ORIGINAL RESEARCH ARTICLE

A GFR-Based Method to Predict the Effect of Renal Impairment on the Exposure or Clearance of Renally Excreted Drugs: A Comparative Study Between a Simple GFR Method and a Physiologically Based Pharmacokinetic Model

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Abstract

Objective The objective of this study was to compare the predictive performances of a glomerular filtration rate (GFR) model with a physiologically based pharmacokinetic (PBPK) model to predict total or renal clearance or area under the curve of renally excreted drugs in subjects with varying degrees of renal impairment.

Methods From the literature, 11 studies were randomly selected in which total or renal clearance or area under the curve of drugs in subjects with different degrees of renal impairment were predicted by PBPK models. In these published studies, drugs were given to subjects intravenously or orally. The PBPK model was generally a whole-body model whereas the GFR model was as follows: Predicted total clearance (CL_T) = CL_T in healthy subjects × (GFR in RI/GFR in H), Predicted AUC = AUC in healthy subjects × (GFR in H/GFR in RI), where *H* is the healthy subjects and *RI* is renal impairment. The predicted clearance or area under the curve values using PBPK and GFR models were compared with the observed (experimental pharmacokinetic) values. The acceptable prediction error was within the 0.5- to 2-fold or 0.5- to 1.5-fold prediction error.

Results There were 33 drugs with a total number of 101 observations (area under the curve, total and renal clearance in subjects with mild, moderate, and severe renal impairment). From PBPK and GFR models, out of 101 observations, 94 (93.1%) and 96 (95.0%) observations were within the 0.5- to 2-fold prediction error, respectively.

Conclusions This study indicates that the predictive power of a simple GFR model is similar to a PBPK model for the prediction of clearance or area under the curve in subjects with renal impairment. The GFR method is simple, robust, and reliable and can replace complex empirical PBPK models.

1 Introduction

Following the administration of a drug, the drug is excreted either by metabolism or by the renal route or by both mechanisms [1]. The liver is the main organ for drug metabolism and the kidneys excrete both unchanged and/or metabolites of a drug. Kidneys remove both endogenous and exogenous substances. The urine formation mainly takes place from glomerular filtration at a rate of 120 mL/min and is a passive process [1]. The glomerular filtrate passes through the tubule where most of the water is reabsorbed. Besides glomerular and tubular filtration, drugs can also be removed by renal secretion, which is an active process. Thus, renal clearance can be described as three distinct processes: glomerular filtration, reabsorption, and secretion [1].

There are a wide variety of kidney diseases but in the case of chronic renal failure, the kidneys cannot regulate the excretion of both endogenous and exogenous substances as efficiently as normal kidneys. If a drug is mainly eliminated by the renal route, then renal impairment can alter the pharmacokinetics of a drug requiring a change in the dosage regimen as compared with subjects with normal renal function. The impact of renal impairment on the pathophysiology has been thoroughly investigated and well documented [2].

Total clearance is the sum of renal and nonrenal clearances. Nonrenal clearance is generally equated with drug metabolism as well as any other route of excretion that is not renal. Renal impairment can also impact drug transport and metabolism [3, 4]. In renal impairment, both total and

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Key Points

In the case of chronic renal failure, the kidneys cannot regulate the excretion of both endogenous and exogenous substances as efficiently as normal kidneys. If a drug is mainly eliminated by the renal route, then the renal impairment can alter the pharmacokinetics of a drug requiring a change in the dosage regimen as compared with individuals with normal renal function.

Physiologically based pharmacokinetic (PBPK) models have been suggested for the prediction of area under the curve (AUC), or total and renal clearances of drugs in patients with mild to severe renal impairment.

A simple glomerular filtration rate method was used to predict AUC, or total and renal clearances of drugs in patients with mild to severe renal impairment and compared with the PBPK model.

The results of the study indicated that the predictive power of the simple glomerular filtration rate model was as robust as a PBPK model for the prediction of clearance or AUC in subjects with renal impairment.

renal clearance of drugs are affected. The US Food and Drug Administration categorizes renal impairment in the following five categories based on the creatinine clearance or estimated glomerular filtration rate (eGFR). Based on creatinine clearance, the five categories of renal impairment are as follows [5]: normal ≥ 90 mL/min; mild = 60–89 mL/min; moderate = 30–59 mL/min; Severe = 15–29 mL/min; and kidney failure ≤ 15 mL/min.

