Clin Pharmacokinet (2013) 52:1127–1134
DOI 10.1007/s40262-013-0101-6

SHORT COMMUNICATION

Amikacin Maturation Model as a Marker of Renal Maturation to Predict Glomerular Filtration Rate and Vancomycin Clearance in Neonates

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Published online: 12 September 2013

Abstract
Background and Objective Amikacin clearance has recently been proposed as a marker of renal maturation in neonates. However, the predictive value of this marker is still unknown. The objective of the present exploratory study was to evaluate the predictive performance of renal maturation model derived from amikacin to predict the glomerular filtration rate (GFR) and vancomycin clearance in neonates.
Methods The GFR and vancomycin clearance in neonates were predicted using a maturation model derived from amikacin via estimation and simulation in a cohort of 116 neonates using non-linear mixed–effects modeling NONMEM® software.
Results Our results demonstrate good correlations between predicted and observed GFR and vancomycin clearance in neonates. The square of the correlation coefficient, and means of the prediction error (2.5th–97.5th percentiles) and absolute prediction error (2.5th–97.5th percentiles) are 0.96, 1.2 % (−39.7 to 30.0 %) and 12.3 % (0.4–39.7 %), respectively, for GFR, and 0.97, −11.3 % (−38.2 to 15.4 %) and 14.0 % (0.5–38.2 %), respectively, for vancomycin. The prediction error is not significantly correlated with age.
Conclusion An amikacin maturation model can precisely reflect maturation of glomerular filtration and thus predict the dosage regimens of other renally excreted drugs by glomerular filtration in neonates.

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1 Introduction

The kidney is the primary organ responsible for drug elimination. From birth onwards, the kidney is in a continuous and rapidly changing state of maturation. The developmental increase in the glomerular filtration rate (GFR) involves active nephrogenesis, which is first seen at approximately 5–6 weeks of gestational age and is complete by 36 weeks of gestational age, followed by postnatal maturation of renal function with changes in renal and intrarenal blood flow [1–3]. The GFR increases rapidly during the first 2 weeks of life and reaches adult levels by the end of the first year of life. Tubular function is immature at birth and matures later than glomerular function; it also achieves adult values during the first year of life [2, 4]. The developmental changes of kidney function affect the pharmacokinetics of a drug in an age-dependent manner, leading to a profound impact on dosage adjustments of renally excreted drugs in neonates [5, 6].

To define optimal dosage regimens of renally excreted drugs in neonates, the quantification of renal maturation is required. By integrating modeling approaches, renal maturation has been described and quantified using different compounds with developmental factors (i.e., bodyweight

and age) as significant covariates [7]. As glomerular filtration is a passive diffusion process and unbound drug is freely filtrated, a practical approach to assess the GFR in neonates is to determine the clearance (CL) of a drug that is exclusively eliminated by glomerular filtration [10]. One of the proposed novel methods is the use of amikacin. De Cock et al. [11] developed a neonatal population pharmacokinetic model of amikacin using data from 874 neonates. Birth weight and postnatal age (PNA) were identified as significant developmental predictors of amikacin CL [11]. As amikacin is eliminated almost entirely by the kidney via glomerular filtration [12], amikacin CL parallels the GFR and can serve as a marker of renal maturation. From a methodology perspective, we hypothesized that an amikacin maturation model could precisely reflect maturation of the glomerular filtration and thus predict the dosage regimens of other renally excreted drugs by glomerular filtration in preterm and term neonates.

