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Renal Clearance in Newborns and Infants: Predictive Performance of Population- Based Modeling for Drug Development

Jian Wang¹, Shaun S. Kumar², Catherine M. Sherwin², Robert Ward², Gerri Baer³, Gilbert J. Burckart⁴, Yaning Wang⁴, and Lynne P. Yao⁵

¹Office of Drug Evaluation IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

²Department of Pediatrics, Division of Clinical Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah, USA

³Office of Pediatric Therapeutics, US Food and Drug Administration, Silver Spring, Maryland, USA

⁴Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

⁵Division of Pediatric and Maternal Health, Office of Drug Evaluation IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Abstract

The objective of this study was to evaluate the predictive performance of population models to predict renal clearance in newborns and infants. Pharmacokinetic (PK) data from eight drugs in 788 newborns and infants were used to evaluate the predictive performance of the population models based on postmenstrual age (PMA), postnatal age, gestational age, and body weight. For the PMA model, the average fold error for clearance ($CL_{\text{predicted}}/CL_{\text{observed}}$) was within a twofold range for each drug in all subgroups. For drugs with > 90% renal elimination, the prediction bias ranged from 0.7–1.3. For drugs with 60–80% renal elimination, the prediction bias ranged 0.6–2.0. Our results suggest that PMA- based sigmoidal maximum effect (E_{max}) model, in combination with bodyweight-based scaling and kidney function assessment, can be used in population PK (PopPK) modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants with normal renal function in clinical trials.

*Correspondence: Lynne P. Yao (Lynne.Yao@fda.hhs.gov) and Yaning Wang (Yaning.Wang@fda.hhs.gov).

AUTHOR CONTRIBUTIONS

J.W., S.S.K., C.M.S., R.W., G.B., G.J.B., Y.W., and L.P.Y. wrote the manuscript. J.W., Y.W., and L.P.Y. designed the research. J.W., S.S.K., Y.W., and L.P.Y. performed the research. J.W., S.S.K., and Y.W. analyzed the data.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DISCLAIMER

The opinions expressed in this article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Clinical pharmacology studies are important for dose selection in pediatric drug development.¹ There is considerable intersubject and intrasubject variability in pharmacokinetics (PKs) in newborns and infants as a result of rapid growth and maturation.²

In population PK (PopPK) modeling, development of covariate models can be used to describe and explain intersubject and intrasubject variability of PK parameters, which provides the opportunity to personalize dosing strategies based on the patient-specific factors.³ For renally eliminated drugs in newborns and infants, clearance is often expressed as a function of growth (size), age- dependent maturation, and kidney function (e.g., serum creatinine).⁴

Maturation changes over time in newborns and infants can be modeled with age indicators, such as postmenstrual age (PMA), postnatal age (PNA), gestational age (GA), and a combination of these.^{4,5} PMA has been used to date a gestation from the mother's known or reported last menstrual period. GA is defined as time elapsed between the first day of the last menstrual period and the day of delivery. PNA is defined as time elapsed from birth.⁶ For drugs that are renally excreted, renal clearance is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. Term infants (PMA ≥ 37 weeks) have a rapid increase in glomerular filtration rate (GFR) during the first 2 weeks of life and reach body surface area-adjusted adult values by the end of the first year after birth.² Premature infants (PMA < 37 weeks) have similar renal maturational changes but have a slower initial increase in GFR because nephrogenesis is not complete before 34–35 weeks of gestation.² Both active tubular secretion and reabsorption are immature at birth (20–30% of adult reference values) and reach adult values within a few years.²