Physiologically based pharmacokinetic (PBPK) models have been suggested for the prediction of total and renal clearances of drugs in patients with mild to severe renal impairment [6–14]. However, it is possible to develop an alternative simple model that is comparable to the PBPK model to predict total and renal clearance of drugs in patients with renal impairment. Hence, the objectives of this study were as follows:

- To evaluate a proposed simple method that can be used to predict area under the curve (AUC) or total and renal clearances of drugs in patients with mild to severe renal impairment.
- To compare the predictive performance of the proposed simple method with the PBPK model for the prediction of AUC or total and renal clearances of drugs in patients with mild to severe renal impairment.

The predicted AUC or total and/or renal clearance of drugs can be then used to select an appropriate dose in patients with different degrees of renal impairment to initiate a first-in-human study in subjects with renal impairment.

2 Methods

2.1 Data Source for the Physiologically Based Pharmacokinetic Model

From the literature, 11 studies [6–14] were randomly selected in which total and/or renal clearance or AUC of drugs in subjects with renal impairment (mild, moderate, and severe) were predicted using PBPK models. Out of 11 studies, three studies had at least six drugs in the analysis. From these studies, total or renal clearance or AUC data for 33 drugs with 101 observations were obtained. In these studies, drugs were given by the intravenous or oral route.

2.2 Proposed Simple Method (Glomerular Filtration Rate Method)

The proposed simple method, hereafter called the "GFR Method", is based on the GFR values in healthy subjects as well as subjects with renal impairment. The following methods were used to predict total and/or renal clearance or AUC of drugs in subjects with renal impairment.

Method I For the prediction of AUC in subjects with renal impairment, the following equation was used:

$$\text{Predicted AUC} = \text{AUC in healthy subjects} \times (\text{GFR in } H/\text{GFR in RI}), \tag{1}$$

where H is healthy subjects and RI is renal impairment.

Method II Prediction of total clearance in subjects with mild, moderate, and severe renal impairment:

$$\text{Predicted total clearance} \left(\text{CL}_T\right) = \text{CL}_T \text{ in healthy subjects} \\ \times (\text{GFR in RI}/\text{GFR in } H). \tag{2}$$

Method III Prediction of renal clearance in subjects with mild, moderate, and severe renal impairment:

$$\text{Predicted renal clearance} \left(\text{CL}_R\right) = \text{CL}_R \text{ in healthy subjects} \\ \times (\text{GFR in RI}/\text{GFR in } H), \tag{3}$$

where CL_T and CL_R are the observed clearances in healthy subjects (H) and GFR in H and in RI were GFR values in the healthy subjects and subjects with different degrees of renal impairment, respectively.

2.3 Statistical Analysis

The accuracy of the methods (PBPK and GFR) for the prediction of total or renal clearance or AUC was assessed by fold-error (FE) as the ratio of predicted-to-observed values:

$$FE = \text{predicted value/observed value.} \qquad (4)$$

An acceptable prediction error in the literature is twofold (0.5–2). Therefore, this traditional approach was taken and a twofold prediction error was used to compare the two methods. However, the author of this article considers a twofold prediction error too high to be acceptable for any practical purpose. Therefore, besides a twofold prediction error criterion, a more stringent comparison was made based on a 30% (0.7–1.3) or 50% (0.5–1.5) prediction error.

Percent error, bias, and precision of the predictive power of the allometric model for clearance and AUC were determined from the following equations. Statistical parameters such as bias or the mean prediction error (MPE), mean absolute error (MAE), and precision in terms of root mean square error (RMSE) were also used to compare the two methods. Bias was calculated according to Eq. (5):

$$MPE = \frac{\sum (\text{predicted} - \text{observed})}{n}. \qquad (5)$$

Mean absolute error was estimated by converting all the negative numbers to positive numbers obtained from Eq. (5).

