Pharmacokinetic predictions for patients with renal impairment: focus on peptides and protein drugs

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Renal impairment may affect the pharmacokinetics of peptide and protein drugs.
- Molecular size is a predictor. Small molecules are eliminated by the kidneys, whereas large molecules (>67 kDa) are not.
- Urinary recovery of peptide and protein drugs in healthy volunteers is not predictive for pharmacokinetic changes in patients with renal impairment.

WHAT THIS STUDY ADDS

- An apparently continuous non-linear relationship between molecular weight and pharmacokinetic alterations as observed in patients with severe renal impairment or end-stage renal disease is described.
- Potentially relevant pharmacokinetic changes were found for drugs with a molecular weight below 50 kDa.
- Analysis of observed pharmacokinetics in patients with severe renal impairment may be a useful approach, especially when urinary recovery in healthy volunteers is not predictive.

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AIM

Drug dosage adjustments in renal impairment are usually based on estimated individual pharmacokinetics. The extent of pharmacokinetic changes in patients with renal impairment must be known for this estimation. If measured data are not available, an estimate based on drug elimination in urine of healthy subjects or patients with normal renal function is commonly made. This is not reliable, however, if renal drug metabolism is involved, as is presumably the case for many peptide and protein drugs. In the present study a new method to predict pharmacokinetic changes for such drugs based on molecular weight was derived.

METHODS

Articles reporting measured pharmacokinetics of peptide and protein drugs in patients with severe renal impairment or end-stage renal disease were identified from the scientific literature, the pharmacokinetic parameter values were extracted and a statistical data synthesis was performed. A sigmoid $E_{\max}$ model was applied and fitted to the data and the prediction error was analyzed.

RESULTS

Overall, 98 peptide and protein drugs were identified. Relevant pharmacokinetic data in patients with renal impairment were found for 21 of these drugs. The average drug clearance was 30% and the average prolongation in half-life was 3.1-fold for low molecular weight peptides or proteins. The median root squared percentage of the prediction error was 18% (drug clearance) and 12% (half-life).

CONCLUSION

An apparently continuous non-linear relationship between molecular weight and pharmacokinetic alterations in patients with severe renal impairment was found. The derived equations could be used as a rough guide for decisions on drug dosage adjustments in such patients.

Introduction

Impaired renal function leads to impaired elimination of many endogenous and exogenous substances, including drugs. Impaired drug elimination in turn may lead to pronounced drug accumulation and higher drug concentrations, hence predisposing the patient to increased drug effects and toxicity, in particular when standard doses for patients with normal renal function are administered. Drug dosage adjustments may thus be required in order to avoid toxicity and maintain beneficial effects. The most common approach to adjust dosages is based on the estimated individual drug elimination capacity [1] which, in turn, is based on the estimated individual renal function. Adequate drug dosage thus depends on accurate pharmacokinetic parameter estimates.

Pharmacokinetic parameter estimates in patients with renal impairment can be obtained by studying patients with different degrees of renal impairment covering the full range from normal renal function to no renal function. Sufficiently accurate estimates can often be obtained by studying only the extremes, i.e. normal renal function and no renal function (i.e. patients with end-stage renal disease (ESRD), who are functionally anuric), and subsequently applying linear interpolation between these extremes. For many drugs a near linear relationship between estimated glomerular filtration rate and drug clearance or elimination rate constant has been shown [1]. Unfortunately, measured pharmacokinetic data in patients with renal impairment are not available for many drugs. To close this gap, predicted pharmacokinetics should be used.

Pharmacokinetic predictions for renal impairment are often based on urinary recovery of unchanged drug in healthy volunteers or patients with normal renal function [2]. For example, the predicted total drug clearance (pCL_{tot}) in patients without residual renal function can be calculated by subtracting the normal renal clearance ($CL_{ren,norm}$) from normal total body clearance ($CL_{tot,norm}$).

$$pCL_{tot,anuric} = CL_{tot,norm} - CL_{ren,norm} \quad (1)$$

Importantly, accurate estimates of renal clearance depend on several factors including complete urine collection, drug stability in urine and absence of renal metabolism. Furthermore, such predictions consider only the unchanged drug. The systemically available fraction must be known for predictions based on data after non-intravenous administration.

