

Modeling and predicting drug pharmacokinetics in patients with renal impairment

Expert Rev. Clin. Pharmacol. 4(2), 261–274 (2011)

Karen Rowland Yeo¹,
Mohsen Aarabi²,
Masoud Jamei¹
and Amin
Rostami-Hodjegan^{1,3}

¹*Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield, S2 4SU, UK*

²*School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran*

³*School of Pharmacy and Pharmaceutical Sciences, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK*

[†]*Author for correspondence:
Tel.: +44 114 292 2332
Fax: +44 114 272 0275
k.r.yeo@simcyp.com*

Current guidance issued by the US FDA to assess the impact of renal impairment on the pharmacokinetics of a drug under development has recently been updated to include evaluation of drugs with nonrenal elimination routes. Renal impairment not only affects elimination of the drug in the kidney, but also the nonrenal route of drugs that are extensively metabolized in the liver. Renal failure may influence hepatic drug metabolism either by inducing or suppressing hepatic enzymes, or by its effects on other variables such as protein binding, hepatic blood flow and accumulation of metabolites. Prior simulation of the potential exposure of individuals with renal impairment may help in the selection of a safe and effective dosage regimen. In this article, we discuss the application of a systems biology approach to simulate drug disposition in subjects with renal impairment.

KEYWORDS: *in vitro*–*in vivo* extrapolation • metabolism • modeling • pharmacokinetics • renal impairment • systems biology

The impact of renal impairment on the pharmacokinetics of many drugs is widely appreciated; chronic kidney disease (CKD) and end-stage renal disease (ESRD) can alter drug disposition by reducing the systemic clearance of renally cleared drugs and affecting protein and tissue binding [1,2]. Over the past decade, there has been evidence demonstrating that renal failure not only alters elimination in the kidney, but also the nonrenal disposition of drugs that are extensively metabolized by the liver [3–6]. It is assumed that dysfunction in the kidney results in pathological changes in other organs, including the liver. It is likely that renal failure influences hepatic drug metabolism, either by inducing or suppressing hepatic enzymes, or by its effects on other variables such as absorption, protein binding, tissue distribution, hepatic blood flow and accumulation of metabolites. Depending on the interplay between these parameters and the characteristics of an administered drug, varying degrees of impaired systemic clearance and first-pass metabolism are anticipated. Other factors that may be responsible for the reduced nonrenal clearance of drugs in renal failure include alterations in transporter systems or transporter activity [6–8].

Patients included in Phase III clinical studies are usually restricted to a well-defined population, and subpopulations, such as patients with CKD

or hepatic impairment, are often excluded or are under-represented. Consequently, data relating to the risk of increased or decreased exposure in subpopulations are limited. Regulatory guidances on conducting studies in patients with CKD are available from both the US FDA [201] and the EMA [202] with recommendations concerning study design, data analysis and labeling. Overall, the two guidances are very similar, recommending that a study be performed in patients with renal impairment if decreased renal function is likely to affect the pharmacokinetics of a drug or its metabolites. In the FDA's 1998 guidance document, the main emphasis was on investigating drugs that are mainly excreted renally [203]. The results of a recent survey of 94 approved new drug applications (NDAs) for small-molecule entities indicated that only 57% of these NDAs included study data in CKD subjects [9]. Of the new drugs that were predominantly eliminated by nonrenal processes, such as hepatic metabolism and or/transporters, 41% had pharmacokinetic data that were significantly altered in subjects with CKD, to such an extent that dose adjustment was recommended. Therefore, the FDA has proposed a decision tree in which drugs eliminated predominantly by nonrenal routes may be investigated initially using a reduced pharmacokinetic study in subjects with ESRD [201]. If the results demonstrate a clinically

significant difference in pharmacokinetics, then a full study would be required. An interesting drug development perspective on the implications of the decision tree has been presented [10].

The primary goal of the studies in patients with impaired renal function is to determine if the pharmacokinetics of the drug are altered to such an extent that dosage should be adjusted from that established in the Phase III clinical trial. Even after assessing the effects of renal impairment on the pharmacokinetics of a drug, data relating to the risk of increased or decreased exposure in sub-populations may be so limited that extensive covariate analysis cannot be performed. Although identification and quantification of covariates, particularly population pharmacokinetic models, is now viewed as an integral part of drug development, determining covariates using this approach is not always straightforward and complications caused by bias and competition between multiple variables are well known and have been described in the literature [11]. At best, it is likely that an average recommended dose can be derived for patients that are categorized according to the extent of their renal insufficiency.

Modeling and simulation of the processes that define the plasma concentration–time course of a drug – namely, absorption, distribution, metabolism and elimination (ADME) – using a mechanistic approach may help to predict the potential exposure of individual patients with CKD to a given dose [12,13]. Development of *in vitro*–*in vivo* extrapolation (IVIVE) approaches to predict pharmacokinetic parameters has accelerated mainly due to the increasing availability of extensive *in vitro* systems that act as surrogates for *in vivo* reactions relevant to ADME and advances in the understanding of the required population variables (demographic, anatomical, genetic and physiological parameters). The purpose of this article is to discuss the application of the IVIVE approach to predict the impact of CKD on pharmacokinetic parameters. The effects of CKD and ESRD on drug disposition have been discussed extensively in other reviews [1,2]. Although an overview of these will be presented, the focus of this article is to discuss how the CKD-induced changes can be incorporated into a physiologically based pharmacokinetic (PBPK) model to simulate and predict drug disposition and its associated variability in patients with renal impairment.

CKD: definitions & scope of the problem

Chronic kidney disease is a progressive loss of renal function over a period of months or years. Markers of renal function include renal plasma and blood flow, glomerular filtration rate (GFR) and tubular function. Among these three parameters of renal function, estimation of GFR and creatinine clearance (CL_{CR}) is the most commonly applied approach to assess renal function. Recent professional guidelines use GFR to classify the severity of CKD in five stages, with stage 1 being the mildest and usually causing few symptoms, and stage 5 being a severe illness with poor life expectancy if

untreated. The US Kidney Disease Outcomes Quality Initiatives of the National Kidney Foundation defines stages of CKD based on the level of kidney function, which are as follows [204]:

- Stage 1: Normal or increased GFR (≥ 90 ml/min/1.73 m²)
- Stage 2: Mild reduction in GFR (60–89 ml/min/1.73 m²)
- Stage 3: Moderate reduction in GFR (30–59 ml/min/1.73 m²)
- Stage 4: Severe reduction in GFR (15–29 ml/min/1.73 m²)
- Stage 5: Kidney failure (GFR <15 ml/min/1.73 m²)

Stage 5 CKD is also called established CKD and is synonymous with the now outdated terms ESRD or chronic renal function. Severe CKD requires one of the forms of renal replacement therapy, which may be in the form of dialysis but ideally constitutes a kidney transplant.

The global increase in the number of patients with CKD and ESRD is a public health challenge in both developed and developing countries [14]. Approximately 8 million Americans have an estimated GFR less than 60 ml/min/1.73 m² and 11 million have an estimated GFR greater than 60 ml/min/1.73 m² but have persistent micro-albuminuria [15]. In the UK, the annual incidence of ESRD is around 100 per 1 million of the population (0.01%), which is expected to continue to rise by 5–6% annually (0.11% in 10 years). This incidence rate is approximately 336 and 135 per million in the USA and Europe, respectively [15,16]. The increase in prevalence of acute renal failure is a direct consequence of the increase in prevalence of diabetes and hypertension [17]. Patients with ESRD often require an average of more than seven medications to manage the underlying condition as well as the comorbid states [18]. Excessive use of drugs and incorrect dosage may lead to an increased risk of nephrotoxicity, which in turn leads to an escalation in the cost of patient care [19]. Thus, appropriate dosing of drugs in renal impairment is an important consideration to avoid an increased incidence of adverse effects and to ensure optimal outcome for the patients. Dose adjustment of drugs excreted by the kidney is made according to the GFR.

Measurement of the rate of excretion of filtration markers such as inulin, iothexol and iothalamate are considered to be the gold standards for estimation of GFR. However, these studies are labor-intensive and consequently, estimates of GFR are more commonly obtained from measurements of CL_{CR} or predictive models and equations based on serum creatinine levels. The equation in Box 1, which is referred to as the Cockcroft–Gault equation [20], is one of the most validated equations used to estimate CL_{CR} and is applicable to patients with stable renal function. In the equation, BSA is the body surface area of the patient in units of m². Although it is recognized that GFR may be overestimated by 10–20% in patients with moderate CKD, the Cockcroft–Gault equation is considered to be adequate for many clinical decisions, including dosage adjustments in patients with impaired renal function. Values ranging from 120 to 140 ml/min are considered to be normal for GFR in an adult male.

Box 1. The Cockcroft–Gault equation.

$$CL_{CR}(\text{ml/min}/1.73\text{m}^2) = \frac{(140 - \text{Age}[\text{years}]) \times \text{weight}(\text{kg})}{0.814 \times \text{SerumCreatinine}(\frac{\mu\text{mol}}{\text{l}})} \times \frac{1.73}{\text{BSA}} [\times 0.85 \text{ if female}]$$

Box 2. The Modification of Diet in Renal Disease study equation.

$$GFR(\text{ml}/\text{min}/1.73\text{m}^2)[\text{MDRD}] = 186 \times (\text{SerumCreatinine}) \left(\frac{\mu\text{mol}}{\text{l}} \right) \times 0.011312^{-1.154} \times \text{Age}^{-0.203} \\ [\times 0.742 \text{ if female}]$$

The relationship that is referred to as the Modification of Diet in Renal Disease (MDRD) study equation (Box 2) [21], has gained increasing acceptance over the past few years. Many clinical laboratories in Australia and the UK routinely report GFR results derived using the MDRD equation along with serum creatinine concentrations. There are fundamental differences between the Cockcroft–Gault and the MDRD equations to estimate GFR. First, the former was originally validated against CL_{CR} as the gold standard, whereas the latter was developed against iothalamate-measured GFR. As creatinine, but not iothalamate, is excreted by both filtration and secretion, CL_{CR} always exceeds iothalamate clearance. Thus, estimates of GFR based on the Cockcroft–Gault equation tend to be higher than those based on the MDRD equation. Second, in contrast to the Cockcroft–Gault equation, which provides estimates of GFR in ml/min, the MDRD equation was developed to predict GFR standardized for a typical-sized adult with BSA of 1.73 m². Therefore, it is necessary to estimate BSA in order to compare GFR estimates by the two methods. After this adjustment is made, the two equations perform similarly when compared with gold standards for measuring GFR; however, some studies have shown the MDRD equation to be superior [21,22]. It has been shown in various studies that MDRD GFR in general underestimates true GFR [23–25], especially in patients with normal GFR, whereas Cockcroft–Gault GFR overestimates true GFR, especially in patients with impaired kidney function [23].