The precision of the methods was estimated by calculating the RMSE according to Eqs. (6–8):

$$\text{Mean square error (MSE)} = \frac{\sum (\text{predicted} - \text{observed})^2}{n}, \qquad (6)$$

$$RMSE = (MSE)^{0.5}. \qquad (7)$$

Mean prediction error, MAE and RMSE were expressed as the percent of mean using Eq. (8):

$$\%MPE, \%MAE \text{ or } \%RMSE = (MPE, MAE, \text{ or } RMSE)$$
$$\times (100)/\text{mean observed AUC or CL.} \qquad (8)$$

3 Results

Thirty-three drugs (oseltamivir carboxylate was in two studies) were evaluated in this study with a total number of 101 observations (AUC, total clearance, and renal clearance in mild, moderate, and severe renal impairment). The AUC, total clearance, or renal clearance in subjects with renal impairment were predicted for 21 drugs (56 observations), 12 drugs (24 observations), and 7 drugs (21 observations),

respectively, by the GFR method and the PBPK model. The results of the PBPK and GFR methods for the studies are summarized in Tables 1, 2, 3, 4, 5 and 6. A description of the results is provided below.

3.1 Hsueh et al. [6]

3.1.1 Prediction of Area Under the Curve

There were seven renally eliminated drugs (adefovir, avibactam, entecavir, famotidine, ganciclovir, oseltamivir carboxylate, and sitagliptin). These drugs are all substrates of renal organic anion transporters [6]. Based on the renal clearance, these drugs can be classified as renally secreted drugs [6]. Avibactam and famotidine were given intravenously whereas the remaining five drugs were given orally.

The authors used a PBPK model to predict the AUC of these seven drugs (Table 1) in subjects with different degrees of renal impairment. There were 21 observations (mild, moderate, and severe renal impairment) and from the PBPK model, the predicted/observed ratio range was 0.57–1.38. All observations (100%) were also within the 50% prediction error. Out of 21 observations, 18 (85.7%) observations were within the 30% prediction error. The MPE, MAE, and RMSE were -5.4%, 9.7%, and 20.7%, respectively.

From the GFR method, the predicted/observed ratio had a range of 0.70–1.90 (Table 1), the next highest ratio was 1.23. All observations (100%) were within the 0.5- to 2.0-fold prediction error, whereas 20 (95.2%) out of 21 observations were within the 50% prediction error. Out of 21 observations, 20 (95.2%) observations were within the 30% prediction error (Table 1). The MPE, MAE, and RMSE were − 13.6%, 14.7%, and 32.5%, respectively.

3.1.2 Prediction of Renal Clearance [6]

The predicted and observed renal clearance of seven drugs by PBPK and GFR methods are shown in Table 2. There were 21 observations and from the PBPK model, the predicted/observed ratio range was 0.55–1.40. All observations (100%) were within the 0.5- to 2.0-fold prediction error or within the 50% prediction error. Out of 21 observations, 16 (76.2%) observations were within the 30% prediction error (Table 2). The MPE, MAE, and RMSE were -9.5%, 21.2%, and 29.9%, respectively.

From the GFR method, the predicted/observed ratio range was 0.86–1.95 (Table 2). All observations (100%) were within the 0.5- to 2.0-fold prediction error, whereas 18 (85.7%) out of 21 observations were within the 50% prediction error. Out of 21 observations, 15 (71.4%) observations were within the 30% prediction error (Table 2). The MPE, MAE, and RMSE were 7.6%, 15.7%, and 20%, respectively.

Table 1 Predicted and observed area under the curve (AUC, ng h/mL) by physiologically based pharmacokinetic (PBPK) and glomerular filtration rate (GFR) methods

Drugs/RI	Observed AUC	Predicted AUC (GFR)	Predicted AUC (PBPK)	Ratio GFR	Ratio PBPK
Adefovir					
Mild	266	332	307	1.25	1.15
Moderate	455	548	628	1.20	1.38
Severe	1244	1217	1466	0.98	1.18
Avibactam					
Mild	17,550	13,466	15187	0.77	0.87
Moderate	25,640	21,753	27075	0.85	1.06
Severe	47,080	42,418	45908	0.90	0.98
Entecavir					
Mild	55	53	42	0.96	0.76
Moderate	76	84	82	1.11	1.08
Severe	172	142	122	0.83	0.71
Famotidine					
Mild	909	1158	1049	1.27	1.15
Moderate	1424	1749	1690	1.23	1.19
Severe	4503	8570	3079	1.90	0.68
Gancicolvir					
Mild	50,500	43,942	41,103	0.87	0.81
Moderate	99,700	69,856	77,006	0.70	0.77
Severe	252,000	227,033	258,880	0.90	1.03
Oseltamivir carboxylate					
Mild	9931	7369	5655	0.74	0.57
Moderate	15,010	14,171	15,091	0.94	1.01
Severe	43,086	34,543	46,278	0.80	1.07
Sitagliptin					
Mild	2888	2504	2160	0.87	0.75
Moderate	4057	4570	3826	1.13	0.94
Severe	6761	8308	5244	1.23	0.78