Although renal metabolism appears to play a minor role for most small molecule drugs, there are some examples where glucuronidation is involved [3]. In contrast, renal metabolism appears to play a major role in the elimination of peptides and proteins. Well known examples include insulin [4, 5] and interferon. Although it was known from animal studies that the kidneys are involved in the elimination of interferon, no interferon was detectable in urine after administration of interferon

alpha-2b in healthy volunteers [6]. However, in patients with ESRD and chronic hepatitis C who were treated with interferon, increased toxicity and also increased beneficial effects were observed [7, 8]. Eventually, a reduced drug clearance and a prolonged half-life of interferon was observed in such patients [9], further substantiating the suspected role of the kidneys in eliminating interferon in humans. It should thus be recognized that the part of the elimination capacity by the kidneys which is attributed to renal metabolism is not 'seen' in urine. Therefore, the commonly used urine-based estimate of renal clearance should perhaps more accurately be referred to as renal excretion clearance. The extent of renal metabolism can be estimated based on data from patients with normal and severely impaired renal function.

Renal elimination of peptide and protein drugs appears to depend largely on the sequence of glomerular filtration, re-uptake into renal tubule cells and intracellular proteolytic degradation [3]. It is thus expected that renal metabolism will decline in parallel with the glomerular filtration rate in patients with renal impairment, further stressing the need to actually study pharmacokinetics in such patients. However, until the results from such studies are available a method for predicting pharmacokinetics is needed.

To predict the presence or absence of an effect of renal impairment on the pharmacokinetics of large-molecule drugs, a cut-off point is usually applied. It is commonly assumed that drugs with a molecular weight similar to albumin (67 000 Da) or higher are not eliminated by the kidneys, since their size is expected to prohibit glomerular filtration. However, it appears unlikely that a single cut-off point exists. In fact, data from patients with hereditary kidney diseases leading to impaired tubular function (where absence of tubular re-uptake can be assumed) indicate a continuous relationship between the molecular weight and the glomerular sieving coefficient of several endogenous proteins [10].

The aims of the present study were (i) to identify peptide and protein drugs where measured pharmacokinetics are available for patients with severely impaired renal function or ESRD, (ii) to analyze the relationship between molecular weight of these drugs and pharmacokinetic changes in such patients and (iii) to evaluate the potential ability of this relationship to predict pharmacokinetics of peptide and protein drugs in patients with severely impaired renal function or ESRD.

Methods

Identification of drugs with measured pharmacokinetics

First, a comprehensive list of peptide and protein drugs was compiled, including therapeutic proteins approved by the US FDA [11]. Second, articles with pharmacokinetic

data in patients with chronic kidney disease and severely impaired renal function (creatinine clearance $<30 \text{ ml min}^{-1}$ or estimated glomerular filtration rate $<30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$) or ESRD were identified by using the pharmacokinetic database NEPharm [12], PubMed search (e.g. by using the phrase 'drugname AND (renal[ti] OR haemodialysis) AND pharmacokinetics') and by screening the reference sections of the identified articles. Third, original publications were obtained and evaluated, where available. For drugs where no relevant articles could be identified, data from the summary of drug characteristics were used.

Statistical data synthesis of pharmacokinetic values

Pharmacokinetic parameter values for drug clearance and elimination half-life were used as presented in the publications, independent from the reported presence or absence of statistically significant differences between patient groups. When drug clearance was not reported, AUC values were used for calculations. When data for patients with severely impaired renal function and patients with ESRD were presented in an article, the data from the ESRD group was used. When two or more comparable studies were found for a drug, mean values were calculated. Data from case reports of single patients were not included.