Chronic kidney disease interferes with the elimination of many drugs as a result of the reduction in GFR and tubular secretion. The lack of dose adjustments in patients with renal insufficiency is an often overlooked, yet preventable, cause of drug dosing error [26]. Despite dose adjustment based on estimates of GFR, patients with CKD still present a large number of adverse events. Over the past decade, there has been emerging evidence to demonstrate that CKD also affects the nonrenal disposition of drugs that are extensively metabolized by the liver. Therefore, it is important to assess how CKD affects drug absorption and distribution, and changes in intestinal, hepatic and renal metabolism. The clinical relevance to pharmacokinetic changes observed in patients with CKD should be assessed on a case-by-case basis. CKD-induced changes in pharmacokinetics are not easily assessed or understood by most healthcare practitioners because these parameters are both drug- and patient-specific. A review by Talbert [18], and more recently by Gabardi and Abramson [1], discusses the impact of CKD on drug disposition through changes in several pharmacokinetic parameters relating to the ADME processes.

IVIVE approaches: impact of CKD on physiological variables

In this section, various IVIVE models for predicting absorption, distribution and clearance (CL) will be described. The key aspect of the IVIVE approach is the separation of information on the system

(i.e., human body) from that of the drug (e.g., physicochemical characteristics determining permeability through membranes, partitioning to tissues, binding to plasma proteins, or affinities towards certain enzymes and transporter proteins) and the study design (e.g., dose, route and frequency of administration, concomitant drugs and food). To our knowledge, this is the first time that the impact of CKD-induced changes on the system parameters of the IVIVE models, which ultimately lead to differences in the pharmacokinetics parameters, has been reported.

The area under the concentration–time curve (AUC) is a measure of the exposure of an individual to a certain drug. The bioavailability of the drug (F) together with the CL and the dose of the drug (D) determine the overall exposure (AUC) according to this equation:

$$AUC = \frac{F \cdot D}{CL}$$

Total CL is defined as the volume of blood completely cleared of drug per unit time and encompasses clearance by the liver, the kidneys and biliary excretion (in the absence of reabsorption from the gut). Although exposure to the drug is determined only by the dose, CL and F, varying shapes of concentration–time profile can occur for a given exposure when the rate of entry (absorption rate, infusion rate, and so on) and rate of elimination are changed. Elimination rate is a function of CL and distribution characteristics.

Bioavailability is defined as the proportion of an oral dose of a drug that reaches the systemic circulation in intact form and is dependent on a number of key factors that are described by the following equation:

$$F = F_a \times F_G \times F_H$$

where f_a is the fraction of dose that enters the gut wall; F_G is the fraction of drug that escapes first-pass metabolism in the gut wall and enters the portal vein; and F_H is the fraction of drug that enters the liver and escapes metabolism during first pass, which then enters the systemic circulation.

The absorption potential of a drug can be estimated from physicochemical properties using both empirical methods [27,28] and physiological models such as the Compartmental Absorption and Transit (CAT) model [29]. The CAT model has been further developed into the Advanced Compartmental Absorption and Transit model [30] and the Advanced Dissolution, Absorption and Metabolism model [31]. In brief, these absorption models consist of physiologically based compartments corresponding to different segments of the GI tract. A series of differential equations are used to describe drug release, dissolution, degradation, metabolism and absorption within each segment and drug transit from one segment to the next. For each drug phase in the small intestine, for example, solid and dissolved drug, a segment is modeled as a well-stirred compartment in which different processes such as dissolution/precipitation, absorption/

efflux/uptake and transit can occur simultaneously. Absorption is influenced by a number of physiological changes in the GI tract, some of which are observed in patients with CKD. Drug absorption may be altered as a result of changes in gastric emptying time and gastric pH, as well as the presence of gut edema [19]. Many patients with kidney impairment suffer from gastroparesis, which can delay gastric emptying [1] and cause prolongation of the maximum concentration (C_{max}) without any apparent effect on the overall extent of absorption (TABLE 1). Conversely, the results of some studies in CKD patients show no delay in gastric emptying [32,33]. Conversion of salivary urea to ammonia by gastric urease may increase the gastric pH [34], which can alter the dissolution or ionization properties of certain drugs, resulting in changes to the bioavailability [8].

Distribution refers to the reversible transfer of a drug from one location to another within the body. The volume of distribution influences the elimination rate and C_{max} and, together with clearance, determines the rate of decline in plasma drug concentrations (elimination rate) – the higher the volume, the longer the residence time in the body and *vice versa*. Since the proportion of the drug in different tissues changes with time (and the tissue–drug concentrations are not necessarily moving in parallel), volume of distribution is not a fixed term and changes with time. The volume of distribution at steady state (V_{ss}) is considered when the ratio of drug in various tissues has reached equilibrium. Traditionally, after a drug has been administered intravenously, V_{ss} is calculated using this formula:

$$V_{ss} = \frac{D}{AUC} \times MRT$$

where D and MRT are the dose and mean residence time, respectively. However, this is an over-simplistic view of the processes involved [35]. Physiologically, an estimate of the volume of distribution is based on an individual's characteristics that go beyond simple links to body size [35] as described by the following equation:

$$V_{ss} = V_p + V_e \times E:P + \sum_i V_i \times K_{p,i}$$

where V_p , V_e and V_i are volumes of plasma, erythrocyte and tissue, respectively, and E:P and $K_{p,i}$ are the relative drug concentrations in erythrocyte and tissue to plasma [36–42]. It is clear from this equation that there are system-related parameters that are characteristic of an individual (composition and volume of tissues) and drug-related ones (binding affinity to red blood cells, plasma protein or certain components of tissues). It is well established that anemia develops in the course of CKD and its severity is related to the duration and extent of kidney failure (TABLE 1) [43]. Lower hemoglobin may result from the reduced erythropoietin synthesis in the kidneys and/or the presence of inhibitors of erythropoiesis. In addition, decreased plasma protein binding of acidic drugs is often observed owing to reduced levels of albumin in the plasma (a direct consequence of hyperalbuminuria) (TABLE 1) [8,205], qualitative changes in albumin binding sites and competition for binding sites by accumulating endogenous substances [44,45]. The unbound fraction of drug in plasma (f_u) for an individual ($f_{u,i}$) based on the concentration of albumin in the plasma ($[P]_i$) can be estimated using the following equation:

$$f_{u,i} = \frac{1}{1 + \frac{(1 - f_u) \times [P]_i}{[P] \times f_u}}$$

where $[P]$ is the average concentration of albumin in the population [46]. Changes in tissue protein binding are not relevant for most drugs, except in the case of digoxin, which leads to a 50% reduction in the V_{ss} in patients with stage 5 CKD [19]. CKD-induced changes in body composition include increased total body water and adipose tissue and decreased muscle mass. Excessive fluid retention, manifesting as increased extracellular fluid, is expected to increase the V_{ss} of hydrophilic compounds [47].

Several models have been developed to quantify the effects of hepatic blood flow, fraction unbound in blood and hepatic intrinsic clearance on hepatic clearance [48]. Among these, the well-stirred model (represented by the two equations below) has been widely used mainly because of its mathematical simplicity and practicality, as shown below:

$$CL_{H,B} = \frac{Q_{H,B} \cdot f_{u,B} \cdot CL_{int,H}}{Q_{H,B} + f_{u,B} \cdot CL_{int,H}}$$

$$F_H = \frac{Q_{H,B}}{Q_{H,B} + f_{u,B} \cdot CL_{int,H}}$$

where $CL_{H,B}$ is hepatic drug clearance based on whole-blood drug concentration, $Q_{H,B}$ is hepatic blood flow and $f_{u,B}$ is the free fraction of drug in blood. The well-stirred model assumes that drug distribution into the liver is perfusion limited with no diffusion delay and that no active transport systems are involved, and that the drug is distributed instantly and homogeneously throughout liver water and that the unbound concentrations in plasma and liver water are identical. Rane *et al.* successfully

Table 1. Key physiological and biochemical parameter changes associated with differing degrees of renal impairment.

Parameter	Control	GFR (ml/min/1.73 m ²)	
		30–59	<30
CYP1A2 (pmol/mg)	52 [58]	33 [63,129–131]	24 [129–131]
CYP2C8 (pmol/mg)	24 [58]	20 [64]	13 [64]
CYP2C9 (pmol/mg)	73 [58]	63 [65]	29 [65]
CYP2C19 (pmol/mg)	14 [58]	5.5 [66]	2.3 [66]
CYP2D6 (pmol/mg)	8.0 [58]	4.6 [67,132,133]	2.1 [132,133]
CYP3A4 (pmol/mg)	137 [58]	73 [68,134,135]	62 [68,135]
Albumin (g.l ⁻¹) M	44.9 [205]	41.6 [136,137,205]	37.6 [136,137,205]
F	41.8 [205]	38.8 [136,137,205]	35.0 [136,137,205]
Hematocrit (%) M	43.0 [43]	39.7 [43]	36.5 [43]
F	38.0 [43]	33.2 [43]	31.3 [43]
Gastric emptying time (h)	0.40 [35]	0.55 [19]	0.65 [19]

F: Female; GFR: Glomerular filtration rate; M: Male.

predicted *in vivo* hepatic metabolic clearance in rats based on *in vitro* data obtained from rat liver microsomes, taking into consideration the hepatic blood flow rate and the unbound fraction in blood [49]. Since then, significant progress has been made on predicting human hepatic metabolic clearance from a variety of *in vitro* systems, including human liver microsomes, recombinant enzymes and hepatocytes [50–55]. The unbound total hepatic intrinsic clearance ($CL_{u_{int,H}}$) can be extrapolated from *in vitro* clearance determined in a variety of *in vitro* systems using scaling factors as described in Barter *et al.* [56] and according to the approach described by Rostami-Hodjegan and Tucker [57]. The two equations shown in Box 3 represent the scaling approaches for recombinantly expressed enzymes and human liver microsomes. In the equations, there are i metabolic pathways for each of j enzymes; 'rh' indicates recombinantly expressed enzyme; $Enz_{abundance}$ is the abundance of the i^{th} CYP enzyme [58]; V_{max} is the maximum rate of metabolism by an individual enzyme; K_m is the Michaelis constant; MPPGL is the amount of microsomal protein per gram of liver; and ISEF is a scaling factor that compensates for any difference in the activity per unit of enzyme between recombinant systems and hepatic enzymes [59].