Data from Ref. [6]

RI renal impairment

3.2 Yee et al. [7]

There were seven renally eliminated drugs (cases 1–4 [drug names not known], oseltamivir carboxylate, cidofovir, and cefuroxime). Two drugs (cases 3 and 4) were given orally whereas the remaining five drugs were given intravenously. Creatinine clearance was estimated by the Cockcroft–Gault formula.

The authors used the PBPK model to predict AUC of all these seven drugs (Table 3). There were 19 observations (mild, moderate, and severe renal impairment) and from the PBPK model, the predicted/observed ratio range was 0.41–1.38. All but one observation (94.7%) were within 0.5- to 2.0-fold prediction error or the 50% prediction error. Out of 19 observations, 12 (63.2%) observations were within the 30% prediction error (Table 3). The MPE, MAE, and RMSE were − 26.1%, 32.0%, and 52%, respectively. These values were calculated by using observed and predicted AUC ratio.

From the GFR method, the predicted/observed ratio range was 0.75–1.97 (Table 3), the next highest prediction error ratio was 1.24. All observations (100%) were within the 0.5- to 2.0-fold prediction error. Out of 19 observations, 18 (94.7%) observations were within the 50% and 30% prediction errors (Table 3). The MPE, MAE, and RMSE were 5.7%, 21.4%, and 35.2%, respectively.

3.3 Sayama et al. [8]

3.3.1 Prediction of Total Clearance

There were 12 drugs in this study and the clearance of these drugs were evaluated in subjects with moderate and severe renal impairment (same 12 drugs). All drugs were given intravenously. The authors predicted the clearance of these 12 drugs using the PBPK model and compared these with the predicted clearance values by setting up a range

Table 2 Predicted and observed renal clearance (CL$_R$, mL/min) by physiologically based pharmacokinetic (PBPK) and glomerular filtration rate (GFR) methods

Drugs/RI	Observed CL$_R$	Predicted CL$_R$ GFR	Predicted CL$_R$ PBPK	Ratio GFR	Ratio PBPK
Adefovir					
Mild	149	128	141	0.86	0.95
Moderate	86	77	74	0.90	0.86
Severe	35	35	27	1.00	0.77
Avibactam					
Mild	76	99	97	1.30	1.28
Moderate	49	61	53	1.25	1.08
Severe	22	31	29	1.42	1.32
Entecavir					
Mild	198	210	201	1.06	1.02
Moderate	136	132	103	0.97	0.76
Severe	40	78	44	1.95	1.10
Famotidine					
Mild	264	227	194	0.86	0.73
Moderate	157	150	110	0.96	0.70
Severe	21	31	16	1.46	0.76
Gancicolvir					
Mild	145	156	156	1.08	1.08
Moderate	61	100	80	1.63	1.31
Severe	21	33	19	1.58	0.90
Oseltamivir carboxylate					
Mild	121	164	170	1.35	1.40
Moderate	70	86	76	1.23	1.09
Severe	26	33	24	1.28	0.92
Sitagliptin					
Mild	242	235	177	0.97	0.73
Moderate	126	130	82	1.03	0.65
Severe	60	68	33	1.14	0.55

Data from Ref. [6]

RI renal impairment

of predicted values with a single observed value (Table 4). For example, isepamicin observed clearance was 40 mL/min and the predicted clearance range by PBPK was 24–47 mL/min, the prediction was considered successful because the observed clearance was within the predicted range.

From the PBPK model, in subjects with moderate renal impairment, 10 out of 12 observations (83.3%) were considered successful because the range of predicted clearance values was within the observed clearance values (Table 4). In subjects with severe renal impairment, 7 out of 12 observations (58.3%) were considered successful (Table 4).