Pharmacokinetic values for healthy subjects or patients with normal renal function were preferably obtained from the same study in which patients with renal impairment were studied, since the experimental setting and analytical methods would be expected to be similar. If such a control group was not available in the original study, we used one of the following sources of pharmacokinetic parameters: First, data from previous publications from the same authors were included. If not available, we employed comparable studies as identified and reported by the authors of the original publication. If none of these sources was available, we used data from studies using the same route of administration and comparable drug doses, pharmacokinetic setting (e.g. single dose or steady-state), duration of observation, drug assay and concomitant diseases.

Pharmacokinetic comparison between impaired and normal renal function

We hypothesized that the drug fraction eliminated by the renal route must be a function of the molecular weight in the case of peptides and proteins. Pharmacokinetic indices of relative changes in patients with renal impairment were calculated, namely fractional drug clearance (f_{CL}) and half-life factor ($f_{t_{1/2}}$). In the case of non-intravenous administration the apparent clearance was applied.

$$f_{\text{CL}} = \frac{\text{CL}_{\text{tot,impaired}}}{\text{CL}_{\text{tot,normal}}} \quad (2)$$

$$f_{t_{1/2}} = \frac{t_{1/2,\text{impaired}}}{t_{1/2,\text{normal}}} \quad (3)$$

These values were related to molecular weight (MW in Da) and a sigmoid E_{max} function (Equation 4) was applied and fitted to the data by using the Microsoft Excel Solver (Microsoft® Office Excel 2003, SP3, Microsoft Corporation), thereby minimizing the sum of squared residuals. Parameters included the hypothetical factor at a molecular weight of zero (f_0), the molecular weight leading to half-maximal changes (M_{50}), and a sigmoidicity constant (γ).

$$\text{predicted} = f_0 + (1 - f_0) \cdot \frac{\text{MW}^\gamma}{\text{MW}^\gamma + M_{50}^\gamma} \quad (4)$$

A linear function and a non-sigmoid E_{max} function (i.e. Equation 4 with $\gamma = 1$) were considered, but eventually rejected based on the sum of squared residuals, the Akaike information criterion and calculated prediction errors.

Prediction of pharmacokinetic changes

As an internal validation, model-predicted and observed pharmacokinetic indices were compared and the percentage of the prediction error, a measure of bias, calculated as the difference between predicted and observed values divided by the observed value, and the root squared percentage of the prediction error, a measure of precision, was calculated, as is commonly applied in pharmacokinetics [13, 14].

Results

Overall, 98 peptide and protein drugs were identified. Relevant pharmacokinetic data for patients with chronic kidney disease and severe renal impairment or ESRD were identified for 21 of these drugs, ranging in molecular weight from 1019 to 150 000 Da (Table 1) [9, 15–46]. Adequate parameters for comparison were found in 20 of these drugs. For rituximab no comparable parameters could be identified for patients with normal renal function due to its time dependent pharmacokinetics (a single dose study in previously untreated patients with an observation time of 2 to 3 months would have been required).

Analysis of the relationship between molecular weight and fractional clearance or half-life factors revealed an apparently continuous and non-linear relationship as described by equation 4 (Table 2, Figure 1). For fractional clearance the estimated parameters were $f_0 = 0.30$, $M_{50} = 35\,618 \text{ Da}$ and $\gamma = 2.42$. When comparing model-predicted and observed values, the median percentage of the prediction error was 0.3%, indicating a successful fit, and the median root squared percentage of the prediction error was 18.3% (interquartile range 10.4 to 36.6%). For the half-life factor the estimated parameters were $f_0 = 3.06$, $M_{50} = 17\,795 \text{ Da}$ and $\gamma = 1.89$. The median percentage of the

Table 1

Pharmacokinetic parameter values of peptide and protein drugs. Values for half-life ($t_{1/2}$) and body weight (WT) were rounded to two and drug clearance (CL) to three significant digits