Drug metabolism & transporters

Drug metabolism is classified according to phase I or phase II processes. The cytochrome P450 (CYP450) family is the major phase I metabolic enzyme system in the liver. Pichette and Leblond have provided a detailed description of metabolic changes observed in renal failure and indicated that CKD was associated with a decrease in the expression of specific liver P450 isoforms secondary to reduced mRNA levels [3]. However, most of these data come from *in vitro* and *in vivo* animal studies. The main hypothesis to explain the decrease in liver CYP activity in CKD appears to be the accumulation of uremic toxins (e.g., urea, indoxyl sulfate and cytokines), which can modulate CYP activity. There are a number of reports that have provided data in support of this hypothesis: indoxyl sulfate inhibited the metabolism of ethoxyresorufin and testosterone in both human liver microsomes and hepatocytes [60]; parathyroid hormone down-regulated hepatic P450 in rat and in cultured hepatocytes [61]; and incubations of microsomes from healthy human livers with serum of CKD patients led to decreases in CYP3A4 (80%), CYP2C9 (40%) and UDP-glucuronyl transferase activities [62]. Acute changes in the clearance of P450 substrates in experimental models and in ESRD patients, associated with an improvement in the uremia (i.e., predialysis vs postdialysis), also support the concept that uremic toxins can directly inhibit drug metabolism and transport in humans. Although there are no human liver data for patients with CKD demonstrating decreased CYP activity, there are many studies [3,4] that have shown that loss of renal function can result in decreased hepatic clearance of drugs metabolized by CYP1A2 [63], CYP2C8 [64], CYP2C9 [65], CYP2C19 [66], CYP2D6 [67] and CYP3A4 [68]. Extrapolation

Box 3. Scaling approach for estimation of hepatic metabolic intrinsic clearance.

$$CL_{u_{int,H}} = \left[\sum_{j=1}^n \left(\sum_{i=1}^n ISEF_{ji} \times \frac{V_{max}(rhEnz) \times Enz_{abundance}}{K_m(rhEnz)} \right) \right] \times MPPGL \times Liverweight$$

$$CL_{u_{int,H}} = CL_{u_{int}}(per_mg_microsomes) \times MPPGL \times Liverweight$$

of these hepatic clearances back to values of metabolic intrinsic clearance (after correcting for differences in protein binding and blood to plasma partitioning) can provide estimates of enzyme abundance in patients with CKD (TABLE 1).

More recently, the contribution of the gut to first-pass metabolism has been increasingly recognized. The intestinal tissue is also endowed with phase I and II enzymes, although at lower levels than those for the liver [69]. Several CYP enzymes have been detected in the human small intestine, including CYP1A2, CYP2D6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5 [70]. Among them, CYP3A4 is the most prominent enzyme present in the human intestine [66,71]. Although the total content of CYP3A in the entire human small intestine is only 1% of that in the liver [67,72], intestinal extraction of CYP3A substrates is often similar to or even exceeds hepatic extraction [73].

An operational model to predict first-pass metabolism in the gut is available. The 'Q_{Gut}' model (see the following equation) retains the form of the 'well-stirred' model but the flow term (Q_{Gut}) is a hybrid of both permeability through the enterocyte membrane and villous blood flow [74,75].

$$F_G = \frac{Q_{Gut}}{Q_{Gut} + fu_G \cdot CL_{u_{int,G}}}$$

where F_G is intestinal availability, fu_G is the fraction of drug unbound in the enterocyte and its value is close to 1 in most cases [71] and $CL_{u_{int,G}}$ is the unbound total gut intrinsic clearance. The parameter Q_{Gut} can be expanded:

$$Q_{Gut} = \frac{Q_{villi} \cdot CL_{perm}}{Q_{villi} + CL_{perm}}$$

where CL_{perm} is a clearance term defining permeability through the enterocyte and Q_{villi} is villous blood flow. Permeability clearance (CL_{perm}) is the product of effective intestinal permeability (P_{eff}) and intestinal cylindrical surface area [71]:

$$CL_{perm} = P_{eff} \times A$$

where A is intestinal cylindrical surface area and is variable among individuals. P_{eff} is related to drug permeability but can be affected by the abundances of intestinal transporters and pH in the gut lumen. $CL_{u_{int,G}}$ can be extrapolated from *in vitro* clearance determined in a variety of *in vitro* systems, including recombinantly expressed systems and human intestinal microsomes (Box 4). In these equations, there are i metabolic pathways for each of j enzymes; MPPGI is the amount of microsomal protein per gram of intestine, and ISEF is a scaling factor that compensates for any difference in the activity per unit of enzyme between recombinant systems and intestinal enzymes.

Although there are no *in vivo* or *in vitro* data derived from human tissues to support this, animal models of CKD have demonstrated reduced activity of intestinal CYP3A4 activity [76] and P-glycoprotein [77]. Reductions in intestinal metabolism and P-glycoprotein-mediated drug transport owing to CKD may cause an increase in the oral bioavailability of some drugs [9]. However, the results of a recent study by Sun *et al.* suggest that when using erythromycin as a model substrate, hepatic CL, but not gut bioavailability, is affected in patients with ESRD [78]. This appears to be the first study in humans to differentiate between the effects of uremia on hepatic versus intestinal clearance.

In addition to reduced metabolic enzyme activity being responsible for the reduced nonrenal clearance of drugs in a number of cases, other mechanisms such as alterations in transporter systems or transporter activity may be involved. Since transporters play an important role in drug disposition and elimination, more and more studies have begun to focus on their change in renal impairment. These have been discussed extensively in a review by Sun *et al.* [78]. In the animal model of CKD, increasing evidence favors the hypothesis that kidney impairment modulates the number of uptake and efflux transporters in liver, kidney and intestine [78]. There is evidence based on animal studies that uremia has an inhibitory effect on the transport of organic anions into the liver [79,80]. Although there are IVIVE approaches available for incorporation of transporters [81,82], there are no relative abundance data or relative activity factors available for human liver that are necessary to correct for differences in uptake between healthy volunteers and subjects with renal impairment.

Renal excretion

All drugs are ultimately removed from the body, either as metabolites or in their unchanged form. The primary route of excretion is through the kidneys and urine, although excretion may also occur via the biliary route and be considered as a true elimination when there is no reabsorption occurring in the intestine. Compromised renal function may affect the pharmacokinetics of a drug if urinary excretion is a substantial contributor to overall elimination. Drug characteristics that determine the extent of renal elimination include physical chemistry (lipophilicity and ionization) [83], plasma protein and erythrocyte binding [84] and affinity to certain transporter proteins in the kidney [85–87]. These mainly affect the fractional tubular reabsorption ($F_{\text{Re-abs}}$), GFR or active secretion ($CL_{\text{u,Sec}}$) of the drug, which are summarized in equation in Box 5 after Levy [84] and Janků [88]. Chronic kidney disease-induced changes in the GFR, protein binding, blood to plasma partitioning and the renal blood flow (Q_{R}) will obviously have a direct impact of the renal clearance of a drug (CL_{R}).

Although a comprehensive review of the literature was performed for all of the system parameters already described, including blood flows, only data relating to key changes are presented in TABLE 1; these include CYP abundance, protein binding, hematocrit and gastric emptying in subjects with varying degrees of renal impairment (GFR <30 ml/min/1.73 m² and 30–59 ml/min/1.73 m²). These system parameters used in conjunction with the ADME models described in this section can be used to assess the impact of CKD on the exposure (AUC and C_{max}) of a drug.

Application of IVIVE to predict pharmacokinetics in patients with renal impairment

In this section we present some examples of application of the IVIVE approach in subjects with renal impairment. The drugs that have been chosen have complex kinetics (undergo auto-inhibition, have metabolites that are potent inhibitors and are taken up into the liver by transporters), undergo extensive metabolism in the liver and have negligible renal clearance. For each example, prior *in vitro* and *in vivo* information on the metabolism and kinetics of the drug were incorporated into the Simcyp Population-based Simulator [206] to predict the exposure of the drug in virtual subjects with renal impairment and compared against *in vivo* data. The system parameters in TABLE 1 were used to generate a population of virtual individuals with varying degrees of renal impairment using a correlated Monte Carlo approach [31]. Residual variability was not incorporated into the simulations.

The Simcyp Simulator adds intrinsic variability (i.e., coefficient of variation for parameters with uni- or multimodal frequency distributions depending on availability of information on the involvement of enzymes or transporters on kinetics and knowledge of phenotype or genotype frequency for such polymorphic enzymes or transporters) to each parameter of the algorithms based on known information in the literature, and utilizes a correlated Monte Carlo approach to generate populations of different virtual individuals with their own unique, but realistic, characteristics. Early attempts to use Monte Carlo methods and to simulate pharmacokinetic behavior in ‘virtual populations’ date back to the mid-1980s. Jackson *et al.* assessed the robustness of different experimental *in vivo* indices to detect and display genetic polymorphisms in human drug-metabolizing activity [89,90]. These simulations were later expanded to demonstrate the effect of variability in ADME parameters on the power of single time point estimates for the assessment of metabolic activity [91]. Coupled with Monte Carlo methods, PBPK modeling has been used to assess the quantitative impact of physiological and environmental factors on human variability in toxicokinetics and pharmacokinetics in other publications [92–94].