Kidney function is described using biomarkers, such as serum creatinine, cystatin C, or related measurement, such as calculated creatinine clearance or GFR.^{3,7} Size, maturation, and kidney development are interdependent factors, and when size and maturation markers are included first as covariates for clearance estimate, kidney function accounts only for deviation from normal kidney function (e.g., due to disease or drug- related nephrotoxicity).⁴ Based on our survey in pediatric drug development and product labeling, bodyweight-based and age-based drug dosing has been used in newborns and infants, supported by covariates representing size and maturation in PopPK modeling.^{8,9} Whether the size- and maturation-based models could be prospectively applied to predict the renal clearance of a drug in the pediatric population with normal function is unknown. Using pooled GFR data in a range of ages from very premature neonates to young adults, Rhodin *et al.*¹⁰ developed a maturation model to examine the influence of bodyweight and PMA on GFR. PMA is considered the more physiologically appropriate covariate as it is best suited to explain the time course of change in clearance from gestation through to adulthood. On the other hand, separating the effects of antenatal development (GA) and postnatal maturation (PNA) may better describe the time- dependent changes that occur in the first month after birth.⁴

The objective of our study was to evaluate the predictive performance of the previous PMA-based model in comparison to GA and PNA-based model in predicting the clearance of drugs that are primarily renally eliminated in newborns and infants with normal renal function.

RESULTS

Data collection

We collected two sets of drug data for analysis (Table 1). The first set contained four drugs that are > 90% renally eliminated: amikacin, vancomycin, gadobutrol, and gadoterate. The reported renal clearances of these drugs ranged from 5.0–7.1 L/hour in healthy adults (Table 1), which is close to average GFR of 7.2 L/hour in healthy adults.¹⁰ The adult data suggest that glomerular filtration plays the most important role in the renal clearance of these drugs. Four other drugs that are 60–80% renally eliminated were included: ampicillin, gentamicin, netilmicin, and meropenem. These drugs likely have additional metabolism and elimination pathways, and/or extrarenal filtration pathways (e.g., net secretion or reabsorption), as described in Table 1. Accordingly, their observed clearances in adults are up to twofold higher or lower than normal adult GFR. All eight drugs were administered intravenously.

Demographics

Demographic data from a total of eight clinical PK studies for the eight drugs were collected (Table 2, Table S1). Data were available from a total of 787 newborns and infants. A total of 24% of subjects ($N = 189$) had a PMA ≥ 42 weeks and < 2 year, 21% of subjects ($N = 163$) had a PMA ≥ 37 and < 42 weeks, and 55% of subjects ($N = 435$) had a PMA < 37 week (Table 2). The study population had a median PNA of 13 days (range: 0–721 days), a median GA of 33 weeks (range: 23–43 weeks), a median PMA of 35 weeks (range 23–143 weeks), and median weight at the time of the study of 2.16 kg (range: 0.39–15.0 kg) (Table 2). The median baseline serum creatinine level was 0.5 mg/dL (range : 0.1–5.5 mg/dL). Of note, 70 patients had serum creatinine values ≥ 1 mg/dL, and 2 of these had values ≥ 2 mg/dL. In addition, the patient demographics, including median and range of PMA, PNA, and GA for each subgroup, are presented by GA categories in Table S2, and a scatterplot matrix of demographics is provided in Figure S1.

Predictive performance

Table 3 presents the predictive performance of drug clearances based on the PMA maturation model and adult clearance estimates for all drugs evaluated.¹⁰ The accuracy (average fold error (AFE)) and precision (average absolute fold error (AAFE)) were determined in three subgroups: < 37 weeks PMA; 37 to < 42 weeks PMA; and ≥ 42 weeks PMA, as defined in the Methods section.

Drugs with > 90% renal elimination in adults

For all four drugs, the AFE was within the twofold range (0.7–1.3) across the three age subgroups. Overall, the precision of the estimates, as measured by AAFE, ranged from 1.2–1.6. For each drug, > 80% of newborns and infants had clearance estimates within the twofold range (Figure 1) in each PMA- based subgroup. Between the four drugs there were no obvious trends in the predicted clearances between subgroups < 37 weeks PMA, 37 to < 42 weeks PMA, and ≥ 42 weeks PMA (i.e., any trends were drug specific). Overall, this model predicted the data for these drugs reasonably well.

