Chapter 4

Predictive Performance of a Recently Developed Population Pharmacokinetic Model for Morphine and its Metabolites in New Datasets of (Preterm) Neonates, Infants and Children

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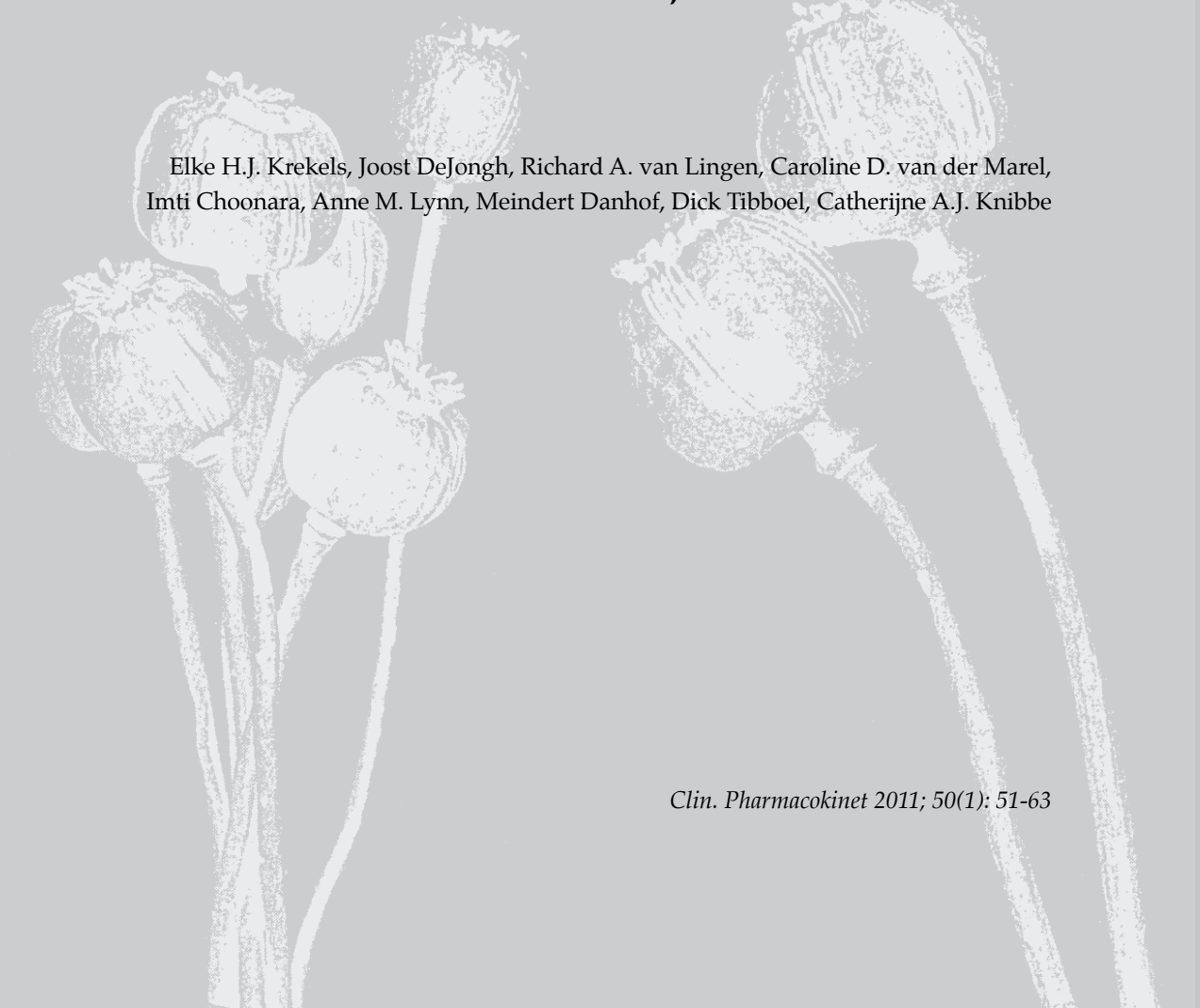

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Abstract

Background and Objective: Model validation procedures are crucial when models are to be used to develop new dosing algorithms. In this study, the predictive performance of a previously published paediatric population pharmacokinetic model for morphine and its metabolites in children younger than three years (original model) is studied in new datasets that were not used to develop the original model.

Methods: Six external datasets including neonates and infants up to one year were obtained from four different research centres. These datasets contained postoperative patients, ventilated patients and patients on extracorporeal membrane oxygenation (ECMO) treatment. Basic observed *versus* predicted plots, normalized prediction distribution error analysis, model refitting, bootstrap analysis, subpopulation analysis and a literature comparison of clearance predictions were performed with the new datasets to evaluate the predictive performance of the original morphine pharmacokinetic model.

Results: The original model was found to be stable and the parameter estimates were found to be precise. The concentrations predicted by the original model were in good agreement with the observed concentrations in the four datasets from postoperative and ventilated patients, and the model-predicted clearances in these datasets were in agreement with literature values. In the datasets from patients on ECMO treatment with continuous venovenous haemofiltration (CVVH) the predictive performance of the model was good as well, whereas underprediction occurred, particularly for the metabolites, in patients on ECMO treatment without CVVH.

Conclusion: The predictive value of the original morphine pharmacokinetic model is demonstrated in new datasets by the use of six different validation and evaluation tools. It is herewith justified to undertake a proof-of-principle approach in the development of rational dosing recommendations – namely, performing a prospective clinical trial in which the model-based dosing algorithm is clinically evaluated.

4.1 Background

Adequate validation studies to establish the predictive performance of population pharmacokinetic (PK) and/or pharmacodynamic (PD) models are often lacking both in the adult and paediatric population [1,2]. Validation procedures are crucial when models are to be used for simulation exercises. Model simulations can for instance be used to optimize dosing algorithms that take individual characteristics such as bodyweight and age into account. Additionally, simulations can be useful in setting-up clinical trials optimizing the information that is obtained while minimizing the burden to each individual in the trial by reducing the number of blood samples that need to be obtained. Without proper validation a model can only be regarded descriptive, limiting the safe use of these models for clinical and research applications.

