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ORIGINAL ARTICLE

Prediction of total and renal clearance of renally secreted drugs in neonates and infants (≤3 months of age)

Iftekhar Mahmood*

Mahmood Clinical Pharmacology Consultancy, LLC, 1709, Piccard DR, Rockville, MD 20850, USA

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**Corresponding author:*
Iftekhar Mahmood
Mahmood Clinical Pharmacology Consultancy, LLC. 1709, Piccard DR, Rockville, MD 20850, USA.
Email: Iftekharmahmood@aol.com

ABSTRACT

Background: Renal excretion is a major route of elimination for many drugs. Renal clearance is the sum of three processes: glomerular filtration, tubular secretion, and tubular re-absorption. Tubular secretion is an active transport process and is immature at birth. In the neonates, renal tubular secretion can be important for the elimination of those drugs which are renally secreted, such as penicillins and cephalosporins.
Aim: The objective of this study was to evaluate the predictive performances of three models to predict total and renal clearance of renally secreted drugs in neonates (≤3 months of age).
Methods: From the literature, clearance values for 12 renally secreted drugs for neonates and adults were obtained. Three models were used to predict the clearances of these drugs. The predictive performances of these models were evaluated by comparing the predicted values of total and renal clearance with the observed clearance values in the neonates.
Results: There were 12 drugs with 22 observations (preterm and term neonates, ≤3 months of age) for total clearance and six drugs with eight observations for renal clearance. For both total and renal clearance, a prediction error of <50% was observed by all three models evaluated in this study.
Conclusions: The proposed models can predict mean total and renal clearances of renally secreted drugs in preterm and term neonates (≤3 months of age) with reasonable accuracy (50% prediction error) and are of practical value during neonatal drug development.
Relevance for Patients: The work may help in dose selection for neonates for medicines that are renally secreted.

1. Introduction

The elimination of xenobiotics from the body takes place by metabolism, by renal route, or by both mechanisms [1,2]. At least for the first few years of life, physiological changes occur rapidly but these changes are not a linear process [1,2]. Renal excretion is a major route of elimination for many drugs. Renal clearance is the sum of three processes: glomerular filtration, tubular secretion, and active or passive tubular re-absorption. In healthy adults, glomerular filtration rate is approximately 120 mL/min [3]. Renal clearance >120 mL/min indicates that the secretion mechanism is involved, whereas renal clearance <120 mL/min indicates tubular re-absorption besides filtration [3]. Regardless of the renal clearance of a drug, it is possible that filtration, secretion, and re-absorption processes are simultaneously taking place.

Tubular secretion is an active transport process and is independent of plasma protein binding but dependent on renal blood flow [3]. Tubular secretion is immature at birth and approaches adult values by 7 months of age [4]. In neonates, renal tubular secretion can be important for the elimination of those drugs which are renally secreted, such as penicillins and cephalosporins [5].

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Empirical models such as allometry and physiologically-based pharmacokinetic (PBPK) models can be used to predict total and renal clearance of drugs in neonates and infants [6-8]. Such predictions can be helpful for dose selection before initiating pediatric clinical trials.

The objective of this study was to predict the clearances of 12 renally secreted drugs in preterm and term neonates (≤3 months of age) using allometry and an unorthodox minimal physiologically-based pharmacokinetic method (mPBPK).

2. Methods

From the literature, the total and renal clearance values for 12 drugs (S1-S27) that are renally secreted (renal clearance in adults >120 mL/min) were selected. These drugs were acyclovir, amoxicillin, ampicillin, carbenicillin, cilastatin, cefotaxime, cimetidine, famotidine, mezlocillin, penicillin G, piperacillin, and ranitidine. The drugs were selected based on the criteria that the drugs are renally secreted in adults and the clearance (CL) values are available for both adults and neonates. Total clearance values were available in both neonates and adults but renal clearance values for many drugs were not available in the neonates. The following methods were used to predict mean clearance values of drugs that are renally secreted and the predicted mean total and renal clearance values were then compared with the observed mean total and renal clearance values.

