A semi-mechanistic model to predict renal clearance of therapeutic proteins linked to a whole body PBPK model

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Iain Gardner, Kate Gill, Linzhong Li, & Masoud Jamei
Simcyp (A Certara Company), Blades Enterprise Centre, Sheffield, UK
k.gill@simcyp.com

Abstract

Purpose: For small proteins and peptides, glomerular filtration and subsequent degradation within the kidney can be a major clearance pathway [1]. Consequently clearance of some proteins varies with renal function. A semi-mechanistic model linking the extent of glomerular filtration to molecular size, coupled with a PBPK model was developed and used to predict the clearance of IL-10, exenatide, enfuvirtide and anakinra in human subjects with normal and impaired renal function.

Method: Simulations were performed using Simcyp (V13 R2). The structure of the PBPK and semi-mechanistic kidney models are shown in Figure 1. Filtration clearance in the kidney (CL_{FIL}) was calculated using glomerular filtration rate (GFR), a parameter describing the restriction of filtration occurring at the glomerulus due to the protein size (θ) and the drug unbound fraction in plasma (fu)

$$CL_{FIL} = GFR * \theta * fu$$

In simulated healthy volunteer subjects θ was calculated using a two-pore model [2,3]. In individuals with renal impairment (GFR < 60 mL/min), θ (limits 0-1) was calculated using the hydrodynamic radius (nm) of the protein

$$\theta = 911030 * (Hydrodynamic\ radius * 10)^{-4.499}$$

For each compound CL was partitioned into two components, CL_{FIL} that varies with an individual's GFR, θ and fu, and an additional clearance component that was assumed to be the same in subjects with both normal and impaired renal function. Simulations were run in both healthy and impaired renal function populations. The results were compared with clinical data.

Results: The relationship between renal function and predicted CL for Il-10, anakinra and exenatide is shown in Figure 5. The enfuvirtide model predicted a CL/F of 1.99 L/h in healthy individuals and 1.39 L/h in subjects with renal impairment (1.4-fold change) compared with reported values of 1.88 and 1.17 L/h (1.6-fold change) [4].

Conclusion: The semi-mechanistic kidney model coupled with a whole body PBPK model was able to simulate the change in clearance of 4 proteins in individuals with differing degrees of renal function with reasonable accuracy.

Purpose

For small proteins and peptides, glomerular filtration and subsequent degradation within the kidney can be a major clearance pathway [1]. Consequently clearance of some proteins varies with renal function. A semi-mechanistic model linking the extent of glomerular filtration to molecular size, coupled with a whole body PBPK model was developed and used to predict the clearance of IL-10, exenatide, enfuvirtide and anakinra in human subjects with normal and impaired renal function.

Methods:

Simulations were performed using Simcyp (V13 R2). The structure of the PBPK and semi-mechanistic kidney models are shown in Figure 1. Filtration clearance in the kidney (CL_{FIL}) was calculated using glomerular filtration rate (GFR), a parameter describing the restriction of filtration occurring at the glomerulus due to the protein size (θ) and the drug unbound fraction in plasma (fu): $CL_{FIL} = GFR * \theta * fu$

In simulated healthy volunteer subjects θ (limits 0-1) was calculated using a previously described two-pore model [2,3]. In individuals with renal impairment (GFR < 60 mL/min) θ was calculated using the following relationship with hydrodynamic radius (nm) of the protein:

$$\theta = 911030 * (Hydrodynamic\ radius * 10)^{-4.499}$$

For each compound CL was partitioned into two components, CL_{FIL} that varies with an individual's GFR, θ and fu, and an additional clearance component that was assumed to be the same in subjects with both normal and impaired renal function (Table 1). Simulations were run in both healthy (North European Caucasian) and impaired renal function populations available within the Simcyp simulator (V13 R2). Where possible the simulated trials were modified to reflect the demographics (age and sex) of the individuals participating in the clinical study. Although included in Figure 1 for completeness the partition ratio (PR), a measure of the effect of charge on glomerular filtration, was not used in these simulations (PR = 1) and all of the filtered protein was assumed to be degraded (i.e. the fraction reabsorbed F_{ra} was set to 0).

The results from the simulations were compared with clinical data. Input parameters and observed clearance values in the clinic for healthy control individuals are given in Table 1. For exenatide, as the compound was dosed by the sub-cutaneous route a value of 1 (CV 10%) was used for fa and a value of 0.4 1/h (CV 30%) was used for ka. For anakinra, as the compound was dosed by the sub-cutaneous route a value of 0.80 (CV 20%) [5] was used for fa and a value of 0.025 1/h (CV 20%) was used for ka.