Drugs with 60–80% renal elimination in adults

The AFE and AAFE for these drugs ranged from 0.6–2.0 and 1.1–2.0, respectively. The bias of the predictions for these drugs was higher when compared with the drugs with > 90% renal clearance (Table 3). Ampicillin, the drug with tubular secretion and biliary elimination, had the poorest prediction. Ampicillin had poorer performance in subgroup < 42 weeks PMA when compared with those > 42 weeks PMA or greater (Table 3, Figure 2).

There was deviation for the prediction of the eight drugs in preterm infants with gestational age < 37 weeks (Figures 1 and 2). For amikacin, gentamicin, and netilmicin most patients in this age group had a ratio < 1, whereas for vancomycin and ampicillin one observes the opposite (i.e., most patients have a ratio > 1). Although such patterns have been observed in preterm infants with GA < 37 weeks, we have not seen similar patterns with other age groups.

Maturation model comparison

To evaluate whether prematurity (GA at birth) had any additional effect for any given PMA, we developed a model using GA and PNA as covariates, assuming different trajectories for their effects, and compared the model with the PMA model. GA was introduced into the model as a covariate on the fraction of adult clearance at birth using different functions. Based on the data available, the effects of GA and PNA on drug clearance were best described as power and asymptotic exponential function, respectively. This model predicted a baseline fractional adult clearance of 40% at birth for term neonates at 37 weeks of GA (Figure S2).

Comparison of predictive performance showed that the PMA model provides slightly better accuracy of prediction than the GA- PNA model for ampicillin and meropenem, whereas the predictive performances are comparable for gentamicin and netilmicin between the two models (Table 4, Figure S3). These results suggest that adding two covariates, GA and PNA, into the clearance model may not improve the model prediction for drug clearance as compared to PMA- based maturation model. The differences between the two maturation models are illustrated in Figure S2.

DISCUSSION

Our study demonstrated that the body weight and PMA- based model could provide an initial prediction of clearance for drugs that are primarily renally eliminated in newborns and infants with normal renal function. The presented model, along with adult clearance for a drug and sparse PK samples in newborns and infants, could be used to inform dosing strategies based on age and weight for newborns and infants in pediatric drug trials. A recent example is gadobenate dimeglumine, a gadolinium-based contrast agent with ~ 95% renal elimination. PK simulations based on the maturation model were used to inform the dose selection in infants.¹¹

Ampicillin, the drug with the lowest percentage of renal clearance (61%) in the study panel, had the poorest predictive performance with an AFE within the 1.6–2.0 range. Biliary excretion accounts for 10% of ampicillin clearance, with ~ 30% of its clearance mechanism

that is unclear. The clearance of ampicillin in healthy adults is approximately twofold that of the adult GFR value, which is indicative of other nonrenal pathways that contribute to their elimination. The cause of the relatively poorer prediction for ampicillin is possibly due to the lower percentage of renal clearance for this drug's total clearance.

Although PMA is the most frequently used descriptor to describe age- dependent maturation in pediatric PopPK modeling, some suggest that characterizing different dynamics of development before birth and maturation after birth is important. For the purpose of model comparison, we developed a renal maturation model using a combination of GA and PNA to separate antenatal and postnatal effects on maturation.⁴ The underlying hypothesis was that using GA and PNA as separate components may capture the rapid rise seen in GFR in the first few days after birth, as it introduces hemodynamic changes in newborns that are suggested to influence the rate of renal maturation,² and GA may have additional effects on maturation trajectory of renal clearance.^{12–15} However, our GA-PNA model showed variable prediction results among the studied drugs, and overall it did not improve the prediction accuracy as compared to the PMA model. One possible explanation is that the parameters for the GA-PNA model were derived from our data on amikacin, vancomycin, gadobutrol, and gadoterate, which may not be optimal due to the limited amount of data available.

Our models did not assess the changes in kidney function due to the following considerations. First, most of the subjects (91%) had baseline creatine levels in the normal range (< 1 mg/dL),¹⁶ as all the studied indications were not related to renal disease. Whether any newborns and infants had drug- related nephrotoxicity or were exposed to prenatal steroids that can increase glomerular formation significantly is unknown. It is possible that a proportion of the patients had a systemic disease (e.g., sepsis), which might have impacted renal function. As such, the addition of data related to disease severity to the model may improve the predication in those patients.