Validation methods have been classified into three categories [2]: (i) basic internal methods (e.g. basic goodness-of-fit plots, uncertainty in parameter estimates and model sensitivity to outliers); (ii) advanced internal methods (e.g. data splitting, resampling techniques and Monte Carlo simulations); (iii) external validation (comparing observations in a new external dataset to predictions obtained using the model that was built on an internal dataset). Additionally, the aptness of model-based dosing algorithms should be assessed in confirmatory prospective clinical trials [3].

Ethical and practical constraints in paediatric studies may complicate the validation steps of paediatric models. Firstly, paediatric studies are often performed during routine clinical practice leading to high variability in drug administration due to different individual needs. Standard validation tools such as a visual predictive check may then not suffice and more sophisticated tools are required. Additionally, the paediatric population is relatively diverse due to the many maturational changes between preterm newborns and 18 year old adolescents, therefore diagnostic tools should not only be applied to the dataset of the population as a whole but also to various (age) subgroups in a dataset. Finally, the limited number of studies performed in this population makes external datasets less available and due to limited numbers of patients in paediatric studies the use of part of the dataset for model building and the other part for the external validation is often not viable either.

Recently a population PK model for morphine and its two major metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) was developed based on data from postoperative and ventilated neonates (including preterms), infants and children up to the age of three years (Chapter 3). This model was validated internally using basic and advanced validation methods and will be referred to as the 'original model'. In the current study the predictive performance of this model and its suitability

for simulation purposes is assessed in an external validation study with six new external datasets using basic and advanced validation methods.

4.2 Methods

Patients and Data

For the external validation study six datasets were available [4–10]. All studies had been approved by local ethic committees and informed parental consent was obtained. The datasets contained patient data not linked to identifiable patient information. An overview of the internal and external datasets is given in table I.

The studies were performed at four different centers, in three different countries and two different morphine salts were administered. To compare the administered doses the amount of administered morphine base was calculated for each individual.

Original Model

A schematic representation of the original model is shown in figure 1. In this model distribution volumes are scaled linearly with bodyweight. Formation clearances (CL_1 and CL_2) and elimination clearances (CL_3 and CL_4) of the morphine metabolites were best described by a bodyweight-based allometric equation with an estimated exponential scaling factor of 1.44. Additionally, within this power-function formation of the metabolites (CL_1 and CL_2) is reduced in neonates younger than ten days.

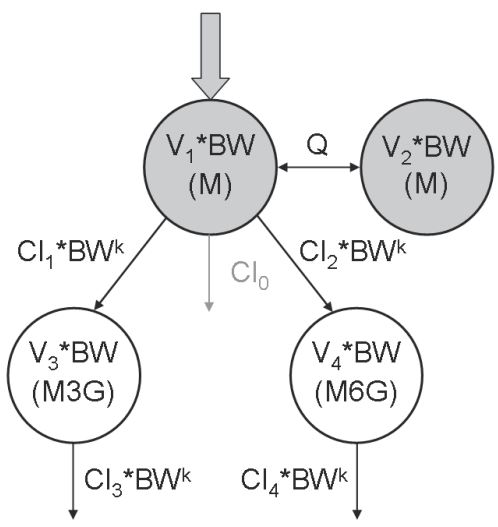

Figure 1. *Schematic representation of the original peadiatric population PK model for morphine and its glucuronides in children younger than three years.*

Table I. *Overview of the internal datasets (Int.) used to develop the original morphine model and external datasets (Ext) in the current external validation of the original morphine model.*

Dataset	Patient Population	Research Center	Number of Patients	Number of Samples	Postnatal Age in days (median, range)	Bodyweight in g (median, range)	Administered Morphine Salt
Int.1. [11]	Postoperative term neonates, infants and children.	Erasmus MC – Sophia Children's hospital (Rotterdam, The Netherlands)	185	M: 618 M3G: 512 M6G: 594	97 (0.1 - 1070)	4700 (1900 – 16800)	Morphine hydrochloride
Int.2. [12]	Preterm and term neonates on artificial ventilation	Erasmus MC – Sophia Children's hospital (Rotterdam, The Netherlands) Isala Clinics (Zwolle, The Netherlands)	63	M: 110 M3G: 132 M6G: 128	0.4 (0.1 – 6.7)	1180 (565 – 3875)	Morphine hydrochloride
Ext.1. [4]	Preterm neonates on artificial ventilation	Isala Clinics (Zwolle, The Netherlands)	41	M: 88 M3G: 111 M6G: 65	1 (0.1 – 13)	1035 (640 – 3550)	Morphine hydrochloride
Ext.2. [5]	Postoperative term neonates and infants	Erasmus MC – Sophia Children's hospital (Rotterdam, The Netherlands)	28	M: 98 M3G: 122 M6G: 115	14 (0.1 – 294)	3100 (1700 – 9300)	Morphine hydrochloride
Ext.3. [6]	Postoperative term neonates and infants	Children's Hospital and Regional Medical Center, (Seattle, WA, USA)	9	M: 16	10.5 (1 – 271)	3800 (2640 – 8100)	Morphine sulphate
Ext.4. [7]	Term neonates and infants on artificial ventilation	Alder Hey Children's hospital (Liverpool, UK)	12	M: 8 M3G: 12 M6G: 10	13 (3 – 354)	3050 (2200 – 8700)	Morphine sulphate
Ext.5. [8,9]	Term neonates on ECMO treatment without CVVH	Erasmus MC – Sophia Children's hospital (Rotterdam, The Netherlands)	14	M: 328 M3G: 326 M6G: 296	1.1 (0.1 – 26.1)	3220 (2150 – 4520)	Morphine hydrochloride
Ext.6. [10]	Term neonates on ECMO treatment with CVVH	Erasmus MC – Sophia Children's hospital (Rotterdam, The Netherlands)	16	M: 167 M3G: 197 M6G: 195	0.5 (0 – 7)	3250 (2700 – 4000)	Morphine hydrochloride

ECMO = extracorporeal membrane oxygenation
CVVH = continuous venovenous hemofiltration

Model Validation and Evaluation

NONMEM VI (ICON, Ellicott City, MD) was used for all model-based simulations and model fitting in the current study.