Box 4. Scaling approach for estimation of intestinal metabolic intrinsic clearance.

$$CL_{\text{u,Int,G}} = \left[\sum_{j=1}^n \left(\sum_{i=1}^n ISEF_{ji} \times \frac{V_{\text{max}_i}(\text{rhEnz}_i) \times \text{EnzAbundance}_i}{K_{\text{m}_i}(\text{rhEnz}_i)} \right) \right] \times \text{MPPGI} \times \text{Intestine_weight}$$

$$CL_{\text{u,Int,G}} = CL_{\text{u,Int}}(\text{per_mg_microsomes}) \times \text{MPPGI} \times \text{Intestine_weight}$$

Paroxetine

Paroxetine is a selective serotonin reuptake inhibitor antidepressant that is used to treat major depression and obsessive–compulsive, panic, social anxiety and generalized anxiety disorders in adult outpatients. It

is extensively metabolized in humans and exhibits nonlinear kinetics during single and multiple dosing [95,96]. After administration of a single dose of paroxetine, there is a sevenfold difference in the median total clearance of poor metabolizers (PMs) and extensive metabolizers (EMs) of CYP2D6, which is then reduced to twofold at steady state. The nonlinear kinetics of paroxetine are much more prominent in EMs than PMs, mainly owing to time-dependent inhibition of the CYP2D6-mediated metabolism [97]. Jornil *et al.* used prior *in vitro* and *in vivo* information on the metabolism and kinetics of paroxetine to predict the exposure in EM and PM individuals during single and multiple dosing regimens [98]. The simulated data were reasonably consistent with *in vivo* data [97]. Hence, this model was used to predict the change in exposure of paroxetine in patients with differing degrees of renal impairment (GFR <30 ml/min/1.73 m² and 30–59 ml/min/1.73 m²) relative to healthy volunteers based on the study design described by Doyle *et al.* [99]. The renal function of the subjects recruited into the study was based on CL_{CR} estimated from serum creatinine levels. After a single oral dose of 30 mg paroxetine, predicted fold increases in C_{max} and AUC_(0-∞) were 1.5- and 1.7-fold, respectively, and 2.1- and 3.2-fold, respectively, for subjects with GFR values between 30–59 and <30 ml/min/1.73 m², respectively, relative to HV; corresponding *in vivo* increases were 1.8- and 1.8- and 2.3- and 3.6-fold, respectively (FIGURE 1). After 14 days of 30 mg paroxetine daily, predicted fold increases in C_{max} and AUC on the last day of dosing relative to those in healthy volunteers were lower, as given by values of 1.3- and 1.3-fold, respectively, and 1.5- and 1.6-fold, respectively, for the two groups. Although observed data were not available for the latter, it is important to understand how the time-dependent inhibition of CYP2D6 propagates through multiple dosing regimens in patients with renal impairment.

Diltiazem

The calcium channel antagonist diltiazem is used in the treatment of hypertension, angina pectoris and some types of arrhythmia, and is often prescribed in patients with renal impairment. The pharmacokinetics of diltiazem in nine patients with severe renal impairment (GFR values based on inulin clearance ranging from 1.8 to 52 ml/min/1.73 m²) receiving a single 120 mg dose have been reported [100]. A direct comparison of the pharmacokinetics of diltiazem against those cited previously for healthy volunteers [101] led the investigators to conclude that diltiazem exposure was similar in both groups during the administration of a single dose.

Box 5. Estimation of renal clearance of a drug.

$$CL_R = Q_R \times \left[\frac{fu_B \times GFR}{Q_R} + \left(1 - \frac{fu_B \times GFR}{Q_R} \right) \times \left(\frac{Q_R \cdot fu_B \cdot CLU_{Sec,int}}{Q_R + fu_B \cdot CLU_{Sec,int}} \right) \right] \times (1 - F_{Re-abs})$$

However, there was considerable variability in peak plasma concentrations of diltiazem across the nine patients with renal impairment; values ranged from 31.9 to 406.4 ng/ml.

This is probably due to the fact that diltiazem undergoes extensive metabolism through multiple pathways, including deacetylation by esterases and CYP-mediated *N*- and *O*-demethylation. *N*-demethylation to desmethyldiltiazem (MA) appears to be the major pathway of elimination in humans and is mediated primarily by CYP3A, with minor contributions from CYP2C8 and CYP2C9 [102,103]. MA is further *N*-demethylated, mainly by CYP3A, to N,N-didesmethyl diltiazem (MD) [104]. Diltiazem causes clinically significant drug–drug interactions with compounds that are metabolized by CYP3A, including midazolam, triazolam, quinidine and simvastatin [105–107]. Thus, inhibition of CYP3A has been attributed to the parent compound and its metabolites, consistent with the accumulation of MA and desacetyl–diltiazem after 2 weeks of administration [108,109]. Subsequently, it was shown that both diltiazem and MA, but not MD, cause time-dependent inhibition through metabolite intermediate complex formation, with MA having a fourfold greater inactivation potency than diltiazem [95]. We have previously published on the development and validation of a mechanistic PBPK

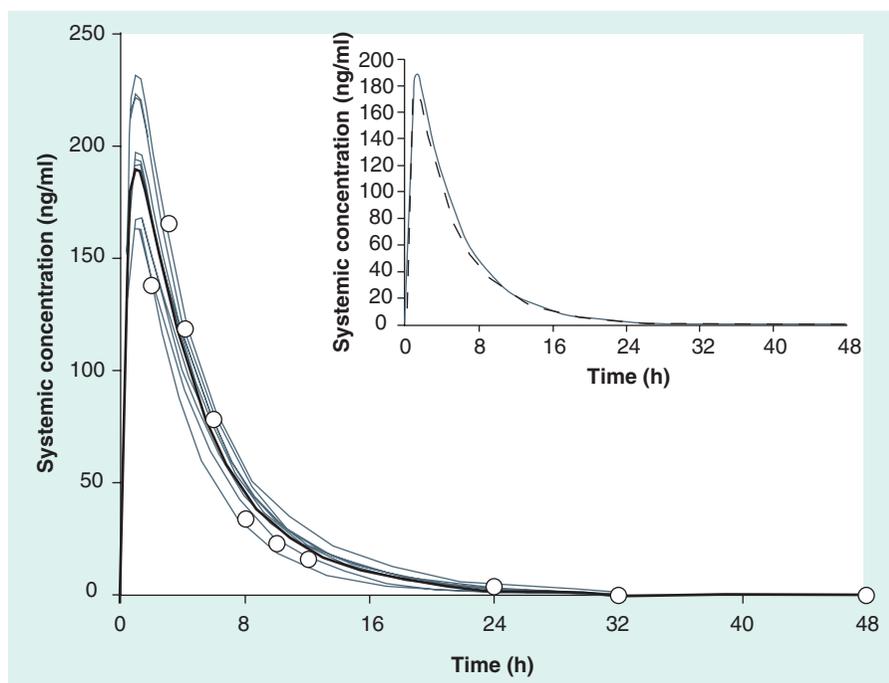


Figure 2. Simulated plasma concentration–time profiles of diltiazem after an oral dose of 120 mg in subjects with severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m²). The gray lines represent individual trials (10 × 9) and the solid black line is the mean of the population (n = 90). Mean observed data (Pozet *et al.* [100]) are overlaid (open circles). Inset: Dashed and solid lines represent simulated plasma concentrations in healthy volunteers and subjects with renal impairment, respectively.

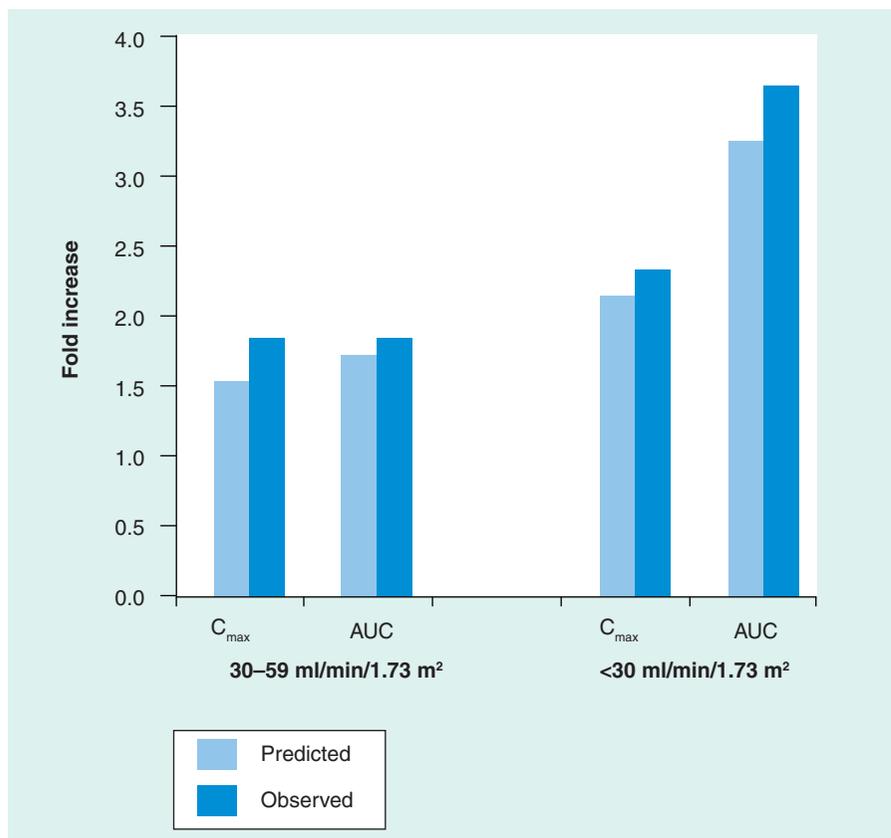


Figure 1. Predicted and observed fold-increases in exposure (C_{\max} and AUC) after a single 30 mg dose of paroxetine in subjects with differing degrees of renal impairment (glomerular filtration rate <30 ml/min/1.73 m² and 30–59 ml/min/1.73 m²) relative to healthy volunteers based on the study design described by Doyle *et al.* [99].

model that considers both competitive and time-dependent inhibition in both gut and liver by both diltiazem and MA, as well as the complex interplay between the two moieties with respect to mutual inhibition of parent compound and its metabolite for both single and multiple dosage regimens [110].

This model was used in conjunction with the system parameters for the population with GFR <30 ml/min/1.73 m² (TABLE 1) to replicate the study reported by Pozet *et al.* [100]. Simulated and observed mean plasma concentration–time profiles of a single 120-mg dose of diltiazem administered to nine patients (five female) aged 22–69 years with severe renal impairment were compared for ten virtual trials (FIGURE 2). As observed for the *in vivo* study, there was considerable variability in peak plasma concentrations of diltiazem across the simulated patients with renal impairment; values ranged from 82.4 to 385 ng/ml. In the case of the observed data, this may be an artefact due to the limited number of blood samples that were taken (seven over a period of 12 h). Simulated profiles of diltiazem for both healthy volunteers and patients with renal impairment are shown in the inset of FIGURE 2. Despite the 45% reduction in CYP3A in patients with CKD, it is not surprising that the predicted exposures are similar because there is a 26% increase in the f_{up} and the contribution of CYP3A metabolism to the overall clearance of diltiazem is less than 50%. During multiple dosing

of diltiazem 120 mg three-times daily for 14 days (data not shown), the accumulation of diltiazem is similar for the two groups.