Second, kidney function modeling (F_{kidney}) remains challenging in newborns as serum creatine levels may be complicated by factors such as maternal transfer or different analytical assays.^{3,17} Alternative biomarkers, such as cystatin C, are not readily available in clinical trials.⁷ In PopPK, when the age- and size- dependent scaling were included first as the covariates for drug clearance, F_{kidney} accounts only for deviation from normal kidney function (i.e., renal impairment).

Lastly, our model evaluation is focused on its use for pediatric drug development (e.g., dosing strategies). Bodyweight- based and age-based dosing are often recommended for newborns and infants, based on the impact of size and maturation on drug clearance.⁸ Accordingly, the age-dependent sigmoidal maximum effect (E_{max}) model in combination with size- based scaling is one of the most widely used clearance models in pediatric drug development.^{8,9} To estimate drug clearance in patients with impaired kidney function, the model should account for changes in kidney function using serum creatinine or other biomarkers. When necessary, additional covariates, such as very low birth weight and small size for GA should also be considered to improve model prediction.

In vancomycin analysis, there was one outlier patient who had a predicted to observed ratio of almost four, which was much higher than the remainder of the patients. This patient was a full-term neonate (GA: 40 weeks; PNA: 8 days) and weight 3.61 kg. This patient had a serum creatinine concentration of 1.41 mg/dL, collected at PNA day 8, which was four times higher than the neonates with the same PMA (mean 0.36 mg/dL). This case suggests that there is a need for the development of dosing guideline for renal impairment even in neonates.

A general limitation to using age-based descriptors, such as PMA or GA, is that there is the possibility that the first date of the mother's last menstruation may be uncertain or unknown.¹⁸ This would result in incorrect calculation of these age descriptors. If these flawed age descriptors are used for prediction, the state of renal maturation may then be incorrect resulting in potentially inappropriate doses. In the future, sensitivity analysis needs to be undertaken to evaluate how clinically significant this age misspecification might entail.

Although our study utilized the data from antibiotics and contrast agents, our finding should be applicable to other drugs or metabolites that are primarily renally eliminated in newborns and infants with normal renal function, with the exception for those drugs: (i) with narrow therapeutic window or (ii) associated with drug-related nephrotoxicity or for treatment of renal disease. The use of a single ratio of twofold for all compounds as reference for predictive performance is arbitrary, without any clinically important safety and efficacy considerations. A predicted/observed ratio of twofold for clearance would potentially lead to inadequate exposure and treatment failure, whereas ratios of 0.5 or lower would represent considerable risk of adverse events. During new drug development, considering the therapeutic window of a drug, therapeutic drug monitoring may be used in conjunction with modeling to ensure appropriate exposure during the course of treatment.

In summary, our study indicates that PMA-based sigmoidal $E_{\max}$ model and bodyweight-based scaling can be used in PopPK modeling for drugs that are primarily eliminated via the renal pathway in newborns and infants with normal renal function. By leveraging prior information, this maturation model, in combination with kidney function assessment, may provide a promising tool to inform initial dose selection for newborns and infants in pediatric clinical trials.

METHODS

Data collection

Clinical PK data were collected from the following sources: (i) the enterprise data warehouse of the Intermountain Healthcare system at the University of Utah, where data were collected as part of a retrospective observational PK study on antibiotics, including amikacin, gentamicin, and vancomycin and (ii) published medical and clinical pharmacology reviews posted at Drugs@FDA. In addition, meropenem data were obtained from www.regulations.gov.¹⁹

Drug clearance and demographic data in newborns and infants were collected for drugs meeting the following criteria: (i) renal pathway accounts for > 60% drug elimination and

(ii) adult clearance is available from published literature. In our analysis, drugs were grouped into two subsets of: (i) > 90% renally eliminated drugs with no significant renal reabsorption and secretion and (ii) 60–80% renally eliminated, where renal reabsorption and secretion are likely or unknown.