Therefore, the objective of the current exploratory study was to evaluate the predictive performance of a renal maturation model derived from amikacin to predict GFR and vancomycin CL in neonates. Vancomycin was selected as a model drug for extrapolation based on the following reasons:

(1) Amikacin and vancomycin have similar chemical and pharmacokinetic characteristics. They are primarily eliminated by the kidney via glomerular filtration and have low protein binding [13, 14]. Therefore, the developmental changes of CL of unbound amikacin and vancomycin should show a similar maturation pattern in neonates.
(2) The pharmacokinetics of both drugs have shown large inter-individual variability. Age, bodyweight, and renal function were the most relevant covariates influencing the CL of both drugs in neonates [8, 9, 15].
(3) Therapeutic drug monitoring of amikacin and vancomycin has been included in the routine care of patients. The CL of both drugs can be easily calculated using the developed models. Amikacin and vancomycin maturation models can be routinely used as markers of renal maturation to predict the dosage regimens of other renally excreted drugs.

2 Methods

The renal maturation model derived from amikacin neonatal pharmacokinetic data was used to predict GFR and vancomycin CL in neonates via estimation and simulation using the non-linear mixed–effects modeling program NONMEM® VII (Icon Development Solutions, Ellicott City, MD, USA)

2.1 Glomerular Filtration Rate (GFR)

2.1.1 GFR in Neonates

The GFR maturation model was developed based on the developmental changes of inulin, mannitol ^{51}Cr-EDTA, iohexol, and sinistrin CL with age. A pooled data analysis was conducted by Rhodin et al. [7] to develop a GFR maturation model, which was used in the present study to calculate observed/reference GFR values in patient cohort (Eqs. 1–2):

$$\mathrm{GFR_{neonate}} = \mathrm{GFR_{adult}} \times \left(\frac{\mathrm{WT_{neonate}}}{70}\right)^{0.75} \times \mathrm{MF} \quad (1)$$

$$\mathrm{MF} = \frac{\mathrm{PMA}^{S}}{\mathrm{PMA_{50}}^{S} + \mathrm{PMA}^{S}} \quad (2)$$

where GFR is the glomerular filtration rate expressed in mL/min, the adult GFR ($\mathrm{GFR_{adult}}$) is 121 mL/min, WT is the bodyweight expressed in kg, MF is maturation function, PMA is postmenstrual age expressed in weeks, $\mathrm{PMA_{50}}$ is the PMA at which GFR reaches half its maximal value, which was reported to be 47.7 weeks, and S is the sigmoidicity coefficient with an estimated value of 3.4 [7].

2.1.2 Predicted GFR from Amikacin

The predicted GFR value in neonates was directly extrapolated from the amikacin maturation model (Eq. 3):

$$\text{Predicted } \mathrm{GFR_{neonate}} = \frac{\mathrm{CL_{amikacin}}}{\mathrm{fu_{amikacin\,neonate}}} \quad (3)$$

where fu is unbound fraction; $\mathrm{CL_{amikacin}}$ is calculated by the equations obtained from the amikacin maturation model as Eqs. 4–6 [11]:

$$\mathrm{CL_{amikacin}} = 0.0493 \times F_{\mathrm{BW}} \times F_{\mathrm{PNA}} \quad (4)$$

$$F_{\mathrm{BW}} = \left(\frac{\mathrm{BW}}{1,750}\right)^{1.34} \quad (5)$$

$$F_{\mathrm{PNA}} = \left(1 + 0.213 \times \frac{\mathrm{PNA}}{2}\right) \quad (6)$$

where F_{BW} and F_{PNA} are impacts of birth weight (expressed in g) and PNA (expressed in days) on amikacin CL, respectively.

The fu of drugs in neonates is estimated using Eq. 7 [16, 17]:

$$\mathrm{fu_{neonate}} = \frac{1}{1 + \frac{(1-\mathrm{fu_{adult}}) \times [P]_{\mathrm{neonate}}}{\mathrm{fu_{adult}} \times [P]_{\mathrm{adult}}}} \quad (7)$$

where $[P]$ is the plasma protein concentration and $\mathrm{fu_{adult}}$ is the average fu of drug in adults.