From the GFR model, 10 out of 12 observations (83.3%) and 7 out of 12 observations (58.3%) were considered successful in subjects with moderate and severe renal impairment, respectively. Because of the predicted range of clearance values, it was not possible to estimate the predicted/observed ratio by the PBPK model but it was possible by the GFR method. From the GFR method, the predicted/observed

ratio was 0.45–1.41 (one value < 0.5) and 0.27–1.45 (two values < 0.5) for moderate and severe renal impairment, respectively.

Overall, from the prediction perspective, both models provided similar results. The results of the study indicated that the prediction of clearance in subjects (58.3%) with severe renal impairment by both methods was not as accurate as in subjects with moderate renal impairment (83.3%). According to recent US Food and Drug Administration draft guidance [5] "A drug is considered to be substantially eliminated by the renal route when the fraction of systemically available drug or active metabolite that is eliminated unchanged in the urine (fe) is 0.3 or greater". According to this definition, it was noted that three drugs (batanopride, cyclophosphamide, and lidocaine) had fe values < 0.3, indicating that these three drugs are not extensively renally excreted and significant non-renal clearance may be involved in the elimination of these drugs. It should be noted that in all the other drugs in

Table 3 Predicted and observed area under the curve ratio (AUCR) by physiologically based pharmacokinetic (PBPK) and glomerular filtration rate (GFR) methods

Drugs/RI	Observed AUCR	Predicted AUCR (GFR)	Predicted AUCR (PBPK)	Ratio[a] (GFR)	Ratio[a] (PBPK)
Case 1					
Moderate	2.4	2.7	2.4	1.12	1.00
Severe	5.4	5.2	2.9	0.97	0.54
Case 2					
Mild	1.6	1.5	1.1	0.94	0.69
Moderate	2.3	2.7	1.9	1.16	0.83
Severe	3.8	4.7	2.7	1.24	0.71
Case 3					
Mild	1.5	1.6	1.4	1.07	0.93
Moderate	2.2	2.6	1.8	1.17	0.82
Severe	4.3	4.8	3.0	1.12	0.70
Case 4					
Mild	1.0	2.0	1.3	1.97	1.30
Moderate	1.5	3.4	2.0	1.15	1.33
Severe	2.1	5.7	2.9	1.20	1.38
Oseltamivir					
Mild	2.4	2.0	2.2	0.85	0.93
Moderate	3.6	3.7	3.3	1.04	0.92
Severe	10.3	8.2	7.5	0.80	0.73
Cidofovir					
Mild	1.6	2.0	2.0	1.24	1.26
Moderate	3.4	3.3	2.2	0.97	0.64
Severe	7.0	6.4	3.6	0.91	0.51
Ceforoxime					
Moderate	1.7	1.9	2.0	1.13	1.18
Severe	9.8	7.4	4.0	0.75	0.41

Data from Ref. [7]

RI renal impairment

[a]Ratio was obtained by dividing predicted AUCR by observed AUCR

the additional studies in this article and in the Sayama et al. study, the fe remained > 0.3, indicating that these drugs are substantially eliminated by the renal route.

In moderate renal impairment, cyclophosphamide- and lidocaine-predicted clearance values by the PBPK model were within the observed range but not for batanopride. From the GFR method, the predicted vs observed clearance ratios of batanopride, cyclophosphamide, and lidocaine were 0.57, 0.45, and 0.66, respectively.

In severe renal impairment, only the predicted clearance value of batanopride by the PBPK model was within the observed range. The predicted vs observed clearance ratios of batanopride, cyclophosphamide, and lidocaine by the GFR method were 0.27, 0.73, and 0.33, respectively, a poor prediction of batanopride and lidocaine. The poor prediction of clearance for these three drugs by both models is not surprising as renal excretion of these three drugs is not extensive. The MPE, MAE, and RMSE could not be

estimated in this study because the exact predicted values were not available for the PBPK method.

3.4 Studies by Different Authors for Different Drugs [9–14]

There were eight drugs in this analysis as listed in Table 5. Ceftadizime and vancomycin were given intravenously, glycopyrronium was a metered dose inhaler, and the remaining five drugs were given orally. The creatinine clearance for ceftadizime, tenofovir, lamivudine, and emtricitabine was determined by the Cockcroft–Gault formula.