Preterm neonates

PMA, which has been used to date gestation from the mother's known or reported last menstrual period, was used to define the GA at birth. Neonates were also grouped by PNA. The following subgroups were used to define more homogeneous groups²⁰: < 37 weeks PMA; 37 to < 42 weeks PMA; and ≥ 42 weeks PMA. For preterm neonates, the following subgroups were analyzed: 23 to < 28 weeks, 28 to < 32 weeks, and 32 to < 37 weeks GA (Table S2).

PopPK analysis

The drugs identified from the different data sources (see Data Collection) were amikacin, vancomycin, gadobutrol, gadoterate, ampicillin, gentamicin, netilmicin, and meropenem. For each drug identified, a PopPK analysis was completed. The parameters in the population models were estimated using the NONMEM software program (version 7.2; ICON Development Solutions, Ellicott City, MD). Interindividual variability in PK parameters was modeled as an exponentiation of random effects ($\exp(\eta_i)$) with residual variability modeled assuming a proportional and additive error model. The first-order conditional estimation method was used for estimation. The NONMEM objective function values and diagnostic plots were used to assess goodness of fit, to suggest covariates to add to the model, and to evaluate the model. For gadobutrol and gadoterate, the PK models were based on the published US Food and Drug Administration clinical reviews and clinical pharmacology reviews for new drug applications.^{21,22}

A standard forward selection and backward elimination procedure was used to evaluate the effects of subject covariates on PK parameters. The selection of baseline covariates was based on the statistical significance and clinical relevance. During forward selection, a covariate contributing at least a 3.84- unit change in the minimum value of the objective function (minimum value of the objective function = $-2 \times \log$ - likelihood, $\alpha = 0.05$, one degree of freedom) and a decrease in interindividual variability on the PK parameter of interest was considered statistically significant. During backward elimination, a covariate was considered significant if it contributed at least a 6.64- unit change in the minimum value of the objective function ($\alpha = 0.01$, one degree of freedom) when removed from the model.

Model predictions

Using each final model, clearance (CL) was predicted ($CL_{\text{predicted}}$) for every subject given their measured covariate values. The drug clearance was then parameterized as follows as described in the literature⁴:

$$CL = \theta_{CL} * F_{\text{size}} * F_{\text{age}} * F_{\text{kidney}}$$

θ_{CL} represents the adult clearance based on published literature data. F_{size} , representing the effect of body weight, was modeled using allometric scaling approach.

$$F_{size} = \left(\frac{Weight}{Weight_{std}} \right)^{0.75},$$

where $Weight_{std}$ is the standard adult weight of 70 kg.

F_{age} , representing the relationship between CL and age, was modeled using a sigmoid E_{max} model:

$$F_{age} = \frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}},$$

where PMA is postmenstrual age. The values in this formula were based on the publication from Rhodin *et al.*¹⁰

Maturation model comparison

Additionally, the age effect on clearance was explored using the combination of GA and PNA. We used the concentration time data from drugs > 90% renally eliminated: amikacin, vancomycin, gadobutrol, and gadoterate to develop this model. The effects of GA and PNA on drug clearance were modeled as linear, power, exponential, and sigmoidal E_{max} functions. The final model was selected as the final covariate model based on the standard PopPK model development procedure.²³ As none of the indications for these studies are renal disease-specific, the F_{kidney} was not parameterized in our study. The following F_{age} equation was derived to predict the clearance for other drugs, including ampicillin, gentamicin, netilmicin, and meropenem:

$$F_{age} = 1 - \left(1 - 0.404 * \left(\frac{GA}{37} \right)^{3.3} \right) * \exp \left(-PNA * \left(\frac{0.693}{20.8} \right) \right)$$

Predictive performance

We compared the $CL_{prediction}$ utilizing bodyweight- based scaling in combination with age-based maturation functions to observed clearance value for each subject. The latter was determined by individual *post hoc* clearance estimate following the standard PopPK analysis for each drug using the observed PK data.