Repaglinide

Repaglinide is a short-acting meglitinide analogue antidiabetic drug used in the treatment of Type 2 diabetes mellitus [111]. It lowers blood glucose concentrations by enhancing glucosestimulated insulin release in pancreatic β -cells. Repaglinide is rapidly absorbed following oral administration and undergoes first-pass metabolism, resulting in a 60% bioavailability. CYP3A4 and CYP2C8 are the main enzymes responsible for the oxidative metabolism of the compound [112,113]. The AUC of repaglinide is increased markedly in homozygous carriers of the SLC01B1 521T>C (Val174Ala) single-nucleotide polymorphism, suggesting that it is a substrate of the SLC01B1-encoded hepatic uptake transporter organic anion transporting polypeptide 1B1 (OATP1B1) [114]. Prior *in vitro* and *in vivo* information on the metabolism and kinetics of repaglinide (including OATP1B1 uptake) were used in the Simcyp Population-based Simulator to simulate the plasma concentration–time profiles of repaglinide and to predict the impact of renal impairment on the pharmacokinetics (C_{\max} and AUC_(0–∞)).

The trial design used for simulation of the plasma drug concentration–time profiles following multiple doses of 2 mg repaglinide was based on the study of Marbury *et al.* [115] (FIGURES 3 & 4). Six healthy subjects (18–42 years of age; one female) and six patients (40–64 years of age; two female) with severe renal impairment (GFR <30 ml/min/m²) received a single dose of 2 mg repaglinide. On days 2–6, 2 mg repaglinide treatment was given preprandially three-times a day, followed by a final single dose on day 7. The renal function of the subjects recruited into the study was assessed by two consecutive measurements of CL_{CR}. After the last of multiple doses (2 mg) in healthy subjects and renal patients, predicted mean AUC_(0–∞) and C_{\max} values ranged from 24.2 to 44.0 ng/ml.h (median 31.7) and 16.5 to 25.8 ng/ml (median 20.7), respectively, and from 35.6 to 77.3 ng/ml.h (median 58.5) and 23.2 to 38.5 ng/ml (median 31.2), respectively (TABLE 2). Corresponding observed mean values were 22.2 ng/ml.h and 16.4 ng/ml and 73.7 ng/ml.h and 29.9 ng/ml, respectively [115]. The predicted increases in AUC_(0–∞) and C_{\max} in subjects with renal impairment relative to healthy volunteers were 1.3- and 1.5-fold, which were lower than the observed values (1.8- and 3.3-fold, respectively). Although it is known that uptake transporters have reduced activity in animal models of CKD [78], there are no quantitative data from human cell systems to use for extrapolation to *in vivo*. It is likely that if a reduction in OATP1B1-mediated uptake

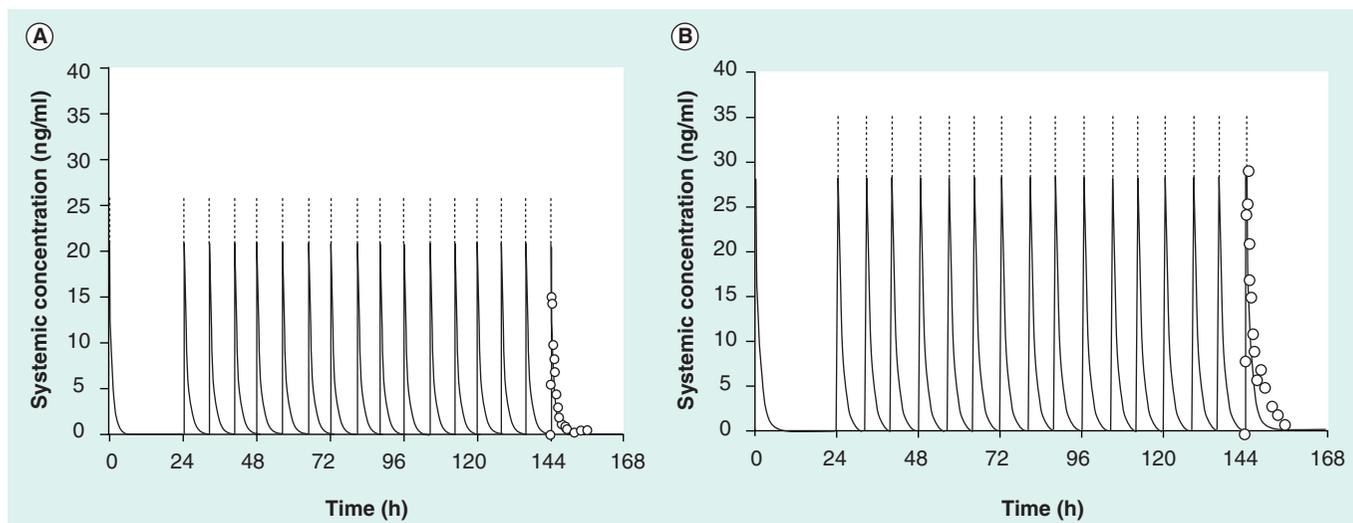


Figure 3. Simulated and observed plasma concentration–time profiles of repaglinide during a dosing schedule of a single dose of 2 mg repaglinide on day 1 followed by 2 mg repaglinide three-times daily on days 2–6 for healthy subjects (A) and for patients with renal impairment (B). The dashed lines represent individual trials (10×6) and the solid black lines are the mean of the population ($n = 60$). The circles are mean observed values from Marbury *et al.* [115].

(which results in reduced metabolism and increased exposure) of repaglinide was incorporated into the model, the observed data in patients with renal impairment would be recovered.

Expert commentary

The pharmaceutical industry and drug regulatory bodies are increasingly embracing the application of modeling and simulation to predict human pharmacokinetics from *in vitro* data and animal models to produce innovative products faster and more safely. Indeed, over the past decade there have been an increasing number of publications on the application of IVIVE approaches in the drug development process [116–127].

Modeling and simulation of ADME processes that define the plasma concentration–time course of a drug also provide a tool

for prediction of interindividual variability in dose–concentration relationships, which is of particular importance to clinicians, as well as scientists working in drug development. Regulatory bodies, notably the FDA in the USA, have already emphasized the need for quantitative description of pharmacokinetics through its Critical Path Initiative, in an attempt to underpin the understanding of efficacy, safety and optimal study design with a view to informing regulatory decisions [128]. The FDA has proposed a decision tree recommending that drugs eliminated predominantly by nonrenal routes should be investigated using a reduced pharmacokinetic study in subjects with ESRD in the first instance [9], followed by a full study if the results demonstrate an important alteration in pharmacokinetics. Therefore, it is envisaged that PBPK modeling will be utilized more frequently to provide an indication of the

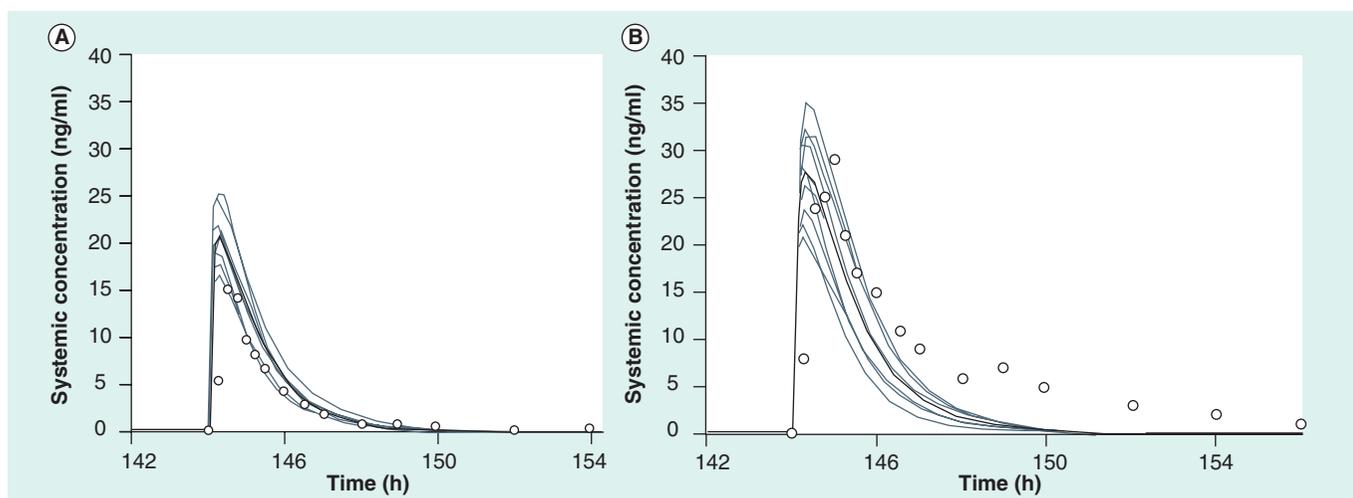


Figure 4. Simulated and observed plasma concentration–time profiles of repaglinide on the last day during a dosing schedule of a single dose of 2 mg repaglinide on day 1 followed by 2 mg repaglinide three-times daily on days 2–6 to healthy subjects (A) and patients with renal impairment (B). The gray lines represent individual trials (10×6) and the solid black lines are the mean of the population ($n = 60$). The circles are mean observed values from Marbury *et al.* [115].

Table 2. Mean predicted C_{max} and AUC values of repaglinide on the last day of 7 days of dosing with 2 mg repaglinide (2 mg for 1 day followed by 2 mg three-times a day for 6 days).

Predicted or observed	Healthy subjects (n = 6)		Patients with renal impairment (n = 6)	
	AUC (ng/ml.h)	C_{max} (ng/ml)	AUC (ng/ml.h)	C_{max} (ng/ml)
Predicted [†]	24.2–44.0 (31.7)	16.5–25.8 (20.7)	35.6–77.3 (58.5)	23.2–38.5 (31.2)
Observed	22.2	16.4	73.7	29.9

[†]A range of mean values for the ten simulated trials and the corresponding median in brackets are shown.

change in drug exposure in special populations that cannot be targeted for ethical reasons, including those with renal impairment, and facilitate the design of more efficient clinical trials. Based on the examples presented in this article, it appears that it may be possible to use IVIVE approaches to predict the pharmacokinetics of drugs eliminated predominantly by nonrenal routes in patients with renal impairment using a PBPK approach. However, more extensive validation of the existing model and additional research into the physiological changes induced by CKD are required to refine the model.