2.1. Methods

2.1.1. Total clearance

Method I: Allometric exponent derived from tubular secretary capacity

Renal secretion data were obtained from Rubin *et al.* [9]. In their study, the authors administered mannitol by intravenous route to children from 2 days to 142 months of age. The body weight of the children ranged from 2.4 kg to 35.5 kg. An allometric plot of body weight and tubular secretary capacity gave an allometric exponent of 1.394 (rounded to 1.4; $r^2 = 0.8$). An allometric exponent of 1.4 was then used to predict clearance of drugs in neonates according to equation 1.

$$\text{Total CL in neonates} = \text{Adult CL} \times (\text{Weight of the child}/70)^{1.4} \quad (1)$$

Method II: A minimal physiological model based on kidney weight, kidney blood flow, and glomerular filtration rate (GFR)

This method is based on a previous proposal of Mahmood [10,11] for the prediction of clearance for renally secreted drugs from animals to humans (interspecies scaling). The clearance of renally secreted drugs in the neonates was predicted based on Mahmood's proposed interspecies scaling method which is as follows:

$$\text{Factor} = (\text{GFR} \times \text{Kidney blood flow})/(\text{Body weight} \times \text{Kidney weight}) \quad (2)$$

Kidney weight, kidney blood flow, and GFR values in a neonate were obtained from the following equations.

$$\text{Kidney weight in the neonate} = 0.010 \times (\text{Body weight})^{0.807} \quad (r^2 = 0.987) \quad (3)$$

$$\text{Kidney blood flow in the neonate} = 0.012 \times (\text{Body weight})^{1.121} \quad (r^2 = 0.983) \quad (4)$$

Where both body and kidney weights are in kilograms and the kidney blood flow is in L/min.

The GFR (mL/min) was allometrically estimated [12] in the neonates according to equation 5.

$$\text{GFR} = 1 \times (\text{body weight})^{1.15} \quad (5)$$

Finally, the clearance of renally secreted drugs in the neonates was predicted according to equation 6.

$$\text{Total CL in the neonate} = (\text{Adult CL} \times \text{Factor} \times [\text{Weight of the neonate}/70])/6.4 \quad (6)$$

The value 6.4 was obtained according to equation 2 from healthy adult subjects (GFR = 120 mL/min, kidney blood flow = 1.12 L/min, kidney weight = 0.3 kg, and body weight = 70 kg).

Method III: Model based on kidney weight and kidney blood flow

In this method, kidney weight and kidney blood flow in the neonates were estimated from equations 3 and 4. The projected kidney weight and kidney blood flow were divided by 0.3 kg (adult value) and 1.12 L/min (adult value), respectively. The sum of these two physiological parameters was then used to predict drug clearance in a neonate according to the following equation:

$$\text{Total CL in the neonate} = \text{Adult CL} \times \text{Sum of the parameters} \times (\text{weight of the neonate}/70)^{0.7} \quad (7)$$

Exponent 0.7 is the exponent for creatinine clearance obtained from the interspecies scaling (rounded from 0.69) [13].

2.1.2. Renal clearance

Renal clearance in the neonates was predicted by equations 1, 6, and 7. In these equations, adult renal clearance rather than total clearance was used.

2.2. Statistical analysis

Percent error between the observed and predicted values was calculated according to the following equation:

$$\%\ \text{Error} = \frac{(\text{Predicted} - \text{Observed}) \times 100}{\text{Observed}} \quad (8)$$

Three categories of prediction errors were used to characterize the accuracy of the prediction. These categories were ≤50%, ≤30%, and ≤20% prediction error. An acceptable prediction error in the literature is two-fold. However, the author of this manuscript considers a two-fold error too high to be acceptable for any practical purpose. Therefore, more rigid acceptable criteria of ≤50% was used as acceptable prediction error.