Drug/Patient group	n	eGFR (ml min ⁻¹)	WT (kg)	Dose	ROA	Dosage	Sampling period	Assay	PK model	CL	$t_{1/2}$	Reference
Agalsidase alfa												
RTX, Fabry's disease	11	65		0.2 mg kg ⁻¹	i.v.	Single	8 h	α -Gal A activity	NCA	3.4 ml min ⁻¹ kg ⁻¹ 3.21 ml min ⁻¹ kg ⁻¹	89 min 77 min	[15]
ESRD, Fabry's disease	6											
Anakinra												
Healthy	12	95	82	1 mg kg ⁻¹	i.v.	Single	24 h	ACELSA	NCA	137 ml min ⁻¹ 18.7 ml min ⁻¹	2.6 h 7.1 h	[16]
ESRD	20	72					96 h					
Darbepoetin alfa												
Healthy	4	94	69	0.75 μ g kg ⁻¹	i.v.	Single	17 days	ELISA	Two compartment	0.164 l h ⁻¹		[17]
CKD	20	24–48		1 μ g kg ⁻¹	s.c.	Single	4 weeks	ELISA	NCA		70 h	[18]
ESRD	131		55	10–90 μ g	i.v.	Single and multiple	168–336 h	ELISA	Two compartment	0.106 l h ⁻¹		[19]
ESRD	10				i.v.	Single	96 h	ELISA		1.6 ml h ⁻¹ kg ⁻¹	25 h	[20]
ESRD	6				s.c.	Single	168 h				49 h	
ESRD	17		76		i.v.	Single	168 h	ELISA	NCA	2 ml h ⁻¹ kg ⁻¹	18 h	[21]
ESRD	11				i.v.	Steady-state	168 h		NCA	1.65 ml h ⁻¹ kg ⁻¹	24 h	
ESRD			58	20–180 μ g	s.c.	Single	336–672 h	ELISA	One compartment	0.158 l h ⁻¹	60 h	[22]
Denosumab												
'Full PK study'				1 mg kg ⁻¹	s.c.					No influence	26 days	[23]
Desmopressin												
Normal (Literature)												
CKD	10	16		0.3 μ g kg ⁻¹	i.v.		26 h	RIA	Two/three compartment.	1.7 ml min ⁻¹ kg ⁻¹ 0.35 ml min ⁻¹ kg ⁻¹	3.5 h 9.7 h	[24]
Normal		103		2 μ g	i.v.	Single	24 h	RIA	Three compartment.	10 l h ⁻¹ 2.9 l h ⁻¹	3.7 h 10 h	[25]
CKD		16										
Digoxin-specific Fab												
Normal, Intoxication	10	>60	64	160–480 mg	i.v.	Single		Calculated	NCA	20.1 ml min ⁻¹	25 h	[26]
Normal (Literature)											23 h	[27]
Normal, Intoxication	3	>79		Various	i.v.	Single		RIA	NCA	31.2 ml min ⁻¹	16 h	
Impaired, Intoxication	7	<30								10.9 ml min ⁻¹	25 h	
ESRD, Intoxication	5		66	80–160 mg	i.v.	Single	204–327 h	RIA	Two compartment.	0.057 ml min ⁻¹ kg ⁻¹	96 h	[28]
Drotrecogin alfa (activated)												
Severe sepsis	680	<20		24 μ g kg ⁻¹ h ⁻¹	i.v.	Continuous infusion		ICAA	NCA	40.1 l h ⁻¹ Lower by 23.7%		[29]
Severe sepsis												
Epoetin beta												
Normal	2	101		130–152 U kg ⁻¹	i.v.	Single	48 h	RIA	NCA	0.12 ml min ⁻¹ kg ⁻¹ 0.08 ml min ⁻¹ kg ⁻¹	8.5 h 10 h	[30]
ESRD	2	0										
Healthy	12			100 U kg ⁻¹	i.v.	Single	48 h	RIA	Various	7.88 ml min ⁻¹ 1.73 m ⁻² 5 ml min ⁻¹ 1.73 m ⁻²	4.9 h 8.3 h	[31]
ESRD	21											
Etanercept												
Healthy	32			10–50 mg	s.c.	Single	480 h	ELISA	Various	0.132 l h ⁻¹ 0.132 l h ⁻¹	75 h 68 h	[32]
Healthy (Literature)				25 mg	s.c.	Single						[33]
ESRD	6			25 mg	s.c.	Steady-state	16–20 weeks	ELISA	Various	0.102 l h ⁻¹	75 h	
Exenatide												
Healthy	8	111	73	10 μ g	s.c.	Single	12 h	IEMA	NCA	3.4 l h ⁻¹ 0.9 l h ⁻¹	1.5 h 6 h	[34]
ESRD	8		64	5 μ g	s.c.	Single	48 h					
Healthy and DM2	71	140	97		s.c.	Single				8.14 l h ⁻¹ 1.3 l h ⁻¹		
ESRD	8				s.c.	Single						