Simulations were performed based on dosing regimen, bodyweight and postnatal age of the children in the new external datasets, to obtain model-based population predicted concentrations. These predicted concentrations were then plotted *versus* the concentrations that were actually observed in these datasets. As population predicted concentrations are based on the fixed effects of the model, this analysis allows for the assessment of the predictive performance of both the structural model, encompassing the parent drug and metabolite model, and the covariate model, encompassing the relationships between the patient characteristics bodyweight and age and the model parameters clearance and distribution volume.

Additionally, a normalized prediction distribution error (NPDE) analysis was performed using the add-on software package that was run in R [13,14]. One-thousand model-predicted concentrations were generated for each observation in the external datasets with simulations based on dosing regimen, bodyweight and age of the patients and with the parameter values (including the inter-individual and residual variability) that were obtained for the original model. The observed concentrations in the external datasets were subsequently compared to these 1000 predicted concentrations [13,14]. In addition to assessing the structural and covariate model, this validation tool also allows for the assessment of how well the model predicts variability within the population.

When the plots of the predicted *versus* observed concentrations and the NPDE analysis showed no trends or bias in the external datasets of the postoperative and ventilated patients (Ext.1 – 4), these datasets were merged and analyzed together. These four external datasets were then combined with the internal datasets used to develop the original model and refitted to this model simultaneously. The resulting parameters could then be compared to the parameters obtained in the original model fit. Additionally, this combined dataset was used in a bootstrap analysis using the PSN software package [15]. For the bootstrap analysis the combined dataset was resampled 500 times and these resampled datasets were subsequently refitted to the model. All parameter estimates were then summarized as means and standard errors and could be compared to the results of the original model fit. Both the model refit and the bootstrap analysis give insight into model stability and the uncertainty of the parameter estimates of the model.

The performance of the covariate model was evaluated in the combined internal and external dataset by investigating subpopulations. It was examined whether bodyweight or age is the best descriptor for the maturation of the PK parameters by plotting *post hoc* PK parameter values obtained from the simultaneous refit *versus* bodyweight and age (both postnatal and postmenstrual) for small for gestational age

(SGA) and appropriate for gestational age (AGA) neonates. Neonates are considered to be SGA when their birth weight is below two standard deviations of the mean birth weight at that gestational age. All other neonates are considered to be AGA.

Lastly, model-predicted total morphine clearances for both the internal and merged external datasets were compared to morphine clearances published in the past twenty years. These reference values were derived from population PK models [16,17] or obtained non-parametrically [7,18–27]. For the original morphine model, total morphine clearances were calculated for each individual in the combined internal and external dataset as the sum of both metabolite formation clearances (CL_1 and CL_2) obtained in the simultaneous model refit. This was done for both population parameter estimates and individual *post hoc* parameter estimates. Population clearance parameters from publications that used a model-based approach and average clearances from publications that used a non-parametric approach were used together with individual patient characteristics (i.e. bodyweight, age and bilirubin concentrations), to calculate the reference total morphine clearances. This was only calculated for individuals in the combined internal and external dataset that met the inclusion criteria of the study described in a particular reference publication. All obtained clearance parameters were subsequently plotted *versus* bodyweight.

Although the original model was not based on data of patients on extracorporeal membrane oxygenation (ECMO) treatment, the predictive performance of the original model was also tested in two datasets with ECMO patients (Ext. 5 & 6). The datasets were evaluated individually by making plots of population predicted concentration *versus* observed concentrations and by performing an NPDE analysis as described above. Due to the inconclusive results on the predictive performance of the model in these two datasets, they were not merged or combined with the internal or other external datasets.

4.3 Results

The external datasets included a total of 37 non-cardiac postoperative patients, 53 ventilated patients, and 30 patients on ECMO treatment, with a total of 705 morphine, 668 M3G, and 681 M6G concentrations. Detailed information on the internal datasets (Int. 1 & 2) and the new external datasets (Ext. 1 – 6) is given in table I.

No trends or biases were observed in the predicted *versus* observed plots and the NPDE results of the four external datasets with postoperative and ventilated patients (Ext. 1 – 4). Figure 2a depicts a plot of the model-based population predicted concentrations *versus* the observed concentrations in these dataset using different symbols for the different datasets. In figure 3 the results of the NPDE analysis are shown, including the NPDE frequency distribution with the mean and standard deviation of this distribution, the NPDE distribution in time and the NPDE distribution *versus* the log value of the concentration. The plots show limited trends or biases in the predictions by the model.

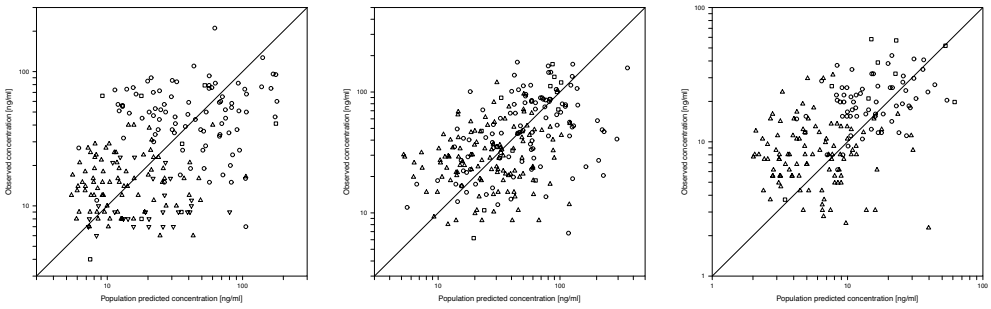

Figure 2. *Results of the external validation representing the concentration predicted by the original model versus the concentrations observed in the external datasets of postoperative and ventilated patients (Ext.1 – Ext.4) for morphine, morphine-3-glucuronide and morphine-6-glucuronide.* ○ *= Ext.1 preterm neonates on artificial ventilation* [4], △ *= Ext.2 non-cardiac postoperative term neonates and infants* [5], ▽ *= Ext.3 non-cardiac postoperative term neonates and infants* [6], □ *= Ext.4 term neonates and infants on artificial ventilation* [7].