2.2 Vancomycin

2.2.1 Vancomycin Clearance (CL) in Neonates

The observed vancomycin CL value was obtained from a prospective, multicenter pharmacokinetic study in neonates. Two hundred and seven serum vancomycin concentrations from 116 neonates with a postmenstrual age that ranged from 24.4 to 49.4 weeks were used for population pharmacokinetic analysis. The observed vancomycin CL was estimated by the original model. This model was internally validated by a number of methods [goodness-of-fit plots, bootstrap, visual predictive check (VPC), normalized prediction distribution errors (NPDE)], followed by a clinical evaluation [18].

2.2.2 Predicted Vancomycin CL from Amikacin

The predicted vancomycin CL was extrapolated from the amikacin maturation model developed by De Cock et al. [11] using Eq. 8. The equation of maturation of amikacin CL was directly used to predict vancomycin CL in neonates as described above [11]:

$$\mathrm{CL}_{\mathrm{vancomycin}} = \mathrm{CL}_{\mathrm{amkacin}} \times \frac{\mathrm{fu}_{\mathrm{vancomycin\ neonate}}}{\mathrm{fu}_{\mathrm{amikacin\ neonate}}} \quad (8)$$

The same method was used to estimate fu in neonates as described above. The fu was reported to be 0.7 for vancomycin and 0.9 for amikacin in adults, respectively [19, 20].

Other pharmacokinetic parameters (volume of distribution, inter-individual variability, and residual variability) were re-estimated using the original dataset to develop the predicted vancomycin pharmacokinetic model.

Model validation of the vancomycin model was based on graphical and statistical criteria. Goodness-of-fit plots, including conditional weighted residuals (CWRES) versus time and CWRES versus population prediction (PRED) were used initially for diagnostic purposes [21]. This model was further evaluated graphically and statistically by VPC and NPDE via simulation [22]. One thousand datasets were simulated using the final population model parameters. For the VPCs, the 50th percentile concentration (as an estimator of the population-predicted concentration) and the 5th and 95th percentile concentrations were plotted against elapsed time. For a model in which random effects are well estimated, approximately 90 % of data points are expected to be within the 5th–95th prediction interval. NPDE results were summarized graphically by default as provided by the NPDE R package (v1.2) [23]: (1) quantile–quantile (QQ) plot of the NPDE; and (2) histogram of the NPDE. The NPDE is expected to follow the N (0, 1) distribution.

2.3 Predictive Performance of Prediction

The predictive performance of prediction was evaluated by calculating the prediction error (PE) and the absolute prediction error (APE), which are calculated using Eqs. 9–10:

$$\mathrm{PE} = \frac{\mathrm{Predicted\ GFR\ or\ vancomycin\ CL} - \mathrm{observed\ GFR\ or\ vancomycin\ CL}}{\mathrm{Observed\ GFR\ or\ vancomycin\ CL}} \quad (9)$$

$$\mathrm{APE} = \frac{\mathrm{ABS(Predicted\ GFR\ or\ vancomycin\ CL} - \mathrm{observed\ GFR\ or\ vancomycin\ CL)}}{\mathrm{Observed\ GFR\ or\ vancomycin\ CL}} \quad (10)$$

where ABS is absolute function. PE and APE are expressed in the result as a percentage.

3 Results

The patient cohort consisted of 116 neonates who were enrolled in a previously published multicenter pharmacokinetic study [18] and represented the real distribution of demographic characteristics of neonates undergoing antimicrobial treatment in neonatal intensive care units. Table 1 summarizes the demographic characteristics of the patient cohort. The age range of the patient cohort was similar to the original amikacin study. A diagram depicting the evaluation process is presented in Fig. 1.

3.1 GFR Prediction

Figure 2a demonstrates the correlation between predicted and observed GFR in neonates. The square of the correlation coefficient is 0.96. The means of the PE and APE are 1.2 % (2.5th–97.5th percentiles: −39.7 to 30.0 %) and 12.3 % (2.5th–97.5th percentiles: 0.4–39.7 %), respectively. The PE is not significantly correlated with postmenstrual age (Pearson correlation 0.12, $p = 0.2$) and current bodyweight (Pearson correlation 0.17, $p = 0.1$).