The bias and precision of $CL_{prediction}$ were assessed through calculation of AFE and AAFE²⁴ using the following:

$$AFE = 10 \frac{1}{N} \sum \log \left(\frac{CL_{predicted}}{CL_{observed}} \right)$$

$$AAFE = 10^{\frac{1}{N} \sum \left| \log \left(\frac{CL_{\text{predicted}}}{CL_{\text{observed}}} \right) \right|},$$

where N denotes the number of neonates in the neonatal dataset. An AFE greater than one suggests a bias toward overprediction, and an AFE less than one suggests a bias toward underprediction. We considered $CL_{\text{predictions}}$ that were within a twofold range of the observed clearances to be successful. In the present analysis, we also determined the percentage of neonates that had predicted clearance values with a twofold error of the observed clearance values.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

- Various renal maturation models have been proposed; however, it remains unclear as to whether these maturation models could be prospectively applied to predict the renal clearance of a drug in newborns and infants during drug development.

WHAT QUESTION DID THIS STUDY ADDRESS?

- The objective of this study was to evaluate the predictive performance of population models to predict renal clearance in newborns and infants using data from eight drugs in 788 newborns and infants.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

- Our study demonstrated that the postmenstrual age (PMA) and bodyweight-based renal maturation model can be reasonably used in population modeling to predict clearance for drugs that are primarily eliminated via the renal pathway. The PMA-based maturation model demonstrated slightly better prediction accuracy than a model using postnatal age and gestational age.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

- PMA-based sigmoidal maximum effect ($E_{\max}$) model, in combination with bodyweight-based scaling and kidney function assessment, can be used in population PK modeling for drugs that are primarily eliminated via renal pathway to inform initial dose selection for newborns and infants with normal renal function in clinical trials.

Figure 1.

Overall performance of clearance (CL) prediction for drugs $> 90\%$ renally eliminated in newborns and infants using a postmenstrual age (PMA)-based model. The circles represent patients with gestational age ≥ 37 weeks, and the triangles represent patients with gestational age < 37 weeks. The colors of red, blue, and dark green represent < 37 weeks PMA, 37 to < 42 weeks PMA, and ≥ 42 weeks PMA, respectively. The dotted lines represent 0.5 and twofold for the ratio of model-predicted CL relative to the observed value.

Figure 2.

Overall performance of clearance (CL) prediction for drugs 60–80% renally eliminated in newborns and infants using a postmenstrual age (PMA)-based model. The circles represent patients with gestational age ≥ 37 weeks, and the triangles represent patients with gestational age < 37 weeks. The colors of red, blue, and dark green represent < 37 weeks PMA, 37 to < 42 weeks PMA, and ≥ 42 weeks PMA, respectively. The dotted lines represent 0.5 and twofold for the ratio of model-predicted relative to the observed value.

Table 1

Drug clearance and renal clearance in adults

Drug	Total clearance (L/hour)	Renal clearance (L/hour)	% Renal clearance	Contribution of nonrenal elimination pathways
Amikacin ²⁵	6.0 ± 0.5	5.0 ± 0.9	94	< 5% metabolism
Gadobutrol ²⁶	6.2	6.2	> 99	No metabolism
Gadoterate ²⁷	7.1	7.1	> 99	No metabolism
Vancomycin ²⁸	5.9 ± 1.5	5.3 ± 2.0	~ 90	~ 10% metabolism
Ampicillin ²⁹	16.9 ± 3.3	10.4 ± 3.7	61	10% Biliary elimination; Likely secretion
Gentamicin ²⁷	6.0 ± 1.8	4.6 ± 1.5	~ 77	No data
Meropenem ^{20,30}	14.6 ± 8.3	10.4 ± 6.4	71	Likely secretion; ~ 30% metabolism
Netilmicin ³¹	5.5 ± 0.8	4.0 ± 0.6	72	No data

Clearance values are presented as mean ± SD, where available.