Table II. *Parameter estimates obtained in the original fit of the model based on the internal dataset (Int. 1 & 2), and the refit and bootstrap of the combined internal and external datasets for postoperative and ventilated patients (Int. 1 & 2 and Ext. 1 – 4).*

Parameters	**original model fit** internal dataset	**refit of the model** internal & external dataset	**Bootstrap** internal & external dataset
	Value (CV%)	*Value (CV%)*	*Value (CV%)*
Fixed effects			
k = exponential scaling factor	1.44 (2.92)	1.44 (2.69)	1.44 (2.62)
$Cl_{1\ PNA < 10\ d}$ (ml/min/kg^k)	3.48 (5.89)	3.09 (5.15)	3.07 (8.37)
$Cl_{1\ PNA > 10d}$ (ml/min/kg^k)	8.62 (8.82)	8.25 (8.18)	8.27 (8.09)
$Cl_{2\ PNA < 10d}$ (ml/min/kg^k)	0.426 (11.1)	0.408 (11.4)	0.410 (10.8)
$Cl_{2\ PNA > 10d}$ (ml/min/kg^k)	0.67 (12.6)	0.699 (12.4)	0.714 (11.8)
Cl_3 (ml/min/kg^k)	2.02 (6.68)	2.19 (5.43)	2.19 (5.53)
Cl_4 (ml/min/kg^k)	1.05 (11.2)	1.11 (11.5)	1.12 (11.0)
Q_{eq} (ml/min)	29.6 (17.8)	28.9 (16.6)	29.7 (16.1)
$V_1 = V_4$ (l/kg)	1.81 (7.62)	1.99 (6.48)	1.99 (6.43)
$V_2 = V_3$ (fraction of V_1)	0.121 (18.2)	0.119 (17.2)	1.22 (17.1)
Inter-individual variability			
ω^2 Cl_1	0.0671 (25.9)	0.104 (18.4)	0.103 (18.5)
ω^2 V_1	0.196 (17.4)	0.23 (18.1)	0.223 (17.9)
ω^2 Cl_3	0.253 (20.1)	0.258 (16.7)	0.253 (16.4)
ω^2 Cl_4	0.146 (13.9)	0.185 (14.2)	0.184 (14.2)
ω^2 Cl_3-Cl_4 interaction	0.164 (13.7)	0.178 (13.4)	0.177 (13.2)
Residual error			
$\sigma^{2,\ prop}$ (morphine)	0.406 (13.3)	0.371 (5.94)	0.368 (11.7)
$\sigma^{2,\ prop}$ (M3G)	0.217 (24.7)	0.206 (19..4)	0.204 (19.0)
$\sigma^{2,\ prop}$ (M6G)	0.0844 (13.6)	0.0967 (12.0)	0.0959 (12.0)
$\sigma^{2,\ add}$ (24 hr post-infusion samples)	10.3 (31.2)	9.36 (30.2)	9.08 (29.5)

Table II gives an overview of (i) parameter estimates obtained in the original model fit (Chapter 3); (ii) parameter estimates of the model refit of the combined internal and four merged external datasets (Int. 1 & 2 and Ext. 1 – 4); (iii) the parameter estimates obtained in the bootstrap of the model with the combined internal and external dataset.

In the combined internal and external datasets, there were 168 neonates of which birthweight and gestational age at birth was known. Of these neonates 24 (=14%) were SGA. In figure 4 the individual *post hoc* parameter estimates of four model parameters are plotted *versus* bodyweight and postmenstrual age using different symbols for SGA and AGA neonates. The figure shows that when distribution volume (V_1) and M3G formation (CL_1) are plotted *versus* bodyweight, the individual *post hoc* estimates for SGA neonates are in line with the *post hoc* estimates for the AGA neonates, which is not the case when they are plotted *versus* postmenstrual age. Additionally the individual *post hoc* parameter estimates of the elimination clearance of M3G and M6G (CL_3 and CL_4) of the SGA neonates are shifted to the left compared to the *post hoc* estimates of the AGA neonates when plotted *versus* bodyweight. When plotted *versus* postmenstrual age the *post hoc* estimates of the elimination of the morphine metabolites of the SGA neonates are more in line with the values of the AGA neonates.

Figure 5 shows total morphine clearance values *versus* bodyweight. Population and individual *post hoc* predictions from the original model are shown in solid and open black circles respectively. The two lines represent children that are older and younger then ten days. Clearances calculated based on previously published clearance values are depicted with grey solid circles.

Figure 6 shows the plot of population predicted concentrations *versus* observed concentrations for the two datasets that included children on ECMO treatment (Ext.5 & 6) using different symbols for the two datasets. Predictions for dataset 6 are less biased than for dataset 5, particularly for the metabolites. In figure 7 the results of the NPDE analysis using only external dataset 6 are shown, showing limited trends or biases in the NPDE distributions.