3. Results

In this study, there were 12 drugs with 22 observations for total clearance and six drugs with eight observations for renal clearance. In Table S1 (in Supplementary File), the observed

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total and renal clearance values in adult subjects used for the prediction of total and renal clearance of the drugs in the neonates are presented.

3.1. Total clearance

In Table 1, the predicted and observed total clearance values for 12 drugs are shown. In Table 2, the percent prediction error for total clearance by three methods is shown.

The allometric exponent derived from tubular secretary capacity was 1.4 (Method I). When this exponent was used according to equation 1, an excellent prediction of drug clearance in the neonates was noted. Out of 22 observations, ≤50%, ≤30%, and ≤20% prediction error was noted for 22 (100%), 19 (86%), and 14 (64%) observations, respectively (Table 2).

For minimal physiological method (Method II), out of 22 observations, ≤50%, ≤30%, and ≤20% prediction error was noted for 22 (100%), 20 (91%), and 14 (64%) observations, respectively (Table 2).

For Method III, which is also a minimal physiological model and is even simpler than method II, out of 22 observations, ≤50%, ≤30%, and ≤20% prediction error was noted for 22 (100%), 20 (91%), and 16 (73%) observations, respectively (Table 2). The highest prediction error by Methods I, II, and III were 33%, 33%, and 36%, respectively.

Table 1. Predicted and observed total clearances (mL/min) of drugs by three methods.

Drugs	Chronological age	Observed CL	Predicted CL		
			Method I	Method II	Method III
Acyclovir	0 – 3 months	7.8±2.3	7.6	8.0	8.8
Amoxicillin	Preterm	1.3±0.4	1.3	1.2	1.1
Ampicillin	Preterm (2.6 days)	1.1±NR	1.0	1.0	0.9
Ampicillin	Preterm (15.4 days)	2.3±NR	2.1	2.1	2.0
Ampicillin	Term (2.9 days)	3.6±NR	2.9	2.9	2.9
Ampicillin	Term (13.4 days)	5.5±NR	3.7	3.7	3.9
Carbenicillin	Term	7.4±2.3	6.3	6.4	6.7
Cefotaxime	Preterm (1.1 kg)	1.3±0.3	1.2	1.2	1.1
Cefotaxime	Preterm (1.8 kg)	3.4±1.4	2.5	2.4	2.3
Cefotaxime	Preterm (2.6 kg)	4.8±2.6	4.1	4.1	4.2
Cilastatin	Term	2.1±1.1	2.1	2.1	2.2
Cilastatin	Preterm	0.6±0.2	0.7	0.7	0.6
Cimetidine	Preterm	4.2±NR	3.3	3.2	3.0
Cimetidine	Term	12.5±NR	12.2	12.4	13.2
Famotidine	Preterm-Term	5.7±3.4	4.6	4.6	4.7
Famotidine	0 – 3 months	16.7±NR	11.5	12.0	13.3
Mezlocillin	Preterm	2.4±1.1	2.2	2.1	2.1
Penicillin G	Preterm	1.2±0.3	1.2	1.1	1.1
Piperacillin	29 – 31 weeks	2.2±0.8	1.5	1.5	1.4
Piperacillin	33 – 35 weeks	3.4±0.8	2.6	2.6	2.5
Piperacillin	38 – 42 weeks	8.6±1.2	6.2	6.3	6.6
Ranitidine	Term	14.7±8.9	10.2	10.4	10.9

Method I: Allometric exponent derived from tubular secretary capacity, Method II: Minimal physiological model based on kidney weight, KBW, and GFR, Method III: Model based on kidney weight and KBW. NR: Not reported, GFR: Glomerular filtration rate, KBW: Kidney blood flow, CL: clearance

3.2. Renal clearance

In Table 3, the predicted and observed renal clearance values for six drugs are shown. The renal clearance values for other six drugs were not available in the neonates. In Table 4, the percent prediction error for total clearance by three methods is shown.