Table 1
Continued

Drug/Patient group	n	eGFR (ml min ⁻¹)	WT (kg)	Dose	ROA	Dosage	Sampling period	Assay	PK model	CL	t _{1/2}	Reference
rhG-CSF ESRD	10			50 µg m ⁻²	i.v.	Single	24 h	RIA		AUC × 3	t _{1/2} × 2	[35]
Goserelin Normal CKD		10–20		250 µg	s.c.	Single Single		RIA		133 ml min ⁻¹ 32 ml min ⁻¹	4.2 h 12 h	[36]
Growth hormone Normal	6			200 µg	i.v.	Single	150 min	IRMA	Two compartment	265 ml min ⁻¹ m ⁻²	14 min	[37]
ESRD	6									79.9 ml min ⁻¹ m ⁻²	26 min	
Healthy	24	127		50–310 µg m ⁻² h ⁻¹	i.v.	Continuous infusion	120 min	IRMA	One compartment	115–208 ml min ⁻¹ m ⁻²	3.5–8.7 h	[38]
ESRD	6	6–11								71–175 ml min ⁻¹ m ⁻²	9.6–16 h	
Interferon alfa-2b Normal, HCV ESRD, HCV	10 10			3 × 10 ⁶ IU	s.c.	Single	36 h	ELISA	NCA		5.3 h 9.6 h	[9]
Interleukin-2 Normal, malignant tumour (Literature)				700 000 JRU	i.v.	Single	24 h	ELISA	Two compartment	116 ml min ⁻¹	1.5 h	[39]
ESRD, renal cell carcinoma	4			350 000–700 000 JRU	i.v.	Single				50.5 ml min ⁻¹	1.7 h	
Octreotide Healthy CKD										9.6 l h ⁻¹ 4.5 l h ⁻¹		[40]
Pegfilgrastim Normal	7	99	83	6 mg	s.c.	Single	48 h	ELISA	NCA		51 h	[41]
ESRD	6		81								65 h	
Peg-interferon alpha-2a Normal	6	>100		90 µg	s.c.	Single	336 h 504 h	ELISA		118 ml h ⁻¹ 80 ml h ⁻¹	76 h 117 h	[42]
CKD	6	20–40										
Peg-interferon alpha-2b Normal	6	105	81	1 µg kg ⁻¹	s.c.	Single	168 h	ECLA	NCA	26.4 ml min ⁻¹	40 h	[43]
ESRD	6		90							12.9 ml min ⁻¹	52 h	
Normal	6	129.7	84	1 µg kg ⁻¹	s.c.	Multiple	168 h	ECLA	NCA	25.3 ml min ⁻¹	52 h	[44]
CKD	7	18.9	96							14.1 ml min ⁻¹	65 h	
Rituximab ESRD	9			50–375 mg m ⁻²	i.v.	Single	84 days	ELISA	NCA		12 days	[45]
Triptorelin Healthy	6	165.8	79	0.5 mg	i.v.			RIA	Various	2.67 ml min ⁻¹ kg ⁻¹ 1.25 ml min ⁻¹ kg ⁻¹	2.8 h 7.7 h	[46]
CKD	6	8.1	70									