Five-year view

While the use of IVIVE in conjunction with PBPK models appears to have been accepted by the pharmaceutical industry and regulatory bodies, it is likely that application of this approach

to special populations, including those with renal impairment, will take longer to adopt owing to the high risk of adverse events associated with these individuals. Based on the examples provided in this article, it appears that it may be possible to extrapolate this approach to patients with renal impairment. Further research into the effects of CKD on the system parameters required for IVIVE will hopefully aid in the development of more robust models.

Acknowledgement

The authors thank James Kay for his assistance with the preparation of this manuscript.

Financial & competing interests disclosure

This work was funded by Simcyp Limited and the authors are employees of, and/or shareholders in, the company. Simcyp Simulator is freely available, following completion of the training workshop, to approved members of academic institutions and other nonprofit organizations for research and teaching purposes. Mohsen Aarabi has no conflicts of interest that are directly relevant to the contents of this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Renal impairment not only affects elimination of the drug in the kidney, but also the nonrenal route of drugs that are extensively metabolized in the liver.
- The US FDA guidance to assess the impact of renal impairment on the pharmacokinetics of a drug under development has recently been updated to include evaluation of drugs with nonrenal elimination routes.
- Prior simulation of the potential exposure of individuals with renal impairment may help in the selection of a safe and effective dosage regimen.
- In addition to reduced metabolic enzyme activity being responsible for the reduced nonrenal clearance of drugs in a number of cases, other mechanisms such as alterations in transporter systems or transporter activity may be involved.
- These factors can be accommodated using a 'systems biology' approach and full physiologically based pharmacokinetic models.
- Although results generated using the physiologically based pharmacokinetic models appear to be reasonably consistent with observed data for patients with renal impairment, more extensive validation is required.
- Quantitative data relating to *in vitro*–*in vivo* extrapolation of transporters, including relative activity factors, are required to incorporate the effects of renal impairment on transporter-mediated uptake.

References

Papers of special note have been highlighted as:

• of interest

- Gabardi S, Abramson S. Drug dosing in chronic kidney disease. *Med. Clin. North Am.* 89, 649–687 (2005).
- Balant LP, Dayer P, Fabre J. Consequences of renal insufficiency on the hepatic clearance of some drugs. *Int. J. Clin. Pharmacol. Res.* 3, 459–474 (1983).
- Pichette V, Leblond FA. Drug metabolism in chronic renal failure. *Curr. Drug Metab.* 4, 91–103 (2003).
- Dreisbach AW, Lertora JJ. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. *Semin. Dial.* 16, 45–50 (2003).
- Korashy HM, Elbekai RH, El-Kadi AO. Effects of renal diseases on the regulation and expression of renal and hepatic drug-metabolizing enzymes: a review. *Xenobiotica* 34, 1–29 (2004).
- Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am. J. Kidney Dis.* 42, 906–925 (2003).

• **Excellent discussion on the impact of chronic kidney disease (CKD) on drug metabolism and transport.**

- Sun H, Frassetto L, Benet LZ. Effects of renal failure on drug transport and metabolism. *Pharmacol. Ther.* 109, 1–11 (2006).

- 8 Nolin TD, Naud J, Leblond FA, Pichette V. Emerging evidence of the impact of kidney disease on drug metabolism and transport. *Clin. Pharmacol. Ther.* 83, 898–903 (2008).
- 9 Zhang Y, Zhang L, Abraham S *et al.* Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clin. Pharmacol. Ther.* 85, 305–311 (2009).
- **Regulatory view on assessing pharmacokinetics in patients with CKD.**
- 10 Lalonde RL, Wagner JA. Drug development perspective on pharmacokinetic studies of new drugs in patients with renal impairment. *Clin. Pharmacol. Ther.* 86, 557–561 (2009).
- **Interesting industry perspective on current US FDA guidance relating to conducting studies in patients with CKD.**
- 11 Ribbing J, Jonsson EN. Power, selection bias and predictive performance of the population pharmacokinetic covariate model. *J. Pharmacokinetic. Pharmacodyn.* 31, 109–134 (2004).
- 12 Rostami-Hodjegan A, Tucker GT. Simulation and prediction of *in vivo* drug metabolism in human populations from *in vitro* data. *Nat. Rev. Drug Discov.* 6, 140–148 (2007).
- **Provides background to the *in vitro*–*in vivo* extrapolation approach.**
- 13 Gibson GG, Rostami-Hodjegan A. Modeling and simulation in prediction of human xenobiotic absorption, distribution, metabolism and excretion (ADME): *in vitro*–*in vivo* extrapolations (IVIVE). *Xenobiotica* 37, 1013–1014 (2007).
- 14 Foley RN. Clinical epidemiology of cardiovascular disease in chronic kidney disease. *J. Ren. Care* 36(Suppl. 1), 4–8 (2010).
- 15 Hamer RA, El Nahas AM. The burden of chronic kidney disease. *Br. Med. J.* 332, 563–564 (2006).
- 16 Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 298, 2038–2047 (2007).
- 17 Atkins RC. The epidemiology of chronic kidney disease. *Kidney Int. Suppl.* 94, S14–S18 (2005).
- 18 Talbert RL. Drug dosing in renal insufficiency. *J. Clin. Pharmacol.* 34, 99–110 (1994).
- 19 Lam YW, Banerji S, Hatfield C, Talbert RL. Principles of drug administration in renal insufficiency. *Clin. Pharmacokinet.* 32, 30–57 (1997).
- 20 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 16, 31–41 (1976).
- 21 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med.* 130, 461–470 (1999).
- 22 Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N. Engl. J. Med.* 354, 2473–2483 (2006).
- 23 Rule AD, Gussak HM, Pond GR *et al.* Measured and estimated GFR in healthy potential kidney donors. *Am. J. Kidney Dis.* 43(1), 112–119 (2004).
- 24 Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft–Gault equations in the estimation of GFR in health and in chronic kidney disease. *J. Am. Soc. Nephrol.* 16(2), 459–466 (2005).
- 25 Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft–Gault equations for estimating renal function. *J. Am. Soc. Nephrol.* 16(3), 763–773 (2005).
- 26 Cantu TG, Ellerbeck EF, Yun SW, Castine SD, Kornhauser DM. Drug prescribing for patients with changing renal function. *Am. J. Hosp. Pharm.* 49, 2944–2948 (1992).
- 27 Dressman JB, Amidon GL, Fleisher D. Absorption potential: estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* 74, 588–589 (1985).
- 28 Artursson P, Karlsson J. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. *Biochem. Biophys. Res. Commun.* 175, 880–885 (1991).
- 29 Yu LX, Amidon GL. A compartmental absorption and transit model for estimating oral drug absorption. *Int. J. Pharm.* 186, 119–125 (1999).
- 30 Agoram B, Woltoz WS, Bolger MB. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv. Drug Deliv. Rev.* 50(Suppl. 1), S41–S67 (2001).
- 31 Jamei M, Turner D, Yang J *et al.* Population-based mechanistic prediction of oral drug absorption. *AAPS J.* 11, 225–237 (2009).
- 32 Wright RA, Clemente R, Wathen R. Gastric emptying in patients with chronic renal failure receiving hemodialysis. *Arch. Intern. Med.* 144, 495–496 (1984).
- 33 McNamee PT, Moore GW, McGeown MG, Doherty CC, Collins BJ. Gastric emptying in chronic renal failure. *Br. Med. J.* 291, 310–311 (1985).
- 34 St Peter WL, Redic-Kill KA, Halstenson CE. Clinical pharmacokinetics of antibiotics in patients with impaired renal function. *Clin. Pharmacokinet.* 22, 169–210 (1992).
- 35 Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: a tale of ‘bottom-up’ vs ‘top-down’ recognition of covariates. *Drug Metab. Pharmacokinet.* 24, 53–75 (2009).
- 36 Sawada Y, Hanano M, Sugiyama Y, Harashima H, Iga T. Prediction of the volumes of distribution of basic drugs in humans based on data from animals. *J. Pharmacokinetic. Biopharm.* 12, 587–596 (1984).
- 37 Berezkhovskiy LM. Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. *J. Pharm. Sci.* 93, 1628–1640 (2004).
- 38 Poulin P, Theil FP. *A priori* prediction of tissue:plasma partition coefficients of drugs to facilitate the use of physiologically-based pharmacokinetic models in drug discovery. *J. Pharm. Sci.* 89, 16–35 (2000).
- 39 Poulin P, Schoenlein K, Theil FP. Prediction of adipose tissue: plasma partition coefficients for structurally unrelated drugs. *J. Pharm. Sci.* 90, 436–447 (2001).
- 40 Poulin P, Theil FP. Prediction of pharmacokinetics prior to *in vivo* studies. 1. Mechanism-based prediction of volume of distribution. *J. Pharm. Sci.* 91, 129–156 (2002).
- 41 Rodgers T, Leahy D, Rowland M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J. Pharm. Sci.* 94, 1259–1276 (2005).