Table 2

Distribution of newborns and infants in age categories

Drugs (n)	42 weeks PMA (n)	37 to < 42 weeks PMA (n)	< 37 weeks PMA (n)	PNA (days)	GA (weeks)	PMA (weeks)	Body weight (kg)	SCR (mg/dL)
Amikacin (108)	22	11	75	10 (3–625)	29 (23–41)	31 (25–127)	1.29 (0.45–11.28)	0.38 (0.2–0.96)
Gadobutrol (43)	39	4	0	212 (6–696)	40 (40–40)	70 (41–139)	7.2 (2.80–14.20)	0.27 (0.1–0.66)
Gadoterate (45)	41	4	0	266 (4–721)	40	78 (39–143)	8.00 (3.00–15.00)	0.24 (0.14–0.42)
Vancomycin (92)	22	31	39	13 (2–367)	36 (24–41)	39 (25–89)	2.61 (0.53–8.26)	0.5 (0.18–1.67)
Ampicillin (73)	5	31	37	2 (0–24)	36 (24–41)	37 (25–43)	2.47 (0.50–4.19)	0.6 (0.2–2.5)
Gentamicin (143)	46	48	49	1 (0–711)	37 (23–43)	38 (23–135)	3.12 (0.40–12.00)	0.6 (0.18–5.5)
Meropenem (200)	13	31	156	21 (1–92)	28 (23–40)	32 (24–51)	1.54 (0.39–6.50)	0.5 (0.1–1.9)
Netilmicin (83)	1	3	79	10 (2–121)	27 (23–41)	29 (24–43)	1.00 (0.47–3.00)	0.77 (0.27–1.67)
All drugs (787)	189	163	435	13 (0–721)	33 (23–43)	35 (23–143)	2.16 (0.39–15.00)	0.5 (0.1–5.5)

GA, gestational age; PMA, postmenstrual age; PNA, postnatal age; SCR, serum creatinine.

Table 3

Predictive performance of drug clearance in newborns and infants

Drug	42 weeks PMA			37 to < 42 weeks PMA			< 37 weeks PMA		
	AFE	AAFE	PER (%)	AFE	AAFE	PER (%)	AFE	AAFE	PER (%)
Drugs with > 90% renal elimination in adults									
Amikacin	1.3	1.5	81.8	1.2	1.4	90.9	0.8	1.3	97.3
Gadobutrol	0.9	1.2	100.0	0.7	1.3	100.0	NA	NA	NA
Gadoterate	0.9	1.4	87.8	0.8	1.6	75.0	NA	NA	NA
Vancomycin	1.0	1.3	100.0	0.9	1.2	96.8	1.2	1.2	100.0
Drugs with 60–80% renal elimination in adults									
Gentamicin	1.2	1.2	100.0	1.2	1.2	100.0	1.0	1.2	100.0
Netilmicin	1.1	1.1	100.0	0.6	1.7	66.7	0.7	1.5	92.4
Meropenem	1.0	1.4	92.3	1.0	1.2	100.0	1.0	1.2	98.1
Ampicillin	1.6	1.6	80.0	2.0	2.0	54.8	2.0	2.0	51.4

AAFE, absolute average fold error; AFE, average fold error; PER, percentage of infants with a fold error between 0.5 and 2, indicating a twofold difference from the observed clearance; NA, not applicable; PMA, postmenstrual age.

Predictive performance of drug clearance in newborns and infants using GA-based and PNA-based maturation model

Table 4

Drug	42 weeks PMA			37 to < 42 weeks PMA			< 37 weeks PMA		
	AFE	AAFE	PER (%)	AFE	AAFE	PER (%)	AFE	AAFE	PER (%)
Gentamicin	1.2	1.3	95.9	1.3	1.3	97.8	1.7	1.7	91.7
Netilmicin	0.9	1.2	100.0	1.6	1.6	100.0	0.7	1.5	75
Meropenem	1.4	1.4	92.5	1.2	1.4	76.9	1.2	1.3	96.8
Ampicillin	2.5	2.5	13.5	2.3	2.3	20	2.8	2.8	16.1

AAFE, absolute average fold error; AFE, average fold error; GA, gestational age; PER, percentage of infants with a fold error between 0.5 and 2, indicating a twofold difference from the observed clearance; PNA, postnatal age.