Compound	MW (kDa)	fu	Observed CL (L/h)	Predicted CL_{FIL} (L/h)	Additional CL (L/h)	Reference
Exenatide	4.2	1	8.1	7.3	1.2 (CV 50%)	Linneberg, Br. J. Clin. Pharmacol., 2007, 64, 317
IL-10	18	1	~ 3.7	4.8	0	Andersen, J. Clin. Pharmacol., 1999, 39, 1015
Anakinra	17.3	1	8.2	5	3.2 (CV 30%)	Yang, Clin. Pharm. Ther., 2003, 74, 85
Enfuvirtide	4.5	0.08	1.4	0.6	0.8 (CV 10%)	Zhang, CPT, 2002, 72, 10; Tebas, J AIDS, 2008, 47, 342.

Table 1 Input values for MW and fu used in the simulations. The observed Clearance values with the source of the data are also listed; together with the predicted renal filtration clearance (CL_{FIL}) for each of the compounds and any assigned additional clearance used in the simulations.

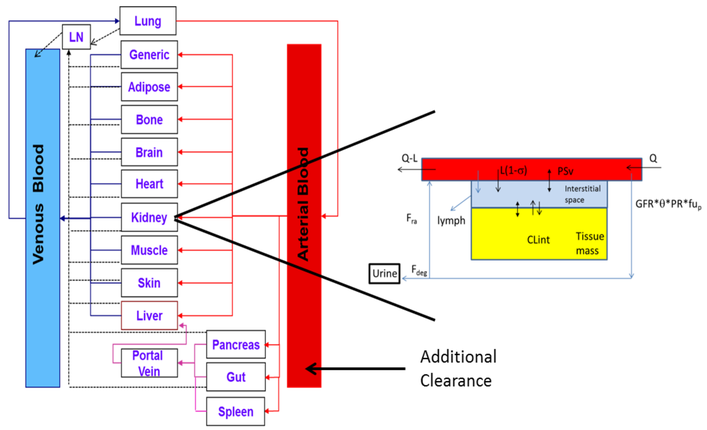

Figure 1: Structure of the full PBPK model and the semi-mechanistic model used in the kidney compartment.

Results

The 2-pore model used to calculate the glomerular sieving coefficient (θ) were able to accurately capture the observed relationship between hydrodynamic radius of ficoll and the measured glomerular sieving coefficient in humans (Figure 2).

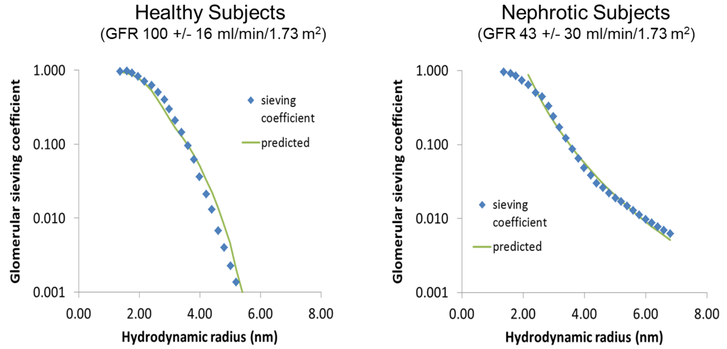

Figure 2: Observed (blue diamond) and predicted (green line) values of glomerular sieving coefficient in healthy subjects and in subjects with impaired renal function (GFR 43 mL/min). Observed data was taken from [2] calculations were performed as described in the methods section.

The simulated plasma concentration profiles for IL-10 in individuals with varying degrees of renal function are shown in Figure 3. There was reasonable agreement for simulated and observed data for IL-10.

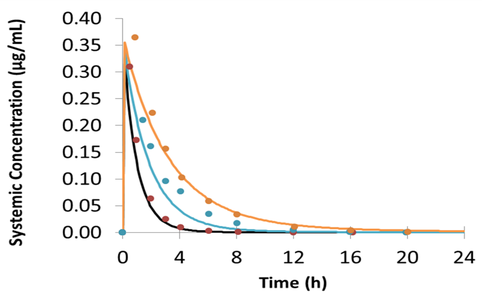

Figure 3: Simulated plasma concentrations of IL-10 in healthy subjects (black line) and in subjects with impaired renal function (GFR 30-60 mL/min) (blue line) and GFR < 30 mL/min (orange line). The dots represent observed data in healthy subjects (black dots; creatinine CL > 80 mL/min/m²) and in patients with moderate (blue dots; creatinine clearance 15-29 mL/min/m²) and severe (orange dots creatinine clearance < 15mL/min./m²) renal impairment. For reference a typical 70 kg individual has a body surface area of 1.73 m².