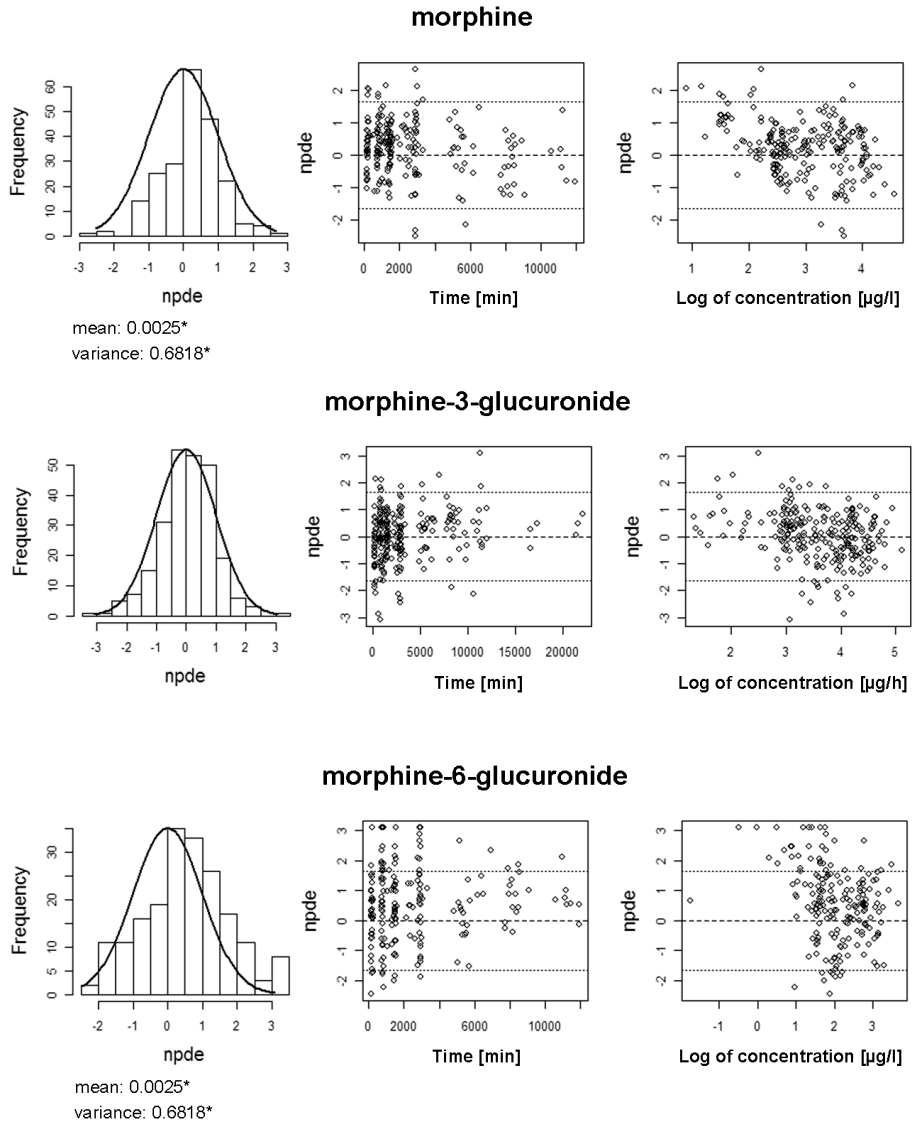

Figure 3. *Results of the external validation with the NPDE method using external datasets of postoperative and ventilated patients (Ext.1 – Ext.4). The histograms show the NPDE frequency distribution in the merged external dataset for morphine, morphine-3-glucuronide and morphine-6-glucuronide, the solid line indicates a normal distribution. The values for the mean and variance of the NPDE distribution are given below each histogram with * indicating a significant difference of a mean of 0 and a variance of 1 at the $p < 0.05$ level as determined by the Wilcoxon signed rank test and the Fisher test of variance. The distribution of NPDE versus time after first dose and NPDE versus the log of the concentration are also shown. The dotted lines represent the 90% distribution of the NPDE.*

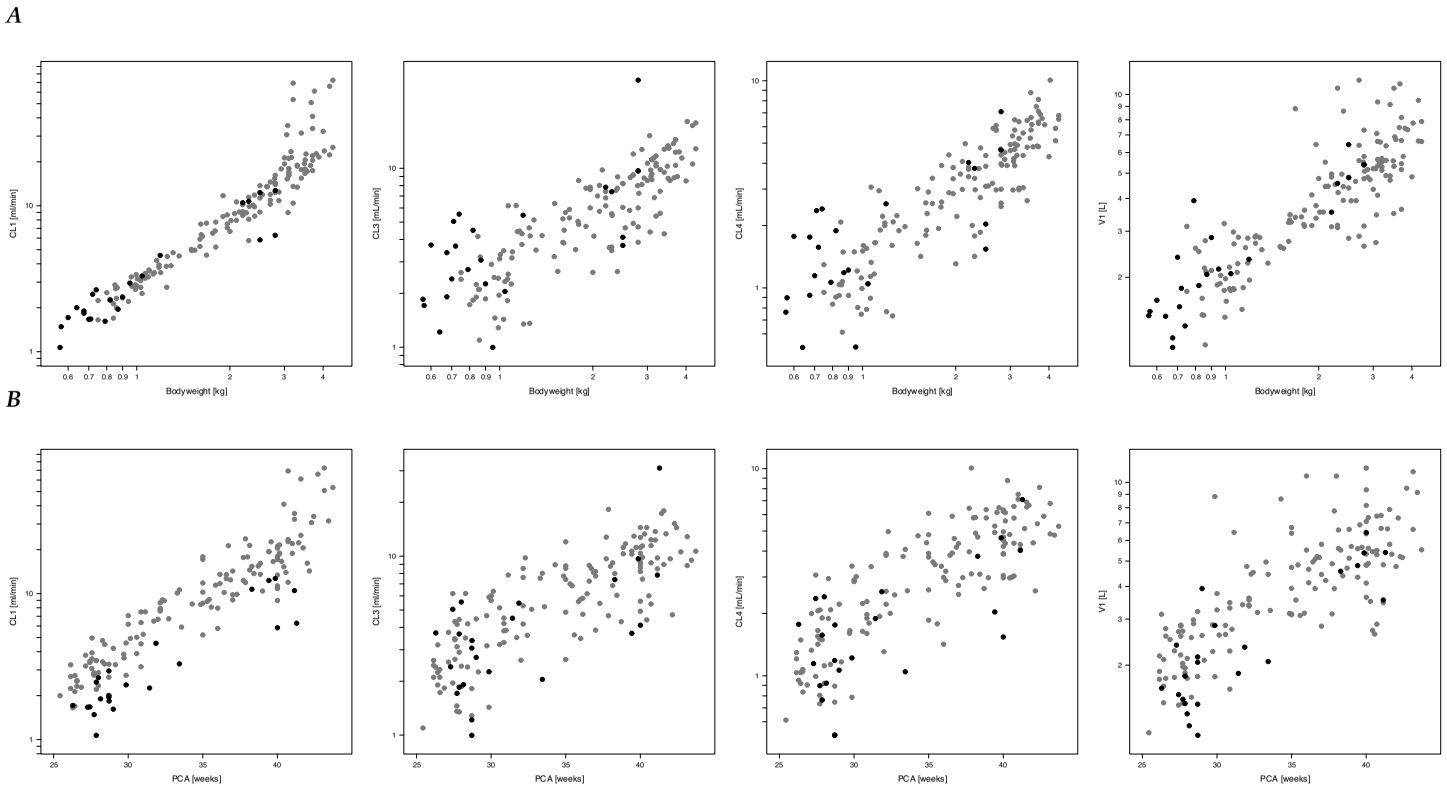

Figure 4. *Plots of individual post hoc parameter estimates of glucuronidation clearance of morphine to morphine-3-glucuronide (CL_1), distribution volume (V_1), elimination clearance of morphine-3-glucuronide (CL_3) and morphine-6-glucuronide (CL_4) versus A) bodyweight and B) postconceptual age (PCA) in neonates.* ● *= neonates appropriate for gestational age (AGA)* ● *= neonates small for gestational age (SGA).*