- 42 Rodgers T, Rowland M. Physiologically based pharmacokinetic modeling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J. Pharm. Sci.* 95, 1238–1257 (2006).
- 43 Hsu CY, McCulloch CE, Curhan GC. Iron status and hemoglobin level in chronic renal insufficiency. *J. Am. Soc. Nephrol.* 13(11), 2783–2786 (2002).
- 44 Vanholder R, De Smet R, Ringoir S. Factors influencing drug protein binding in patients with end stage renal failure. *Eur. J. Clin. Pharmacol.* 44(Suppl. 1), S17–S21 (1993).
- 45 Vanholder R, Van Landschoot N, De Smet R, Schoots A, Ringoir S. Drug protein binding in chronic renal failure: evaluation of nine drugs. *Kidney Int.* 33, 996–1004 (1988).
- 46 McNamara PJ, Alcorn J. Protein binding predictions in infants. *AAPS PharmSci.* 4(1), E4 (2002).
- 47 Aranoff G, Berns J, Brier M *et al.* *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults (Volume 4)*. American College of Physicians, Philadelphia, PA, USA (1999).
- 48 Wilkinson GR. Clearance approaches in pharmacology. *Pharmacol. Rev.* 39, 1–47 (1987).
- 49 Rane A, Wilkinson GR, Shand DG. Prediction of hepatic extraction ratio from *in vitro* measurement of intrinsic clearance. *J. Pharmacol. Exp. Ther.* 200, 420–424 (1977).
- 50 Houston JB. Utility of *in vitro* drug metabolism data in predicting *in vivo* metabolic clearance. *Biochem. Pharmacol.* 47, 1469–1479 (1994).
- 51 Iwatsubo T, Suzuki H, Sugiyama Y. Prediction of species differences (rats, dogs, humans) in the *in vivo* metabolic clearance of YM796 by the liver from *in vitro* data. *J. Pharmacol. Exp. Ther.* 283, 462–469 (1997).
- 52 Obach RS. Prediction of human clearance of twenty-nine drugs from hepatic microsomal intrinsic clearance data: an examination of *in vitro* half-life approach and nonspecific binding to microsomes. *Drug Metab. Dispos.* 27, 1350–1359 (1999).
- 53 Galetin A, Brown C, Hallifax D, Ito K, Houston JB. Utility of recombinant enzyme kinetics in prediction of human clearance: impact of variability, CYP3A5, and CYP2C19 on CYP3A4 probe substrates. *Drug Metab. Dispos.* 32, 1411–1420 (2004).
- 54 Riley RJ, McGinnity DF, Austin RP. A unified model for predicting human hepatic, metabolic clearance from *in vitro* intrinsic clearance data in hepatocytes and microsomes. *Drug Metab. Dispos.* 33, 1304–1311 (2005).
- 55 Howgate EM, Rowland Yeo K, Proctor NJ, Tucker GT, Rostami-Hodjegan A. Prediction of *in vivo* drug clearance from *in vitro* data. I: impact of inter-individual variability. *Xenobiotica* 36, 473–497 (2006).
- 56 Barter ZE, Bayliss MK, Beaune PH *et al.* Scaling factors for the extrapolation of *in vivo* metabolic drug clearance from *in vitro* data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. *Curr. Drug Metab.* 8, 33–45 (2007).
- 57 Rostami-Hodjegan A, Tucker GT. 'In silico' simulations to assess the 'in vivo' consequences of 'in vitro' metabolic drug–drug interactions. *Drug Discov. Today Tech.* 1(4), 441–448 (2004).
- 58 Rowland Yeo K, Rostami-Hodjegan A, Tucker GT. Abundance of cytochromes P450 in human liver: a meta analysis. *Br. J. Clin. Pharmacol.* 57(5), 687 (2004).
- 59 Proctor NJ, Tucker GT, Rostami-Hodjegan A. Predicting drug clearance from recombinantly expressed CYPs: intersystem extrapolation factors. *Xenobiotica* 34, 151–178 (2004).
- 60 Haneda M. [Mechanisms for the development and progression of diabetic nephropathy]. *Nippon Rinsho* 64(Suppl. 2), 427–432 (2006).
- 61 Michaud J, Naud J, Chouinard J *et al.* Role of parathyroid hormone in the downregulation of liver cytochrome P450 in chronic renal failure. *J. Am. Soc. Nephrol.* 17, 3041–3048 (2006).
- 62 Taburet AM, Singlas E. Drug interactions with antiviral drugs. *Clin. Pharmacokinet.* 30, 385–401 (1996).
- 63 Bauer LA, Bauer SP, Blouin RA. The effect of acute and chronic renal failure on theophylline clearance. *J. Clin. Pharmacol.* 22(1), 65–68 (1982).
- 64 Chapelsky MC, Thompson-Culkin K, Miller AK, Sack M, Blum R, Freed MI. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. *J. Clin. Pharmacol.* 43(3), 252–259 (2003).
- 65 Dingemans J, van Giersbergen PL. Influence of severe renal dysfunction on the pharmacokinetics and metabolism of bosentan, a dual endothelin receptor antagonist. *Int. J. Clin. Pharmacol. Ther.* 40(7), 310–316 (2002).
- 66 Naesdal J, Andersson T, Bodemar G *et al.* Pharmacokinetics of [14C]omeprazole in patients with impaired renal function. *Clin. Pharmacol. Ther.* 40(3), 344–351 (1986).
- 67 Balant L, Francis RJ, Tozer TN, Marmy A, Tschopp JM, Fabre J. Influence of renal failure on the hepatic clearance of bufuralol in man. *J. Pharmacokin. Biopharm.* 8(5), 421–438 (1980).
- 68 Vinik HR, Reves JG, Greenblatt DJ, Abernethy DR, Smith LR. The pharmacokinetics of midazolam in chronic renal failure patients. *Anesthesiology* 59(5), 390–394 (1983).
- 69 Pang KS. Modeling of intestinal drug absorption: roles of transporters and metabolic enzymes (for the Gillette Review Series). *Drug Metab. Dispos.* 31, 1507–1519 (2003).
- 70 Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC. The human intestinal cytochrome P450 "pie". *Drug Metab. Dispos.* 34, 880–886 (2006).
- 71 Paine MF, Khalighi M, Fisher JM *et al.* Characterization of interintestinal and intrainestinal variations in human CYP3A-dependent metabolism. *J. Pharmacol. Exp. Ther.* 283, 1552–1562 (1997).
- 72 Yang J, Tucker GT, Rostami-Hodjegan A. Cytochrome P450 3A expression and activity in the human small intestine. *Clin. Pharmacol. Ther.* 76, 391 (2004).
- 73 Thummel KE, O'Shea D, Paine MF *et al.* Oral first-pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin. Pharmacol. Ther.* 59(5), 491–502 (1996).
- 74 Rostami-Hodjegan A, Tucker GT. The effects of portal shunts on intestinal cytochrome P450 3A activity. *Hepatology* 35, 1549–1550; author reply 1550–1541 (2002).
- 75 Yang J, Jamei M, Yeo KR, Tucker GT, Rostami-Hodjegan A. Prediction of intestinal first-pass drug metabolism. *Curr. Drug Metab.* 8, 676–684 (2007).
- 76 Leblond FA, Petrucci M, Dube P, Bernier G, Bonnardeaux A, Pichette V. Downregulation of intestinal cytochrome P450 in chronic renal failure. *J. Am. Soc. Nephrol.* 13, 1579–1585 (2002).
- 77 Schinkel AH. The physiological function of drug-transporting P-glycoproteins. *Semin. Cancer Biol.* 8, 161–170 (1997).
- 78 Sun H, Frassetto LA, Huang Y, Benet LZ. Hepatic clearance, but not gut availability, of erythromycin is altered in patients with end-stage renal disease. *Clin. Pharmacol. Ther.* 87, 465–472 (2010).