ACELSA antibody-capture enzyme-linked immunoassay, AUC area under the curve, CKD chronic kidney disease, DM2 diabetes mellitus type 2, ECLA electrochemiluminescence assay, eGFR estimated glomerular filtration rate or creatinine clearance (as reported in the respective study), ELISA enzyme-linked immunosorbent assay, ESRD end-stage renal disease, HCV hepatitis C virus, ICAA immunocapture-amidolytic assay, IEMA immunoenzymetric assay, IRMA immunoradiometric assay, JRU Japan reference unit, n number of subjects, NCA non-compartmental analysis, PK pharmacokinetic, RIA radioimmunoassay, ROA route of administration, RTX renal transplant.

Table 2

Pharmacokinetic changes in severe renal impairment or end-stage renal disease

Drug	Molecular weight (Da)	Fractional clearance	Half-life factor
Agalsidase alfa	50 000	0.94	0.87
Anakinra	17 257	0.14	2.69
Darbepoetin alfa	38 000	0.72	0.86
Denosumab	147 000	1.00	
Desmopressin	1 069	0.25	2.76
Digoxin-specific Fab	46 200	0.29	2.82
Drotrecogin alfa (activated)	55 000	0.76	
Epoetin beta	30 400	0.65	1.45
Etanercept	150 000	0.77	1.04
Exenatide	4 186	0.16	4.00
rhG-CSF	18 800	0.33*	2.00
Goserelin	1 269	0.24	2.86
Growth hormone	22 124	0.51	2.06
Interferon alfa-2b	19 500	0.48	1.81
Interleukin-2	15 600	0.43	1.18
Octreotide	1 019	0.47	
Pegfilgrastim	38 800	1.11*	1.26
Peg-interferon alpha-2a	40 000	0.68	1.54
Peg-interferon alpha-2b	31 000	0.52*	1.28
Triptorelin	1 311	0.47	2.72

*Calculated based on reported AUCs.

Figure 1

Pharmacokinetic changes in severe renal impairment or end-stage renal disease. For example, a fractional clearance (f_{cl}) of 0.4 indicates that the observed total body clearance of a drug was 40% of the observed clearance in healthy subjects or patients with normal renal function. Similarly, a half-life factor ($f_{t_{1/2}}$) of 3 indicates a three-fold prolongation of half-life in renal failure. The continuous lines represent the fitted sigmoid E_{max} model (equation 4). The broken lines represent the hypothetical condition of no change

prediction error was 6.6%, indicating slight overprediction, and the median root squared percentage of the prediction error was 11.6% (interquartile range 7.2–26.6%). Predictions for the fractional clearance ranged from 61% (pegfilgrastim) to 294% (anakinra) and predictions of the half-life factor ranged from 46% (digoxin-specific Fab) to 183% (interleukin-2) of the observed value.

Discussion

In recent years, peptide- and protein-based drugs have become an increasingly important class of drugs, often for severely ill patients. Even though peptide and protein drugs have been described as subject to renal metabolism and elimination, data on measured pharmacokinetics in

patients with chronic kidney disease and severe renal impairment or ESRD are not available for many drugs. Therefore, a method for predicting pharmacokinetic changes of peptide and protein drugs in patients with renal impairment might be useful for adjusting drug dosages until measured pharmacokinetics in such patients become available. In the present study we analyzed the relationship between molecular weight of a drug and changes in drug clearance and half-life in patients with severe renal failure or ESRD based on published pharmacokinetics. Our results indicate that there could, in fact, be a continuous relationship rather than a sharp cut-off point (Figure 1).