3.2 Vancomycin Prediction

The concentration–time profile of vancomycin is shown in Fig. 3. The predicted pharmacokinetic parameters (CL and volume of distribution) of vancomycin using the amikacin maturation model are comparable with those observed in the original vancomycin study (Table 2). Figure 2b demonstrates the correlation between predicted and observed vancomycin CL. The square of the correlation coefficient is 0.97. The means of the PE and APE are −11.3 %

(2.5th–97.5th percentiles: −38.2 to 15.4 %) and 14.0 % (2.5th–97.5th percentiles: 0.5–38.2 %), respectively. The PE is not significantly correlated with birth weight (Pearson correlation 0.10, $p = 0.3$), current bodyweight (Pearson correlation 0.09, $p = 0.4$), and PNA (Pearson correlation 0.12, $p = 0.2$). Model diagnostics indicated acceptable goodness-of-fit for the final model. As shown in Fig. 4, CWRES versus population-predicted concentrations and time are unbiased. Figs. 3 and 5 show the VPC and NPDE evaluations after 1,000 simulations of predicted vancomycin pharmacokinetic model. The VPC of the final model shows that observed vancomycin concentrations were well predicted by the amikacin maturation model (Exact Binomial Test, 11.6 % out of limits observed, 95 % CI 7.6–16.8). The mean and variance of the NPDE are −0.11 and 0.95.

Table 1 Baseline characteristics of neonates used in the simulation cohort ($n = 116$)

Characteristics	Number	Mean (SD)	Median (range)
Sex (F/M)	57/59		
Birth weight (g)		1,331 (839)	1,010 (510–3,930)
Current bodyweight (g)		1,700 (964)	1,416 (460–5,680)
GA (weeks)		31 (4)	30 (24–42)
PNA (days)		26 (25)	17 (1–120)
PMA (weeks)		33.8 (5.3)	32.7 (24.4–49.4)

F female, *GA* gestational age, *M* male, *PMA* postmenstrual age, *PNA* postnatal age, *SD* standard deviation

4 Discussion

The dosage regimen used in initial clinical studies in neonates is often based on empirical scaling methods [24]. The commonly used method for initial dosing selection in children is to normalize the adult dose by bodyweight or body surface area (i.e., mg/kg or mg/m^2), assuming a linear relationship between bodyweight or surface area and dose [24, 25]. Evaluation of these empirical methods has already shown imprecision of prediction of drug CL in young children. The prediction bias is even more pronounced in neonates [26]. The pharmacokinetic bridging studies based on modeling and extrapolation approaches have shown attractive results in predicting dosing in adults and children [25, 27, 28]. These studies, however, are limited in neonates [10, 17].

This exploratory study confirmed for the first time the predictive value of amikacin CL as a marker reflecting renal maturation during the neonatal period. The results supported the clinical implication of this bridging method to predict dosage regimens of other renally excreted drugs in neonates. The model derived from amikacin could accurately predict the GFR in neonates, as reflected by the

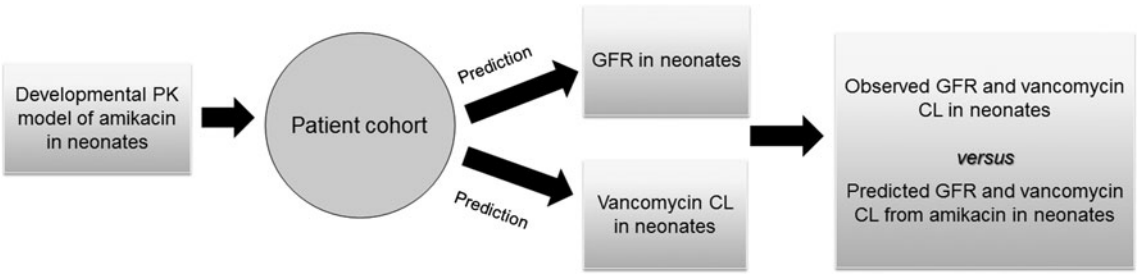

Fig. 1 Diagram depicting the evaluation process of amikacin maturation model as a marker of renal maturation to predict the GFR and vancomycin CL. *CL* clearance, *GFR* glomerular filtration rate, *PK* pharmacokinetic