In these studies, the authors used the PBPK model to predict AUC for eight drugs (Table 5) in subjects with different degrees of renal impairment. There were 16 observations for these eight drugs and from the PBPK model, the predicted/observed ratio range was 0.30–1.89. Fifteen observations (93.8%) were within the 0.5- to 2.0-fold prediction error. Out of 16 observations, 14 (87.5%) and 11 observations (68.8%)

Table 4 Predicted and observed clearance (mL/min) by physiologically based pharmacokinetic (PBPK) and glomerular filtration rate (GFR) methods

Drugs	Observed	Predicted (PBPK)	Predicted (GFR)	Predicted ratio (GFR)
Moderate RI				
Isepamicin	40	24–47	37	0.93
Zanamivir	38	28–52	51	1.34
Cefepime	37	28–53	44	1.19
Cidofovir	26	29–54	30	1.15
Enprofylline	32	31–56	45	1.41
Carumonam	41	32–58	38	0.93
Meropenem	39	32–56	34	0.87
Tomopenem	34	34–65	43	1.26
Cefotetan	46	43–73	45	0.98
Batanopride	94	52–84	54	0.57
Cyclophospha-mide	71	54–87	32	0.45
Lidocaine	77	67–95	51	0.66
Severe RI				
Isepamicin	20	8–23	20	1.00
Zanamivir	23	13–34	25	1.09
Cefepime	22	14–35	23	1.05
Cidofovir	11	15–37	16	1.45
Enprofylline	8	17–40	11	1.38
Carumonam	21	19–39	29	1.38
Meropenem	23	18–37	27	1.17
Tomopenem	17	24–51	18	1.06
Cefotetan	33	33–72	36	1.09
Batanopride	63	47–80	17	0.27
Cyclophospha-mide	44	49–81	32	0.73
Lidocaine	45	65–96	15	0.33

Data from Ref. [8]

RI renal impairment

were within the 50% and 30% prediction error, respectively. The MPE, MAE, and RMSE were 15.4%, 25.7%, and 77.1%, respectively.

From the GFR method, the predicted/observed ratio range was 0.66–1.73 (Table 5). All 16 observations (100%) were within the 0.5- to 2.0-fold prediction error, whereas 14 (87.5%) out of 16 observations were within the 50% prediction error. Out of 16 observations, 13 observations (81.3%) were within the 30% prediction error. The results of the analysis for eight drugs are shown in Table 5. The MPE, MAE, and RMSE were 5.9%, 13%, and 32.5%, respectively.

In Table 6, the results of the study are summarized. Overall, the results of this study indicated that the predictive performance (the prediction of AUC or total and renal clearance of drugs in subjects with different degrees of renal

impairment) of a simple GFR method is as robust and accurate as a complex PBPK model.

4 Discussion

In this study, a comparative assessment of a simple model based on GFR and a PBPK model for the prediction of total and renal clearance or AUC in subjects with varying degrees of renal impairment was evaluated. The overall results from 33 drugs and 101 observations indicated that the predictive power of the GFR method was comparable to that of the PBPK model for predicting drug clearances or AUC for subjects with renal impairment.

The current study was undertaken with the objective of finding a simple method that can be used in place of the PBPK model for achieving the same objective. The simple model was based on GFR values in patients with different degrees of renal impairment. It is well established that the total or renal clearance of drugs is linearly related (a good correlation) with the GFR values [15]. Therefore, it was hypothesized that a simple GFR model may be used to predict AUC or total or renal clearance of drugs without requiring the complexities of a PBPK model or any other empirical model. Indeed, the results of the study showed that to predict AUC or clearance of drugs in subjects with different degrees of renal impairment, one does not need a dozen organs or tissues, blood flow to these organs, and many physiological parameters. In other words, a PBPK model is not needed for this purpose.

The two PBPK studies [7, 8] used in this comparative study indicated that the AUC or clearance of drugs in subjects with mild and moderate renal impairment could be predicted fairly accurately but the prediction of these parameters may not be as accurate in subjects with severe renal impairment. Yee et al. [7] concluded that the accuracy of predictions was lower for the severe renal impairment population using the PBPK method, the PBPK model might be suitable for prospective predictions for early decision making, but the PBPK method could not be used for dose recommendations.