Whether pharmacokinetic changes are clinically relevant depends on the pharmacodynamics of a drug (e.g. the therapeutic index). In general, reduction in drug clearance of less than 20% or prolongation in half-life of less than 1.25 fold are rarely clinically relevant. Thus, based on our analysis potentially relevant changes should be expected for drugs with a molecular weight below 50 000 Da. Half-maximal changes due to renal failure were predicted for drugs with a molecular weight of 35–36 000 Da (considering drug clearance) or 17–18 000 Da (considering half-life). This discrepancy could be explained by concomitant changes in the volume of distribution, since a reduction in the volume of distribution is expected to lead to a shorter half-life as reported for peg-interferon [43]. However, this discrepancy could also be explained by methodological differences between the pharmacokinetic studies. Clearance and half-life values in particular are difficult to estimate accurately for drugs with a very long half-life. Nevertheless, our estimate for low molecular weight peptides and proteins of an average reduction in total drug clearance to one third ($f_{0,CL} = 0.3$) is consistent with the estimated three-fold prolongation of half-life ($f_{0,t_{1/2}} = 3.06$). Conversely, the average fraction eliminated renally (f_{ren}) is estimated as 0.7 based on clearance and as 0.67 based on half-life, decreasing to zero with an increasing molecular weight, providing further evidence for the proposed general relationship (equation 5), where f_{ren} is the true renally eliminated fraction, normal renal function is indicated by 'norm' and no renal function is indicated by 'anuric'.

$$f_{ren} = \frac{CL_{ren,norm}}{CL_{tot,norm}} = 1 - \frac{CL_{tot,anuric}}{CL_{tot,norm}} \approx 1 - \frac{t_{1/2,norm}}{t_{1/2,anuric}} \quad (5)$$

We propose that the derived continuous non-linear relationships (equation 4 for fractional clearance and half-life factor) could be used as a rough estimate to guide drug dosage in patients with impaired renal function. For single doses, dose adjustments might not be required unless there is a change in volume of distribution or drug effects are closely correlated with the area under the curve. For repeatedly administered drugs, drug clearance is commonly used to calculate maintenance doses. For drugs

with long administration intervals the half-life could be a more appropriate marker.

There are several limitations concerning the present analysis. First, our analysis was based on a relatively low number of studies and many studies included a relatively low number of patients. However, the results from these studies are valuable and should be used since they provide the best evidence currently available. Second, in some cases data from several studies were combined. Differences in study design may limit comparability, especially for drugs with dose- or time-dependent pharmacokinetics. Such characteristics are commonly observed for peptide and protein drugs and are presumably due to target-mediated drug disposition, as suspected in the case of rituximab, where the half-life increases after repeated administration [47]. A comparison of drug clearance values between studies is especially sensitive to differences between drug assays. A comparison of half-life values between studies is especially sensitive to study design, although clearance might also be affected. An important factor is observation time, especially in the case of a multi-exponential concentration decline. Furthermore, differences between mathematical methods may have an impact. For example, analyses based on a one compartment model typically lead to higher estimates of drug clearance and lower estimates of half-life as compared with those derived using a two compartment model. However, when data from several studies were compared, these factors were considered and we preferred control data from studies conducted by the same research group. Third, we analyzed only the extremes of renal function. It is thus unclear whether linear interpolation between values for normal renal function and no renal function is possible for peptide and protein drugs. This relationship has rarely been analyzed so far. Data for peg-interferon alpha-2b indicate that interpolation may be possible [43]. Fourth, the percentage of the prediction error for our model was calculated using the same data which were used to derive the mathematical model. The true error will thus most probably be larger, which could be evaluated only prospectively once new data become available. Fifth, we considered only molecular weight due to the observed relationship between molecular weight and glomerular sieving of endogenous proteins [10] and the easy availability of these values. However, other factors such as the three-dimensional configuration of the drug and electric charge could also play a role. Hence, the hydrodynamic size might be a better parameter [48] but values for specific drugs are rarely communicated in the scientific literature.

In conclusion, we found an apparently continuous non-linear relationship between molecular weight of a drug and pharmacokinetic alterations as observed in patients with severe renal impairment or ESRD. The derived equations could be used as a rough guide for predictions on drug dosage adjustments in such patients.

Competing Interests

There are no competing interests to declare.

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