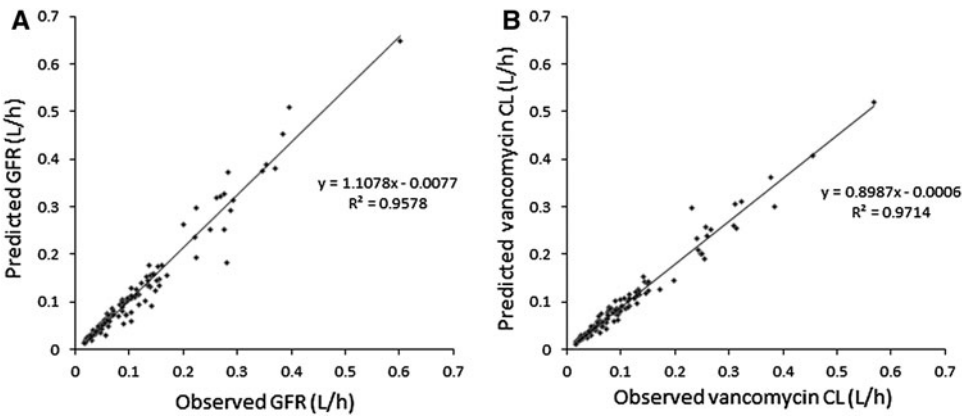

Fig. 2 Predicted versus observed GFR and vancomycin CL in neonates: **a** GFR, **b** vancomycin CL. The predicted GFR and vancomycin CL were extrapolated based on an amikacin maturation model [11]. The observed GFR was calculated using a GFR maturation model [7]. The observed vancomycin CL was obtained using a vancomycin pharmacokinetic model [18]. *CL* clearance, *GFR* glomerular filtration rate

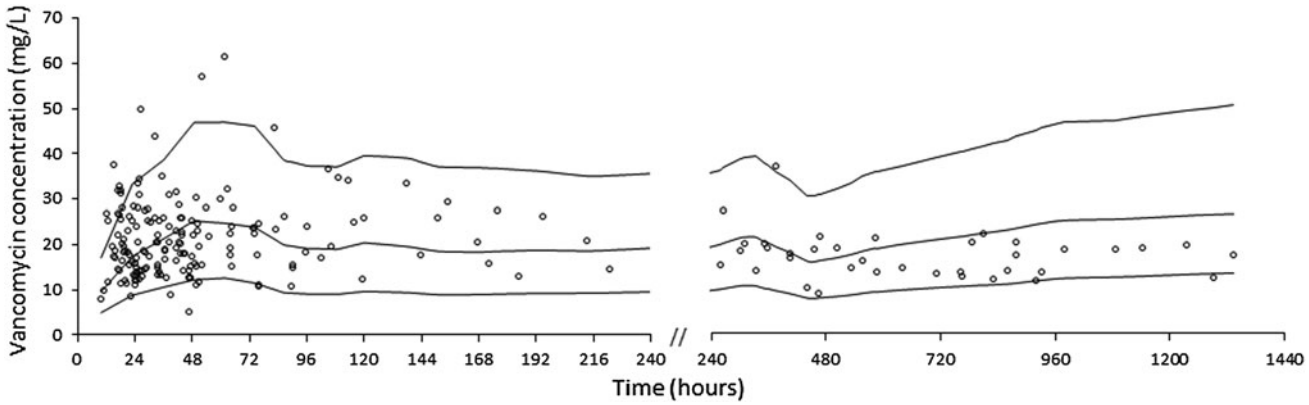

Fig. 3 Concentration–time profile of vancomycin in neonates and visual predictive check of the vancomycin pharmacokinetic model. Observed concentration data are plotted using a *circle*. The *solid lines* represent the 5th, 50th, and 95th percentiles of simulated data ($n = 1{,}000$)