The allometric exponent derived from tubular secretary capacity (Method I) provided a fairly good prediction of renal clearance in preterm and term neonates. Out of eight observations, ≤50%, ≤30%, and ≤20% prediction error was noted for 8 (100%), 7 (88%), and 3 (38%) observations, respectively (Table 4).

For minimal physiological method (Method II), out of eight observations, ≤50%, ≤30%, and ≤20% prediction error was noted

Table 2. Number of observations with percent prediction error in total clearances of drugs.

Methods	Percent prediction error (*n*=22)		
	≤50, *n* (%)	≤30, *n* (%)	≤20, *n* (%)
Method I	22 (100)	19 (86)	14 (64)
Method II	22 (100)	20 (91)	14 (64)
Method III	22 (100)	20 (91)	16 (73)

The number in parenthesis are percent of total observations. The highest prediction error by methods I, II, and III were 33%, 33%, and 36%, respectively

Table 3. Predicted and observed renal clearances (mL/min) of drugs by three methods.

Drugs	Age	Observed CL	Predicted CL		
			Method I	Method II	Method III
Acyclovir	0–3 months	5.1±1.9	6.0	6.9	6.3
Cilastatin	Term	1.4±0.3	1.3	1.3	1.3
Cilastatin	Preterm	0.3±0.1	0.4	0.4	0.4
Cimetidine	Term	6.8±NR	5.5	6.0	5.7
Famotidine	Preterm-term	11.7±1.3	7.5	8.7	7.9
Famotidine	0–3 months	4.0±NR	3.0	3.0	3.0
Mezlocillin	Preterm	1.3±0.6	1.6	1.5	1.5
Ranitidine	Term	6.9±6.6	8.8	9.4	9.0

Method I: Allometric exponent derived from tubular secretary capacity, Method II: Minimal physiological model based on kidney weight, KBW, and GFR, Method III: Model based on kidney weight and KBW. NR: Not reported, GFR: Glomerular filtration rate, KBW: Kidney blood flow, CL: clearance

Table 4. Number of observations with percent prediction error in renal clearances of drugs.

Methods	Percent prediction error (*n*=8)		
	≤50, *n* (%)	≤30, *n* (%)	≤20, *n* (%)
Method I	8 (100)	7 (88)	3 (38)
Method II	8 (100)	6 (75)	3 (38)
Method III	8 (100)	6 (75)	3 (38)

The highest prediction error by methods I, II, and III were 36%, 42%, and 37%, respectively

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for 8 (100%), 6 (75%), and 3 (38%) observations, respectively (Table 3).

For Method III, out of eight observations, ≤50%, ≤30%, and ≤20% prediction error was noted for 8 (100%), 6 (75%), and 3 (38%) observations, respectively (Table 3). The highest prediction error by methods I, II, and III were 36%, 42%, and 37%, respectively

The results of this study indicated that an allometric exponent of 1.4 can predict the clearance of renally secreted drugs in the neonates with accuracy. The other two physiologically-based minimal models provided equally accurate prediction. Overall, all three models provided similar results. Furthermore, these three models are very simple to use but models I and III are even simpler than model II.

4. Discussion

At birth, kidneys are anatomically and functionally immature and as a result, the renal function in newborns is limited. In general, the GFR in neonates is 30 – 40% of adult values [14]. By the end of the third week, GFR is about 50 – 60% of the adult values [14]. The GFR increases rapidly during the first 2 weeks of life because of a postnatal drop in renal vascular resistance and an increase in renal blood flow. GFR then rises steadily until adult values are reached at 8 – 12 months of age [14].

Tubular secretion is an active transport process and is independent of plasma protein binding but dependent on renal blood flow [4]. Drug secretion also depends on the affinity of the drug for carrier proteins in the proximal tubule, the rate of transport across the tubular membrane, and the rate of delivery of the drug to the site of secretion [4]. Tubular secretion { XE "tubular secretion" } is immature at birth and approaches adult values by 7 months of age [4].