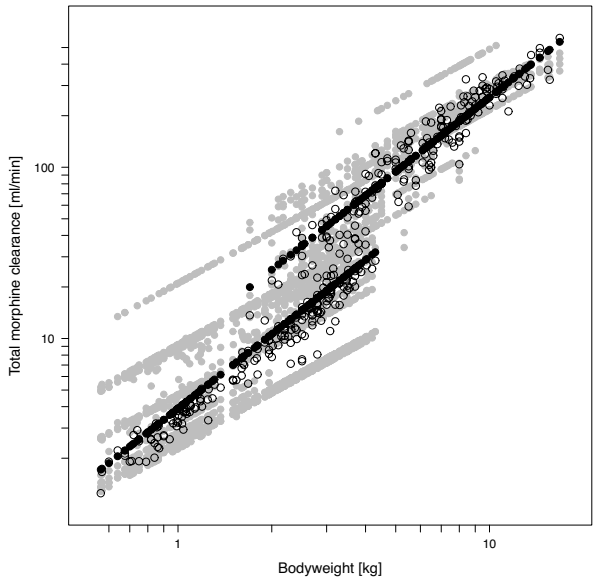

Figure 5. *Total morphine clearance values versus bodyweight for the patients in the internal and external datasets (Int. 1 & 2 and Ext. 1 – 4). ● = population predictions from the original model, ○ = individual post hoc estimates from the original model. ● = values reported in literature over the past 20 years [7,18–27].*

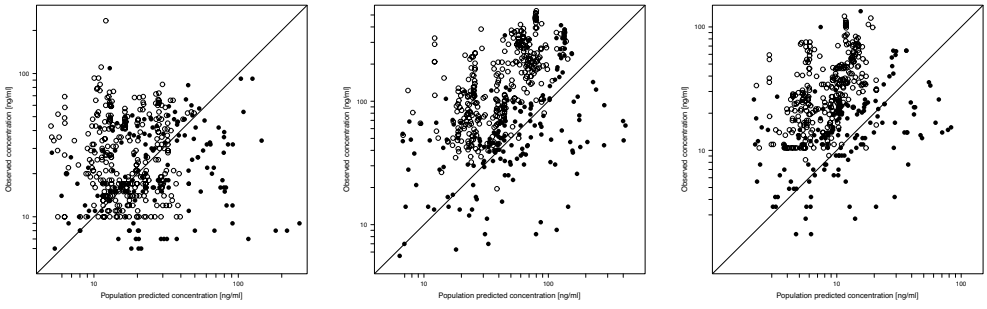

Figure 6. *Results of the external validation representing the concentrations predicted by the original model versus observed concentrations in the external datasets of patient receiving ECMO treatment for morphine, morphine-3-glucuronide, and morphine-6-glucuronide. ○ = Ext.5 term neonates on ECMO treatment without CHHV [8,9], and ● = Ext.6 term neonates on ECMO treatment with CVVH [10].*

