow. In addition, inclusion of the physiological principles
improved the understanding of the pharmacokinetic properties of
solifenacin by interpretation of model estimates. For example, the
agreement between the model estimated bioavailability and the
bioavailability obtained in a clinical study (Kuipers et al., 2004)
indicates that bioavailability of solifenacin is mainly affected by
the first-pass metabolism in the liver. In addition, the 10-fold
difference between the measured CL\textsubscript{in vitro} (results not published)
and the estimated CL\textsubscript{in vivo} (0.00451 l H\textsuperscript{-1} h\textsuperscript{-1} g liver protein\textsuperscript{-1};
Table 5) indicated the involvement of influx hepatic drug trans-
porters promoting the in vivo hepatic clearance of solifenacin (Wu
and Benet, 2005). This 10-fold difference is well above the average

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Control</th>
<th>Liver-Impaired</th>
<th>Renal-Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild\textsuperscript{b}</td>
<td>Moderate\textsuperscript{b}</td>
</tr>
<tr>
<td>V\textsubscript{SS} (liters)</td>
<td>604</td>
<td>771</td>
<td>447</td>
</tr>
<tr>
<td></td>
<td>637 (451–664)</td>
<td>768 (532–1030)</td>
<td>499 (395–633)</td>
</tr>
<tr>
<td>CL (l/h)</td>
<td>7.76</td>
<td>6.24</td>
<td>4.17</td>
</tr>
<tr>
<td></td>
<td>6.75 (5.31–8.60)</td>
<td>4.48 (3.15–6.34)</td>
<td>5.50 (4.06–7.66)</td>
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<tr>
<td></td>
<td>0.988</td>
<td>0.798</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>0.701 (0.513–0.990)</td>
<td>0.817 (0.525–1.26)</td>
<td>0.428 (0.265–0.653)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} GFR classification based on the Cockcroft-Gault equation.
\textsuperscript{b} Predictions assuming differences in CL\textsubscript{in} for GFR <40 ml/min/1.73 m\textsuperscript{2}.

**TABLE 6**

Posterior predictive check for V\textsubscript{SS}, CL, and renal clearance in various pathological conditions

For every pharmacokinetic parameter, the first row depicts the median of the observed values (post hoc analysis) and the second row depicts the simulated median and the 95% confidence interval of the posterior distribution (n = 1000). In the control group only data from study 1 and 2 were used.
5-fold difference that Hallifax et al. (2010) demonstrated as not sufficient to support the role of hepatic transporters.

For the extrapolation of the pharmacokinetics of solifenacin to patients with hepatic and renal impairment, only the physiological parameters were adapted according to expected alterations as reported in the literature (Table 3) or to the alterations observed in the patients included in the clinical trials (Table 4). Of interest, the observed changes in physiological parameters are in good agreement with the values derived from the literature. Hence, the expected alterations as reported in the literature are deemed suitable for predictions of the pharmacokinetics under these disease conditions, except for the albumin plasma concentration in liver-impaired patients whose reported differences of 0.68 (Table 3) were not supported by the observed data, which showed no differences (Table 4). Because solifenacin mainly binds to AGP, it is expected that the difference in albumin concentration has only a minimal impact on the model performance. This is confirmed by the fact that the predictions using literature-reported changes in the physiological parameters are comparable to the predictions using the observed parameters (Fig. 4). Therefore, the slight overprediction of the terminal half-life of liver-impaired patients is caused by the relatively low number of patients included in this study and the cross-study differences in solifenacin concentrations also observed for the control group (Fig. 3).

For predictions of the pharmacokinetic time course in renal-impaired patients, alterations in CL were initially assumed to be limited to increased AGP concentration and decreased GFR. Evaluation of these predictions, as depicted in Table 6 and Fig. 5, indicates that imposing only these assumptions results in underprediction of CL. Considering a decrease in the hepatic intrinsic clearance for renal-impaired patients with a GFR lower than 40 ml/min/1.73 m² resulted in a better prediction of CL (Fig. 6; Table 6). This alteration in hepatic clearance represents literature evidence that hepatic transporters are likely to be altered under renal-impaired conditions (Nolin et al., 2008). The quantification of the potential changes in the activity of the hepatic uptake transporter appears to be independent of the type of the transporter involved and is in agreement with the hepatic clearance reductions reported by Dreisbach and Lertora (2003). The accuracy of these extrapolations also supports the role of hepatic transporters.

Additional evidence that hepatic transporters play a more prominent role than renal transport mechanisms is provided by the fact that the semiphysiological model adequately predicted the urine extraction of the semi-physiological model accounting for tubular secretion represents literature evidence that hepatic transporters are likely to be altered under renal-impaired conditions (Nolin et al., 2008). The quantification of the potential changes in the activity of the hepatic uptake transporter appears to be independent of the type of the transporter involved and is in agreement with the hepatic clearance reductions reported by Dreisbach and Lertora (2003). The accuracy of these extrapolations also supports the role of hepatic transporters.

Overall, application of the semiphysiological model to predict the time course of solifenacin concentration in renal- and liver-impaired patients shows that distribution of solifenacin is mainly driven by differences in $f_{d}$ and intrinsic clearance and less by other key physiological variables that may change under disease conditions. For example, underestimation of body composition by the anthropometric equations (Himmelfarb et al., 2002; Proulx et al., 2005) did not influence the accuracy of the pharmacokinetic predictions (Table 6) in liver- and renal-impaired patients. For other populations, like obese patients, body composition may play a more prominent role than protein binding in the determination of the time course of drug concentration.

In conclusion, the proposed semiphysiological approach combines physiological principles with the nonlinear mixed-effects modeling, allowing estimation of population and random-effects properties of solifenacin. Moreover, the semiphysiological approach enables prediction of the time course of solifenacin concentration in liver- and renal-impaired patients by using a priori knowledge of changes in physiological parameters. To this end, the semiphysiological approach is instrumental for prediction of altered pharmacokinetics of compounds influenced by disease conditions.

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Authorship Contributions

Participated in research design: Strougo, Krawinkel, Danhof, and Freijer.

Performed data analysis: Strougo.

Wrote or contributed to the writing of the manuscript: Strougo, Yassen, and Freijer.

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