Table 2 Observed versus predicted vancomycin pharmacokinetic parameters

Parameters	Observed (mean ± SD)	Predicted[a] (mean ± SD)
Clearance (L/h)	0.108 ± 0.099	0.108 ± 0.102
Volume of distribution (L)	0.888 ± 0.439	1.033 ± 0.519

SD standard deviation

[a] The predicted vancomycin pharmacokinetic parameters were based on an amikacin maturation model

developmental changes of inulin, mannitol ^{51}Cr-EDTA, iohexol, and sinistrin CL with postmenstrual age. Moreover, the amikacin maturation model gave a reasonable prediction of vancomycin CL. The prediction bias was not significantly correlated with developmental factors (age and bodyweight), indicating that renal maturation as reflected by amikacin could be used to predict the dosage regimens of the other renally eliminated drugs without age-related bias.

Vancomycin was selected as a model drug to evaluate the predictive performance of amikacin maturation model because of the reasons outlined in the Introduction of this article. Although the renal tubular secretion and non-renal pathways might account for 30 % of total CL of vancomycin in adults [29], these pathways are immature in neonates and will not have an impact on the CL extrapolation from amikacin to vancomycin. The results also supported our hypothesis: the PE is small (about −10 %) and was not related to age during the whole neonatal period. The impact of protein binding is another key factor for extrapolation, as only the free fraction was eliminated by glomerular filtration. The free fractions of amikacin and vancomycin were not reported in neonates, and thus we used an equation developed by McNamara and Alcorn [16] to predict the values of free fraction in neonates from adults. The conversion factor ($\frac{fu_{vancomycin\ neonate}}{fu_{amikacin\ neonate}}$) was taken into consideration when extrapolating from amikacin to vancomycin.

The maturation of glomerular filtration is rapid and continuous during the neonatal period. The direct assessment of the GFR in neonates is often impractical because of difficulties in urine collection. Different methods have been used to predict renal maturation in neonates, using either endogenous (creatinine [30]) or exogenous compounds (inulin [31, 32], sinistrin [33], iohexol [34], radiolabeled isotope [35, 36], aminoglycosides [10]). The most common method is serum creatinine CL; however, the use of creatinine concentration as the marker of GFR was limited in neonates, as the influence of residual maternal-derived creatinine and interference with proteins, ketoacids, bilirubin, cephalosporins, etc. may lead to inaccuracies in predicting renal function in neonates [37, 38] and has shown significant impact on the transferability of dosing recommendations in different clinical settings [39]. Determination of the GFR based on measurement of the CL of injected substances (e.g., inulin, sinistrin, iohexol, radiolabeled isotope) that are exclusively excreted via glomerular filtration improved the accuracy of prediction. Rhodin et al. [7] performed a population meta-analysis in which the data comprised measured GFR (using polyfructose, ^{51}Cr-EDTA, mannitol, or iohexol) from eight studies and 923 patients, and involved very premature neonates to adulthood. They found that a sigmoid hyperbolic model could precisely describe the non-linear relationship between GFR maturation and postmenstrual age after standardizing size effect using allometric scaling. However, these procedures are labor intensive and not entirely free of risk for the neonates, making routine application difficult in neonatal clinical practice.