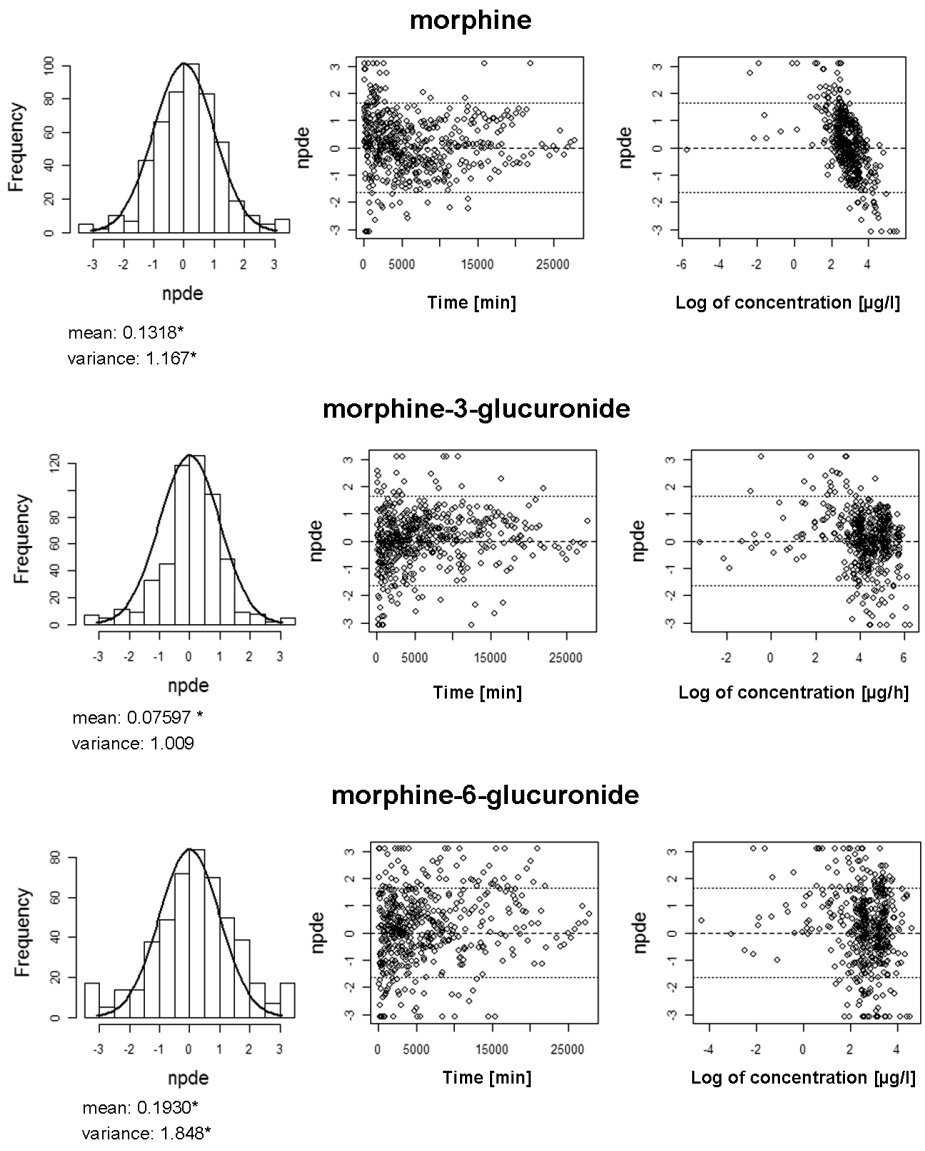

Figure 7. *Results of the external validation with the NPDE method using external dataset 6 (neonates on ECMO treatment with CVVH). The histograms show the NPDE frequency distribution in the merged external dataset for morphine, morphine-3-glucuronide and morphine-6-glucuronide, the solid line indicates a normal distribution. The values for the mean and variance of the NPDE distribution are given below each histogram with * indicating a significant difference of a mean of 0 and a variance of 1 at the $p < 0.05$ level as determined by the Wilcoxon signed rank test and the Fisher test of variance. The distribution of NPDE versus time after first dose and NPDE versus the log of the concentration are also shown. The dotted lines represent the 90% distribution of the NPDE.*

4.4 Discussion

In many publications on population PK and PD models results of even basic validation procedures are lacking. In adults only 28% of the population PK models and 26% of the population PD models were found to be adequately evaluated [1]. In the paediatric population advanced internal evaluations are performed on merely 16% of the models and external validations are performed on only 9% of the models [2]. Our group recently developed a population PK model for morphine glucuronidation in neonates (including preterms) infants and children up to three years which was validated internally using basic and advanced methods (Chapter 3). The internal validation procedure showed that the model can adequately describe the dataset used to develop the model, but when a model is to be used to derive dosing algorithms, descriptive properties are not enough. Therefore the predictive performance of the original model and thereby the validity of the use of the original morphine PK model for simulation purposes in this age group needed to be established as well. This can only be done in an external validation procedure for which in the current analysis six external datasets were available and basic and advanced validation methods were used. Moreover, the predicted morphine clearances are compared to literature values published in the past twenty years.

Two of the external datasets (Ext.3 & 4) originate from medical centers other than the centers from which the internal datasets were obtained. Irrespective of the center at which the studies were performed or the morphine salt that was administered, the predictive performance of the original morphine PK model was found to be good in the external datasets of postoperative and ventilated patients younger than one year. Figure 2 shows that the model can predict morphine and metabolite concentrations without bias in all individuals in the external datasets on the basis of dose, bodyweight and postnatal age alone. The spread in the observed data, which reflects the variability within the overall population, is equally large above and below the line of unity. The NPDE analysis in figure 3 confirms that the original model predicts morphine and metabolite concentrations accurately and detects only a slight over-estimation of the variability which was also observed in the internal validation procedure. The refit of the combined internal and merged external datasets (Int. 1 & 2 and Ext. 1 – 4) and the bootstrap analysis performed with this entire dataset show the original PK model for morphine in these young patients to be stable and the estimated parameters to be precise (table II). This means that the concentrations that were measured upon blood collections in these external datasets could have been adequately predicted based on individual characteristics that are readily available in clinical practice (bodyweight and age), thereby reducing the need for (extensive) blood sampling in drug monitoring.

The results of this external validation also strengthen the confidence in the obtained covariate relationships. This is important because in the paediatric population there is a strong correlation between bodyweight and age, leading to an ongoing debate on which of these characteristics to use as a descriptor for maturational changes in population PK models in this population. Some incorporate bodyweight *a priori* as a covariate using a bodyweight based allometric equation with fixed exponents of 0.75 for clearance and 1 for distribution volume [28]. The paediatric population PK model that is evaluated in the current study was developed by regarding bodyweight and age as conventional covariates in a systematic covariate analysis. In model development bodyweight was found to be a better descriptor of the maturation of morphine PK parameters than age and its influence was best described by a bodyweight based allometric equation with an estimated exponent of 1.44 for clearance and 1 for distribution volume (Chapter 3). Additionally, within this power-function metabolite formation was found to be reduced in neonates younger than ten days. In this external validation procedure, the original model showed to generate adequate predictions in a patient population up to one year of age.

The current analysis also demonstrates that the correlation between bodyweight and age is different in neonates that are SGA compared to their AGA counterparts. Therefore insights into the use of bodyweight or age as descriptors for maturational changes on drug PK can be obtained by studying these two subpopulations. For M3G formation clearance (CL_1) and distribution volume (V_1), the same relationship for SGA and AGA neonates was found when plotted *versus* bodyweight, which is not the case when plotted *versus* postmenstrual age (figure 4 a and b). Although shrinkage was 26.3% and 31.7% respectively, which renders plots using *post hoc* parameter estimates less reliable, this suggests that that bodyweight is indeed the most appropriate descriptor to describe maturational changes in the distribution volume and glucuronidation of morphine. For the elimination clearance of M3G and M6G (CL_3 and CL_4) the relationship with bodyweight is different for SGA and AGA neonates while the relationship between CL_3 and CL_4 and postmenstrual age in SGA and AGA neonates is more similar (figure 4 c and d). With 14.6% and 13.0% respectively, shrinkage was sufficiently low for the *post hoc* estimates of these parameters to be reliable. Bodyweight appears not to be the most optimal descriptor of the maturation rate of the elimination of the morphine metabolites and age may be a better descriptor. Based on these results an age-based exponential equation for the elimination clearances was tested, but this did not significantly improve the model (data not shown). According to the rule of parsimony this was therefore not incorporated into the model. An explanation for this could be the strong correlation between bodyweight and age in this population. Possibly the use of either of the two covariates results in maturation profiles that are very similar over the entire age-range.