- **Interesting study that investigates the impact of CKD on CYP3A4 in gut versus the liver.**
- 79 Veau C, Leroy C, Banide H *et al.* Effect of chronic renal failure on the expression and function of rat intestinal P-glycoprotein in drug excretion. *Nephrol. Dial. Transplant.* 16, 1607–1614 (2001).
- 80 Gibson GG, Clarke SE. Incorporation of cytochrome b5 into rat liver microsomal membranes. Impairment of cytochrome P-450-dependent mixed function oxidase activity. *Biochem. Pharmacol.* 35, 4431–4436 (1986).
- 81 Kusuha H, Sugiyama Y. *In vitro–in vivo* extrapolation of transporter-mediated clearance in the liver and kidney. *Drug Metab. Pharmacokinet.* 24(1), 37–52 (2009).
- 82 Kusuha H, Sugiyama Y. Pharmacokinetic modeling of the hepatobiliary transport mediated by cooperation of uptake and efflux transporters. *Drug Metab. Rev.* 42(3), 539–550 (2010).
- 83 Tucker GT. Measurement of the renal clearance of drugs. *Br. J. Clin. Pharmacol.* 12(6), 761–770 (1981).
- 84 Levy G. Effect of plasma protein binding on renal clearance of drugs. *J. Pharm. Sci.* 69, 482–483 (1980).
- 85 Song IS, Shin HJ, Shim EJ *et al.* Genetic variants of the organic cation transporter 2 influence the disposition of metformin. *Clin. Pharmacol. Ther.* 84(5), 559–562 (2008).
- 86 Urban TJ, Brown C, Castro RA *et al.* Effects of genetic variation in the novel organic cation transporter, OCTN1, on the renal clearance of gabapentin. *Clin. Pharmacol. Ther.* 83(3), 416–421 (2008).
- 87 Wang ZJ, Yin OQ, Tomlinson B, Chow MS. OCT2 polymorphisms and *in-vivo* renal functional consequence: studies with metformin and cimetidine. *Pharmacogenet. Genomics* 18(7), 637–645 (2008).
- 88 Janku I. Physiological modeling of renal drug clearance. *Eur. J. Clin. Pharmacol.* 44, 513–519 (1993).
- 89 Jackson PR, Tucker GT, Lennard MS, Woods HF. Polymorphic drug oxidation: pharmacokinetic basis and comparison of experimental indices. *Br. J. Clin. Pharmacol.* 22(5), 541–550 (1986).
- 90 Jackson PR, Tucker GT. Pharmacokinetic-pharmacogenetic modeling in the detection of polymorphisms in xenobiotic metabolism. *Ann. Occup. Hyg.* 34(6), 653–662 (1990).
- 91 Jackson PR, Tucker GT, Woods HF. Backtracking booze with Bayes – the retrospective interpretation of blood alcohol data. *Br. J. Clin. Pharmacol.* 31(1), 55–63 (1991).
- 92 Sato A. The effect of environmental factors on the pharmacokinetic behaviour of organic solvent vapours. *Ann. Occup. Hyg.* 35(5), 525–541 (1991).
- 93 Clewell HJ 3rd, Andersen ME. Use of physiologically based pharmacokinetic modeling to investigate individual versus population risk. *Toxicology* 111(1–3), 315–329 (1996).
- 94 Nestorov I. Modeling and simulation of variability and uncertainty in toxicokinetics and pharmacokinetics. *Toxicol. Lett.* 120(1–3), 411–420 (2001).
- 95 Haddock RE, Jackson D, Woods FR. Paroxetine: lack of effect on hepatic drug metabolizing enzymes. *Acta Psychiatr. Scand. Suppl.* 350, 93–94 (1989).
- 96 Kaye CM, Haddock RE, Langley PF *et al.* A review of the metabolism and pharmacokinetics of paroxetine in man. *Acta Psychiatr. Scand. Suppl.* 350, 60–75 (1989).
- 97 Sindrup SH, Brosen K, Gram LF *et al.* The relationship between paroxetine and the sparteine oxidation polymorphism. *Clin. Pharmacol. Ther.* 51(3), 278–287 (1992).
- 98 Jornil J, Jensen KG, Larsen F, Linnert K. Identification of cytochrome P450 isoforms involved in the metabolism of paroxetine and estimation of their importance for human paroxetine metabolism using a population-based simulator. *Drug Metab. Dispos.* 38(3), 376–385 (2010).
- 99 Doyle GD, Laher M, Kelly JG, Byrne MM, Clarkson A, Zussman BD. The pharmacokinetics of paroxetine in renal impairment. *Acta Psychiatr. Scand. Suppl.* 350, 89–90 (1989).
- 100 Pozet N, Brazier JL, Aissa AH *et al.* Pharmacokinetics of diltiazem in severe renal failure. *Eur. J. Clin. Pharmacol.* 24(5), 635–638 (1983).
- 101 Morsell PL, Rovei V, Mitchard M, Durand A, Gomerai R, Larrinban J. Pharmacokinetics and metabolism of diltiazem in man (observations in healthy volunteers and angina pectoris patients). In: *New Drug Therapy with Calcium Antagonists. Diltiazem Hakone Symposium.* Bing RJ (Ed.) 152–167, Excerpta Medica, NY, USA (1978).
- 102 Pichard L, Fabre I, Daujat M, Domergue J, Joyeux H, Maurel P. Effect of corticosteroids on the expression of cytochromes P450 and on cyclosporin A oxidase activity in primary cultures of human hepatocytes. *Mol. Pharmacol.* 41(6), 1047–1055 (1992).
- 103 Sutton D, Butler AM, Nadin L, Murray M. Role of CYP3A4 in human hepatic diltiazem N-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. *J. Pharmacol. Exp. Ther.* 282(1), 294–300 (1997).
- 104 Zhao P, Lee CA, Kunze KL. Sequential metabolism is responsible for diltiazem-induced time-dependent loss of CYP3A. *Drug Metab. Dispos.* 35(5), 704–712 (2007).
- 105 Backman JT, Olkkola KT, Aranko K, Himberg JJ, Neuvonen PJ. Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br. J. Clin. Pharmacol.* 37(3), 221–225 (1994).
- 106 Laganieri S, Davies RF, Carignan G *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and quinidine. *Clin. Pharmacol. Ther.* 60(3), 255–264 (1996).
- 107 Varhe A, Olkkola KT, Neuvonen PJ. Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin. Pharmacol. Ther.* 59(4), 369–375 (1996).
- 108 Hoglund P, Nilsson LG. Pharmacokinetics of diltiazem and its metabolites after single and multiple dosing in healthy volunteers. *Ther. Drug Monit.* 11(5), 558–566 (1989).
- 109 Montamat SC, Abernethy DR. N-monodesmethyl diltiazem is the predominant metabolite of diltiazem in the plasma of young and elderly hypertensives. *Br. J. Clin. Pharmacol.* 24(2), 185–189 (1987).
- 110 Rowland Yeo K, Jamei M, Yang J, Tucker GT, Rostami-Hodjegan A. Physiologically based mechanistic modeling to predict complex drug–drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut – the effect of diltiazem on the time-course of exposure to triazolam. *Eur. J. Pharm. Sci.* 39(5), 298–309 (2010).
- 111 Dornhorst A. Insulinotropic meglitinide analogues. *Lancet* 358(9294), 1709–1716 (2001).
- 112 Kajosaari LI, Laitila J, Neuvonen PJ, Backman JT. Metabolism of repaglinide by CYP2C8 and CYP3A4 *in vitro*: effect of fibrates and rifampicin. *Basic Clin. Pharmacol. Toxicol.* 97(4), 249–256 (2005).
- 113 Bidstrup TB, Bjornsdottir I, Sidelmann UG, Thomsen MS, Hansen KT. CYP2C8 and CYP3A4 are the principal

- enzymes involved in the human *in vitro* biotransformation of the insulin secretagogue repaglinide. *Br. J. Clin. Pharmacol.* 56(3), 305–314 (2003).
- 114 Niemi M, Backman JT, Kajosaari LI *et al.* Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. *Clin. Pharmacol. Ther.* 77(6), 468–478 (2005).
- 115 Marbury TC, Ruckle JL, Hatorp V *et al.* Pharmacokinetics of repaglinide in subjects with renal impairment. *Clin. Pharmacol. Ther.* 67(1), 7–15 (2000).
- 116 Wang YH. Confidence assessment of the Simcyp time-based approach and a static mathematical model in predicting clinical drug–drug interactions for mechanism-based CYP3A inhibitors. *Drug Metab. Dispos.* 38(7), 1094–1104 (2010).
- 117 Gandelman K, Zhu T, Fahmi OA *et al.* Unexpected effect of rifampin on the pharmacokinetics of linezolid: *in silico* and *in vitro* approaches to explain its mechanism. *J. Clin. Pharmacol.* 51(2), 229–236 (2010).
- 118 Foti RS, Rock DA, Wienkers LC, Wahlstrom JL. Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies using *in vitro* data and *in vivo* simulation. *Drug Metab. Dispos.* 38(6), 981–987 (2010).
- 119 Polasek TM, Sadagopal JS, Elliot DJ, Miners JO. *In vitro–in vivo* extrapolation of zolpidem as a perpetrator of metabolic interactions involving CYP3A. *Eur. J. Clin. Pharmacol.* 66(3), 275–283 (2010).
- 120 Emoto C, Murayama N, Rostami-Hodjegan A, Yamazaki H. Utilization of estimated physicochemical properties as an integrated part of predicting hepatic clearance in the early drug-discovery stage: impact of plasma and microsomal binding. *Xenobiotica* 39(3), 227–235 (2009).
- 121 Zhao P, Ragueneau-Majlessi I, Zhang L *et al.* Quantitative evaluation of pharmacokinetic inhibition of CYP3A substrates by ketoconazole: a simulation study. *J. Clin. Pharmacol.* 49(3), 351–359 (2009).
- **Application of modeling and simulation to optimize study design.**
- 122 Bouzom F, Walther B. Pharmacokinetic predictions in children by using the physiologically based pharmacokinetic modeling. *Fundam. Clin. Pharmacol.* 22(6), 579–587 (2008).
- 123 Hyland R, Dickins M, Collins C, Jones H, Jones B. Maraviroc: *in vitro* assessment of drug–drug interaction potential. *Br. J. Clin. Pharmacol.* 66(4), 498–507 (2008).
- 124 Youdim KA, Zayed A, Dickins M *et al.* Application of CYP3A4 *in vitro* data to predict clinical drug–drug interactions; predictions of compounds as objects of interaction. *Br. J. Clin. Pharmacol.* 65(5), 680–692 (2008).
- 125 Rakhit A, Pantze MP, Fettner S *et al.* The effects of CYP3A4 inhibition on erlotinib pharmacokinetics: computer-based simulation (SimCYP) predicts *in vivo* metabolic inhibition. *Eur. J. Clin. Pharmacol.* 64(1), 31–41 (2008).
- 126 De Buck SS, Mackie CE. Physiologically based approaches towards the prediction of pharmacokinetics: *in vitro–in vivo* extrapolation. *Expert Opin. Drug Metab. Toxicol.* 3(6), 865–878 (2007).
- 127 Einolf HJ. Comparison of different approaches to predict metabolic drug–drug interactions. *Xenobiotica* 37(10–11), 1257–1294 (2007).
- 128 Lalonde RL, Kowalski KG, Hutmacher MM *et al.* Model-based drug development. *Clin. Pharmacol. Ther.* 82, 21–32 (2007).
- 129 Anjum S, Swan SK, Lambrecht LJ *et al.* Pharmacokinetics of flutamide in patients with renal insufficiency. *Br. J. Clin. Pharmacol.* 47(1), 43–47 (1999).
- 130 De Martin S, Orlando R, Bertoli M, Pegoraro P, Palatini P. Differential effect of chronic renal failure on the pharmacokinetics of lidocaine in patients receiving and not receiving hemodialysis. *Clin. Pharmacol. Ther.* 80(6), 597–606 (2006).
- 131 Pere P, Salonen M, Jokinen M, Rosenberg PH, Neuvonen PJ, Haasio J. Pharmacokinetics of ropivacaine in uremic and nonuremic patients after axillary brachial plexus block. *Anesth. Analg.* 96(2), 563–569 (2003).
- 132 Dimmitt DC, Shah AK, Arumugham T *et al.* Pharmacokinetics of oral and intravenous dolasetron mesylate in patients with renal impairment. *J. Clin. Pharmacol.* 38(9), 798–806 (1998).
- 133 Lehmann CR, Heironimus JD, Collins CB *et al.* Metoclopramide kinetics in patients with impaired renal function and clearance by hemodialysis. *Clin. Pharmacol. Ther.* 37(3), 284–289 (1985).
- 134 Muirhead GJ, Wilner K, Colburn W, Haug-Pihale G, Rouviex B. The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br. J. Clin. Pharmacol.* 53(Suppl. 1), 21S–30S (2002).
- 135 Kleinbloesem CH, van Brummelen P, van Harten J, Danhof M, Breimer DD. Nifedipine: influence of renal function on pharmacokinetic/hemodynamic relationship. *Clin. Pharmacol. Ther.* 37(5), 563–574 (1985).
- 136 Aparicio M, Chauveau P, De Precigout V, Bouchet JL, Lasseur C, Combe C. Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. *J. Am. Soc. Nephrol.* 11(4), 708–716 (2000).
- 137 Stenvinkel P, Heimbürger O, Paulter F *et al.* Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int.* 55(5), 1899–1911 (1999).

Websites

- 201 US FDA. Guidance for industry: pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling (1998) www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf
- 202 EMEA. Guidance for industry: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling (2004) www.emea.europa.eu/pdfs/human/ewp/022502en.pdf
- 203 US FDA. Guidance for industry: pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing and labeling (1998) www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf
- 204 National Kidney Foundation. NKF-KDOQI Considers the Utility of Global Guidelines (2010) www.kidney.org/news/newsroom/nr/KDOQI-Considers.cfm
- 205 National Health and Nutrition Examination Survey 1999–2004 www.cdc.gov/nchs/nhanes.htm
- 206 Simcyp Limited www.simcyp.com

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.