There has been a growing interest in the use of PBPK models for the prediction of human pharmacokinetic parameters as well as for dose selection in early clinical drug development or in drug discovery [16–20]. Physiologically based pharmacokinetic models are widely used for the prediction of pharmacokinetic parameters, mainly clearance or AUC in pediatrics, drug–drug interaction studies, to predict drug concentrations in an organ or tissue, and in disease states such as renal impairment.

Physiologically based pharmacokinetic models are either whole-body or minimal or lumped models [16–25]. Whole-body PBPK models require extensive data (physicochemical

Table 5 Predicted and observed area under the curve (AUC) by physiologically based pharmacokinetic (PBPK) and glomerular filtration rate (GFR) methods

Drugs/RI	Observed AUC	Predicted AUC (GFR)	Predicted AUC (PBPK)	Ratio GFR	Ratio PBPK
Dabigatran (ng h/mL)					
Mild	1727	1525	1580	0.88	0.91
Moderate	2447	2478	2470	1.01	1.01
Severe	4130	4955	6150	1.20	1.49
Ceftadizime (μg h/mL)					
Mild	243	214	231	0.88	0.95
Moderate	382	348	369	0.91	0.97
Severe	756	695	562	0.92	0.74
Vancomycin (μg h/mL)					
Moderate	121	126	164	1.04	1.36
Severe	347	315	255	0.91	0.73
Tenofovir (mg h/L)					
Mild	3.1	3.4	3.9	1.09	1.26
Moderate	6.0	5.5	6.4	0.92	1.07
Emtricitabine (mg h/L)					
Mild	19.9	18.2	14.9	0.91	0.75
Lamivudine (mg h/L)					
Moderate	46	31	14	0.66	0.30
Olaparib (μg h/mL)					
Mild	61	82	85	1.35	1.40
Moderate	71	123	134	1.73	1.89
Glycopyrronium (ng h/mL)					
Mild	103	105	76	1.02	0.74
Moderate	113	176	92	1.55	0.81

Data from Refs. [9–14]

RI renal impairment

properties of drugs, organ or tissue weights, blood flow rates, enzymatic activity) and require specialized software to solve the ordinary differential equations (owing to the complexity of the PBPK model). Over time, it was realized that in a PBPK model not every organ or tissue or physiological parameters were required. This led to the development of 'minimal' or 'lumped' PBPK models [21–25]. Minimal or lumped PBPK models indicate that three to four organs are adequate to construct a robust PBPK model that provides similar results to a whole-body PBPK model. Naturally, in a practical world, a minimal PBPK model is more attractive than a whole-body PBPK model.

Liver and kidneys are the two most important organs of elimination of foreign compounds from the body. Using these two organs and respective blood flow to these organs (in all, four physiological parameters without the need of physicochemical properties of drugs), some 'very minimal physiological' models were developed to predict drug clearance in neonates and toddlers [26–28].

In a study, Mahmood et al. [26] developed a minimal physiological model to predict drug clearances of nine glucuronidated drugs in children < 3 months of age. The model used liver weight, liver blood flow, and UDP-glucuronosyltransferase activities (two organs and one enzymatic activity). This minimal physiological model was compared with the whole-body physiological model and comparable results for mean and individual clearance of these nine drugs were obtained by the two models.

The studies [26–28] indicate that a minimal physiological model developed on a spreadsheet can provide the same results as a whole-body physiological model. The cited works (21–28 and there are many more examples for minimal or lumped PBPK models) indicate that it is not necessary to use all body tissues or organs, blood flow to every organ, and physiochemical information of drugs to develop PBPK models. The current study also indicates that it is possible to replace a PBPK model with a simple model that uses just one physiological parameter in terms of GFR to achieve the same objectives.