Allometric scaling is a very useful tool for the prediction of pharmacokinetic parameters from adults to pediatric populations [6,12-19]. However, in neonates and infants, physiological changes develop very rapidly. Considering these rapid physiological changes which are nonlinear, a single exponent cannot describe the clearance versus body weight or age across all age/weight groups [6,15-17].

In this study, several allometric models were used to predict physiological parameters such as kidneys and liver weights, kidneys and liver blood flows, and GFR. Equation 5 for the prediction of GFR in neonates was originally obtained by an allometric plot of inulin clearance from preterm neonates to adults [12]. This equation provides a reasonable prediction of mean GFR across age (validated by external data) and is comparable with the maturation model [20]. The model [12] is far simpler than the maturation model but is as accurate as the maturation model.

Physiologically-based pharmacokinetic (PBPK) models are also used to predict drug clearance in children. PBPK modeling requires extensive data (physicochemical properties of drugs, organs or tissues, blood flow rates, enzymatic activity, etc.). In PBPK modeling, physiological, physicochemical, and biochemical processes are mathematically described. This method of analysis is generally called "whole-body PBPK model" [21-23]. Overtime, it was realized that in a PBPK model not every organ or tissue as well as many physiological parameters are required to describe concentration-time data. This led to the development of "minimal or lumped PBPK models" [24,25]. The minimal PBPK model indicates that the extensive body organs and information utilized in whole-body PBPK modeling is unnecessary. Thus, the minimal PBPK model is rationale, practical, and as informative and useful as whole-body PBPK model.

Considering the concept of "minimal or lumped PBPK models', Mahmood further simplified PBPK models. In a study, Mahmood *et al.* [26] developed a minimal physiological model to predict drug clearances of 9 glucuronidated drugs in children <3 months of age. The model used liver weight, liver blood flow, and UDP-glucuronosyltransferases (UGT) activities. This simple physiological model was compared with the whole-body physiological model. Comparative results for clearance were obtained by the two models. The unorthodox minimal physiological approach taken in this study indicates that a very simple physiological model can be developed to achieve certain objectives.

In recent years, Mahmood and coauthors have compared minimal physiological or allometric models with whole-body PBPK model and demonstrated that these simple models are as robust and accurate as a whole-body PBPK [26-29].

In the current study, the physiological concept of renal secretion was applied to derive the allometric exponent. Furthermore, two new minimal physiological models were developed to predict the clearance of renally secreted drugs in neonates. The predictive powers of all these three models were excellent.

5. Conclusions

This study indicates that the clearances of drugs which are renally secreted can be predicted in preterm and term neonates (≤3 months of age) with fair degree of accuracy using allometry or by minimal physiological models.

The suggested methods can be used to estimate a first-in-neonatal dose during pediatric drug development based on the knowledge of observed adult clearance and predicted clearance in preterm and term neonates for renally secreted drugs. The application of the proposed methods is in pediatric drug development and is not a substitute for a pediatric clinical trial. The allometric approach and the two minimal physiological models in this study (and some previous studies) indicate that simple approaches can be developed and used with reasonable accuracy.

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Conflict of Interest

The author declares that they have no conflict of interest.

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Supplementary File

Table S1 . Total and renal clearance (mL/min) of drugs in adults used in the scaling.

Drugs	Total clearance	Renal clearance
Acyclovir	307	**242**
Amoxacillin	373	209
Ampicillin	305	272
Carbenicillin	401	320
Cefotaxime	413	250
Cilastatin	208	**133**
Cimetidine	718	**326**
Famotidine	463	**303**
Mezlocillin	317	**228**
Penicillin G	590	NA
Piperacillin	409	304
Ranitidine	743	**584**

Renal clearance values greater than GFR (120 mL/min) are considered renal secretion. Bold numbers are those which were used to predict renal clearance in neonates. GFR: Glomerular filtration rate

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