The influence of the limited number of SGA neonates at the low end of the age and weight-range is then too small to significantly affect the overall model fit of the entire population.

This example illustrates that in paediatrics, in addition to looking at the population as a whole, subsets of the population should also be investigated. Despite the fact that postmenstrual age was not included into the final PK model for statistical reasons the subpopulation analysis in this study demonstrates that the best physiological descriptor for maturational changes (e.g. bodyweight or age) may be different for different PK parameters of the same drug, providing evidence against the *a priori* inclusion of bodyweight as a covariate in paediatric PK models. As it cannot be known beforehand what the best descriptor for maturational changes in PK parameters is, a systematic covariate analysis is always required.

As dosing algorithms are predominantly derived from clearance parameters it is important to assess how well a model can predict these parameters. A direct comparison between model-predicted clearances and 'actual clearances' is however difficult, since clearances can only be derived indirectly from population models or through non-parametric methods that require either steady state or dense data. As an alternative the model-predicted clearances were compared to previously reported values from literature. All but two previously published clearance values scaled linearly with bodyweight, which is reflected in figure 5 by identical slopes in the lines of published clearance parameters. Figure 5 also shows these lines to shift upwards with increasing bodyweight, indicating an increased clearance with increased bodyweight. The clearances predicted by the original morphine model increase exponentially with bodyweight, resulting in a different slope. Also this model predicts higher clearances for children older than ten days compared to their younger counterparts. The model predicted clearances fall nicely within the range of previously published clearances, increasing the confidence in the model-predicted clearances, although the ultimate validation is a prospective clinical study.

The relatively limited availability of suitable data in the paediatric population may hamper the validation of population models in this population. By using existing data, as was done in the current analysis, the number of unnecessary studies in this vulnerable population can be significantly reduced [29,30]. This often requires data sharing but unfortunately there are limiting ethical and practical issues that at present still need to be addressed by the scientific community and society as a whole [31]. Compared to neonates and infants younger than one year, children between one and three years of age are encountered relatively infrequently in paediatric ICUs, and they are less often included in clinical trials. For this population no datasets were available for the external validation of the original morphine model evaluated in this study, leaving this model externally largely unvalidated in this age-range.

Two external datasets (Ext.5 & 6) included a patient population that was not included in the learning dataset for the original model, namely neonates undergoing ECMO treatment. ECMO is an invasive procedure that may influence PK parameters, most often increasing distribution volume and decreasing clearance [32–35]. Additionally, morphine doses were on average higher in these studies compared to the studies of the internal and other external datasets (Ext. 1 – 4). The predictive performance of the original model was investigated in this patient population as well to determine whether, despite these differences, the dosing algorithm in $\mu g/kg^{1.5}/h$ derived from the covariate relationships in the original morphine PK model could still be beneficial in patients on ECMO treatment. The predictive performance of the original model proved to be good for external ECMO dataset 6, although considerable bias towards under prediction, particularly for the morphine metabolites, was observed in external ECMO dataset 5. The duration of the study of dataset 5 was longer than the study of dataset 6 and therefore accumulation was expected, however the NPDE analysis of this individual dataset showed no such trend in time (data not shown). An important difference between the two studies was that the study of dataset 6 was a more recent study and at that time the augmentation of ECMO treatment with continuous venovenous hemofiltration (CVVH) was routine practice, in contrast to the study of dataset 5. Morphine metabolites are eliminated through renal clearance and since CVVH complements renal function this could explain the under-prediction of morphine metabolites by the original model in dataset 5. In fact previous analysis of this dataset showed CVVH augmentation to increase metabolite elimination but not morphine elimination in ECMO treated neonates [9].

Augmentation of ECMO treatment with CVVH has been shown to improve clinical outcome of the treatment and reduce costs [36], therefore CVVH during ECMO has become standard clinical practice in our institution. Since the two ECMO datasets could not be merged due to the conflicting results and as the conditions seen in the study of dataset 6 resemble current clinical practice best, only the NPDE analysis performed with this dataset is shown (figure 7). The NPDE analysis of this dataset indicates a reasonable prediction of median morphine and metabolite concentrations with limited bias over time and over the log value of the concentration range in patients on ECMO treatment with CVVH. Bearing in mind the considerable difference in the patient populations in the internal dataset and in this dataset this result is quite remarkable.

Previously two population PK models for morphine in patients on ECMO treatment were developed based on dataset 5 [8,9]. These studies showed ECMO treatment to affect some of the clearance parameters and the distribution volumes. Also the maturation rates of some of these parameters were shown to be different from postoperative and ventilated patients. Possibly the influence of changes in clearance and distribution volume counterbalance each other during ECMO treatment, resulting

in morphine and metabolite concentrations that are similar to those observed in postoperative and ventilated neonates.

The validation of the predictive performance of the original morphine PK model in these datasets does not imply this model to be optimal in this population, as such optimization would require a laborious separate analysis. The sole purpose of performing this validation procedure was to investigate whether the model-derived dosing algorithms, which are based on the covariate model, could also be suitable in patients on ECMO treatment. By confirming the models predictive performance in neonates on ECMO treatment augmented by CVVH, it is suggested that dosing morphine in $\mu g/kg^{1.5}/h$ could be appropriate in these patients as well.

4.5 Conclusion

In the current analysis the predictive performance of a previously published paediatric PK model for morphine and its metabolites was tested externally in new datasets from postoperative patients, patients on artificial ventilation and patients on ECMO treatment ranging from preterm and SGA neonates to infants of one year. The predictive performance was found to be good in the postoperative and ventilated patients and in patients on ECMO treatment with CVVH. Herewith the suitability of the original model for simulation purposes is confirmed. The establishment of the predictive performance of the model in this study justifies the next step in developing new dosing recommendations, namely a prospective clinical trial. Dosing algorithms previously derived from the original model (Chapter 3) are currently being evaluated at our facilities in postoperative patients younger than one year (Dutch trial registration number NTR1438 [37]) and in neonates on ECMO treatment with CVVH (NTR2180 [37]).

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