Table 6 Summary of the results by the two methods

Methods	0.5- to 2.0-fold error	50% error	30% error
PBPK (AUC) [n = 56]	54 (96.4%)	54 (96.4%)	43 (79.6%)
GFR (AUC) [n = 56]	56 (100%)	52 (92.9%)	51 (91.1%)
Total CL (PBPK) [n = 24][a]	19 (77.8%)[a]	NA	NA
Total CL (GFR) [n = 24][a]	19 (88.9%)[a]	NA	NA
Renal CL (PBPK) [n = 21]	21 (100%)	21 (100%)	16 (76.2%)
Renal CL (GFR) [n = 21]	21 (100%)	18 (85.7%)	15 (71.4%)
Total	N = 101	N = 77	N = 77
PBPK	94 (93.1%)	73 (94.8%)	59 (76.6%)
GFR	96 (95.0%)	70 (90.9%)	66 (85.7%)

AUC from Refs. [6, 7, 9–14], and renal CL from Ref. [6]. Total CL ffrom Ref. [8]

AUC area under the curve, *CL* clearance, *GFR* glomerular filtration rate, *NA* could not be determined, *PBPK* physiologically based pharmacokinetic

[a]Fold-error could not be calculated because the acceptable prediction was within a range; it was assumed that the acceptable prediction error was within twofold

In recent years, allometric models were developed for the prediction of drug clearance in children (from neonates to adolescents) and compared with the PBPK models and the comparison showed that the predictive power of the allometric models was similar to PBPK models [29–32]. The allometric approach is much simpler than the PBPK model, and there is no reason not to use allometry in place of PBPK models if it provides similar results and allometric models are also time and cost effective. Similarly, PBPK models are widely advocated for drug–drug interaction studies. In a recent study [33], Mahmood showed that the clearance of drugs following drug–drug interaction studies can be extrapolated to children from adult drug–drug interaction studies using a simple allometric model with reasonable accuracy.

It should be recognized that all models have uncertainty and some degree of inaccuracy is imbedded into them because the models' accuracy is based on the assumptions and the information provided to the model. In a practical world (especially in the biological system), it is not possible to have all the assumptions and information correct. A very recent example related to the uncertainty of the models is the COVID-19 virus model. The model's predictive power remains uncertain. The model was revised several times because of new information and it is highly unlikely that this model will ever be able to provide some sort of accurate result mainly owing to the continuous change in assumptions and information. This is the nature of models

(uncertainty and inaccuracy) and neither the modelers nor the models are at fault.

In a recent article [34], "On the fallibility of simulation models in informing pandemic responses", Gurdasani and Ziauddeen have very elegantly described the uncertainty in the predictive power of empirical models. The authors write "Empirical, real-world data must be considered alongside mathematical models when devising pandemic responses. Models are fallible and scientists and policy makers must be mindful that an over-reliance on models, and a lack of caution in interpreting them, could be a costly exercise". The reality is that not only for a pandemic but for any predictive purpose, empirical models must be interpreted with great caution for the ultimate application of these models. Models are certainly useful in early drug development, but the ultimate decision to market a drug should be based on clinical trials and real-world data and real observations and not on models.

5 Conclusions

This study indicates that the GFR method, which is far simpler than a PBPK model, can be used to predict AUC or total and/or renal clearance of drugs in subjects with varying degrees of renal impairment with the same magnitude of accuracy as a PBPK model. It is time to search for simpler methods that are less stringent, require very minimal parameters or covariates and less effort, time, and cost. A complex model with unnecessary covariates and parameters is neither attractive nor very practical. As shown in this study, a single physiological parameter in terms of GFR was robust enough to produce a similar result as a PBPK model, which requires a dozen organs, blood flow rates, and physicochemical properties of drugs. There is no reason to use a complex empirical model whose results can also be obtained by a simple method. It should be recognized that a complex model does not necessarily provide a better result than a simple model. In an era of "Fit for Purpose", several models should be tested to find the simplest but reasonably applicable and accurate model for the purpose.

It is also time that regulatory agencies worldwide recognize the uncertainty and inaccuracy of empirical models. New and simpler models should be acceptable in place of traditionally complex models as adding complexity to a model does not necessarily improve the predictive power of a model [23–33]. The new and simpler models will be cost and time effective (as shown in this study and some previously published studies [26–33]) and attention should be focused on their development. A minimal physiological model is a good step in this direction and considering the overall predictive performance of the minimal physiological model, the use of a whole-body physiological model is

questionable. It is also possible to further reduce the minimal physiological model to only a three- or four-parameter PBPK model and where needed include a suitable allometric exponent.

Declarations

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