The use of aminoglycoside CL as the marker of GFR represents a practical solution. Koren et al. [10] calculated

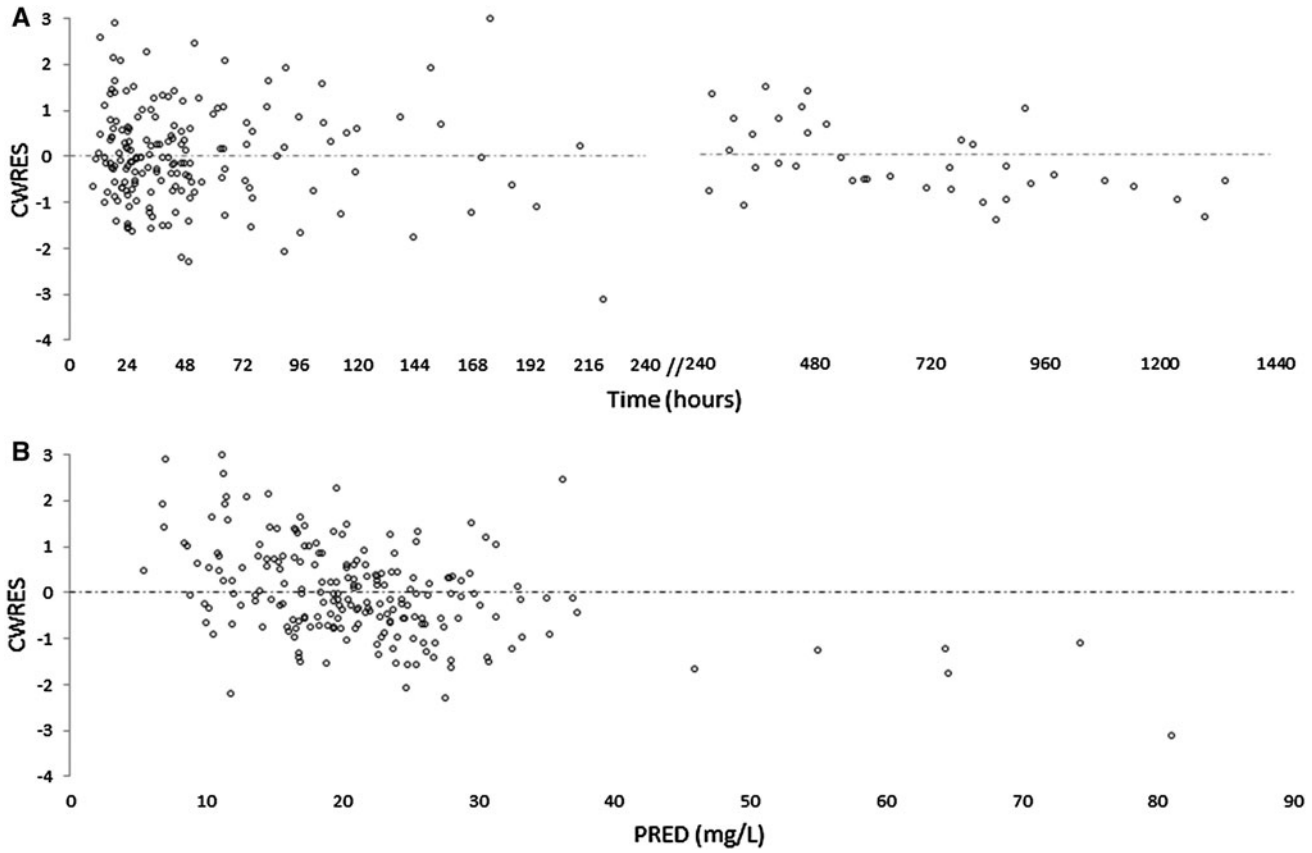

Fig. 4 Goodness-of-fit plots: **a** CWRES versus time; **b** CWRES versus PRED. *CWRES* conditional weighted residuals, *PRED* population prediction