The plasma concentrations in control subjects and subjects with impaired renal function (GFR < 30 mL/min) administered enfuvirtide are shown in Figure 4 The observed difference in CL/F between the control and renally impaired group was 1.6-fold [4] the predicted change in CL/F using the described model was 1.4-fold.

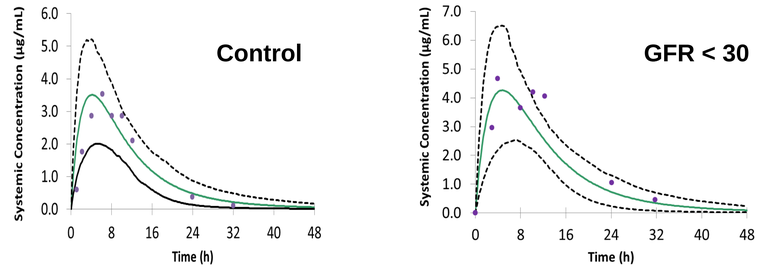

Figure 4: Plasma concentrations of enfuvirtide in healthy subjects (control) and in subjects with impaired renal function (GFR <30 mL/min). The solid green lines represent mean simulated data for a population of 160 (20 trials of 8 subjects) virtual individuals and the dotted black lines represent the 5th and 95th percentiles of the population. The purple dots represent mean observed data in the two populations (data taken from Tebas et al., 2008).

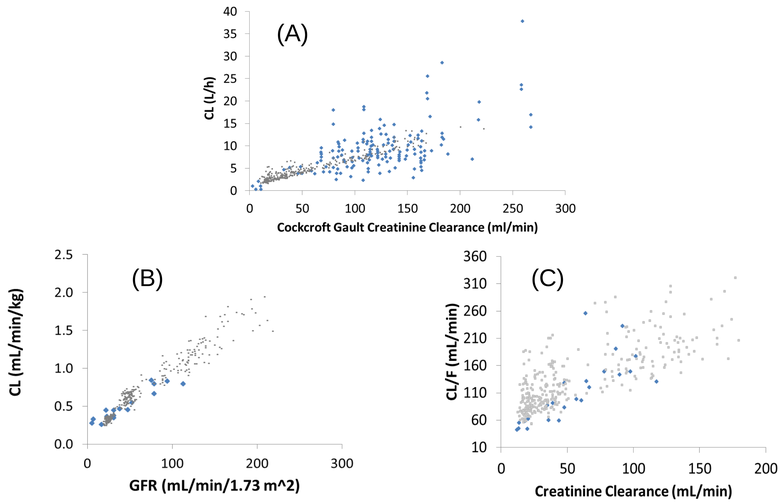

Figure 5: Relationship between plasma clearance and renal function for (A) exenatide, (B) IL-10 and (C) anakinra. Predicted data is shown as grey dots and observed data as blue diamonds (observed data were taken from the sources listed in Table 1). Simulations were conducted for 100 individuals in each of three populations (North European Caucasian, GFR 30-60 mL/min and GFR < 30 mL/min) available within the Simcyp simulator

The simulated and observed relationships between CL (L/h) and creatinine CL or GFR for exenatide, IL-10 and anakinra are shown in Figure 5. For exenatide (Fig 5A) the simulated data captured the observed data in individuals with impaired renal function well but the simulations in subjects with normal renal function had significantly less variability than the clinical observations. The reasons for this discrepancy are unclear at present. The simulations for anakinra showed a trend for decreased CL/F with a decrease in renal function (Figure 5C) although there was an under-prediction of the magnitude of the change. The geometric mean CL/F in the simulations were 187, 133, and 92 mL/min in control, moderate and severe renal impairment subjects, respectively. This compares with reported values of 170, 84.5 and 51.5 mL/min in control, moderate and severely renally impaired subjects [5]. The change in CL with changes in GFR predicted by the model for IL-10 (Fig 5B) agreed well with observed clinical data.

Conclusion

The semi-mechanistic kidney model coupled with a whole body PBPK model was able to simulate the change in clearance of 4 proteins in individuals with differing degrees of renal function with reasonable accuracy.

References

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5. Yang, Clin. Pharm. Ther., 2003, 74, 85