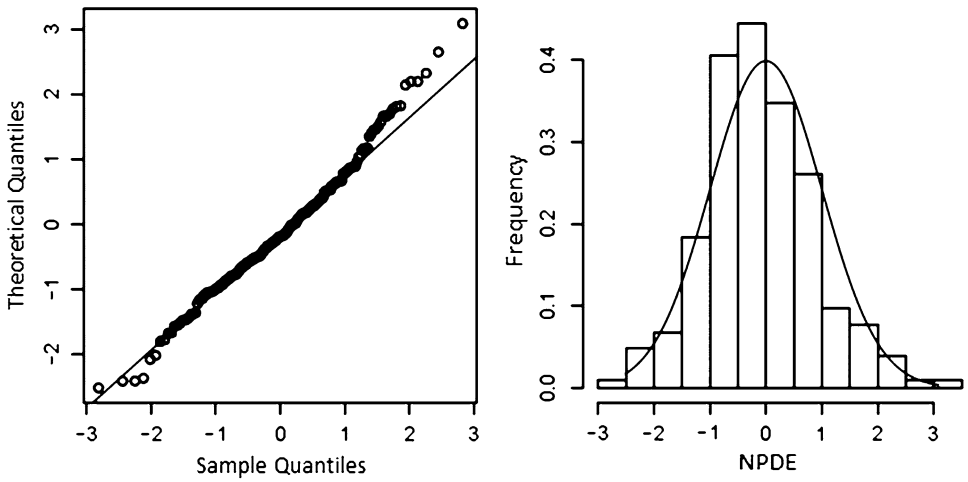

Fig. 5 NPDE of vancomycin prediction in neonates: **a** quantile–quantile plot of the distribution of the NPDE versus the theoretical N (0,1) distribution; **b** histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid. *NPDE* normalized prediction distribution errors

gentamicin pharmacokinetic parameters in 38 newborn infants and found that gentamicin CL correlated well with measured creatinine CL. Our results supported the premise that amikacin CL is a useful index of GFR and could easily be calculated during routine therapeutic drug monitoring. The clinical application of aminoglycoside CL to predict the dosage regimens of other renally excreted drugs has been proposed by Delattre et al. [20, 40], who reported that dosage regimens of the four β-lactams (piperacillin/tazobactam, ceftazidime, cefepime, or meropenem) could be predicted and optimized by using the amikacin pharmacokinetics in critically ill adult septic patients. The validation of predictive performance of an in vivo marker, as conducted in the present analysis, represents an essential step to support the routine application of this approach in neonates. Further research should focus on the feasibility of

application of this marker in new drug development such as prediction of first dose in neonates. The renal CL of a new drug can be predicted based on renal maturation models, taking into account developmental pharmacokinetics.

The limitation of the proposed approach with an amikacin maturation model as a marker of renal maturation is the lack of confirmed impacts of clinical and biological factors on aminoglycoside CL, including effects on sepsis, ventilation, intrauterine growth restriction, and concurrent medication [41–43]. Renal function change in neonates is not only related to age, but also with these factors. Clearly, their impact on neonatal development and maturation is complex, probably even more so in preterm newborns. To our knowledge, all of the published studies are probably underpowered to simultaneously demonstrate their complex effect. A pharmacokinetic meta-analysis is required to investigate and quantify their impacts. Integration of complex covariates into the model can increase the precision of prediction of GFR in neonates.

5 Conclusion

The amikacin maturation model gave reasonable predictions of the GFR and vancomycin CL in neonates without age-related bias. The predictive value of the renal maturation model as reflected by amikacin was confirmed and can be used to predict the dosage regimens of other renally excreted drugs by glomerular filtration in preterm and term neonates.

Acknowledgments This work was supported by "la Foundation PremUp" (Professor Danièle Evain Brion, France) and Global Research in Paediatrics—Network of Excellence (GRIP, EU-funded FP7 project, Grant Agreement number 261060).

The authors declare no conflict of interest related to this work.

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