Clin Drug Investig (2013) 33:523–534
DOI 10.1007/s40261-013-0097-6

ORIGINAL RESEARCH ARTICLE

Developmental Changes in Morphine Clearance Across the Entire Paediatric Age Range are Best Described by a Bodyweight-Dependent Exponent Model

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Published online: 11 June 2013

Abstract
Background and Objective Morphine clearance has been successfully scaled from preterm neonates to 3-year-old children on the basis of a bodyweight-based exponential (BDE) function and age younger or older than 10 days. The aim of the current study was to characterize the developmental changes in morphine clearance across the entire paediatric age range.
Methods Morphine and morphine-3-glucuronide (M3G) concentration data from 358 (pre)term neonates, infants, children and adults, and morphine concentration data from 117 adolescents were analysed using NONMEM 7.2. Based on available data, two models were developed: I. using morphine data; II. using morphine and M3G data.
Results In model I, morphine clearance across the paediatric age range was very well described by a BDE function in which the allometric exponent decreased in a sigmoidal manner with bodyweight (BDE model) from 1.47 to 0.88, with half the decrease in exponent reached at 4.01 kg. In model II, the exponent for the formation and elimination clearance of M3G was found to decrease from 1.56 to 0.89 and from 1.06 to 0.61, with half the decrease reached at 3.89 and 4.87 kg, respectively. Using the BDE model, there was no need to use additional measures for size or age.
Conclusion The BDE model was able to scale both total morphine clearance and glucuronidation clearance through the M3G pathway across all age ranges between (pre)term neonates and adults by allowing the allometric exponent to decrease across the paediatric age range from values higher than 1 for neonates to values lower than 1 for infants and children.

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1 Introduction

The pharmacokinetics of morphine have been widely studied in the paediatric population using different approaches and modeling techniques [1]. In paediatric population pharmacokinetic models, bodyweight was reported to be the most significant covariate for morphine clearance [2–4]. While a variety of bodyweight-based functions have been used, i.e. exponential equations using a 0.75 fixed exponent or an estimated exponent of 1.44, additional age-related variables were needed in all models to adequately describe clearance across paediatric age

ranges [1–5]. This may be explained by the fact that single exponent functions based on bodyweight may not be expected to be suitable for the prediction of drug clearance in children of all ages [6, 7]. However, as bodyweight and age are correlated in a complex and highly nonlinear manner as part of a child's growth and development, the use of both bodyweight and age as covariates on a single parameter may harm the predictive performance of the resulting model [8, 9]. Additionally, many studies on morphine clearance in paediatrics are limited to small age ranges [2–4, 10], and no study has proven adequate extrapolation potential outside the studied age range. This strongly limits the development of unambiguous continuous dosing guidelines for children.

Recently, a bodyweight-dependent exponent (BDE) model was developed to scale clearance from preterm neonates to adults [11]. Using this function, clearance scales with bodyweight on the basis of an allometric function. However, because the allometric exponent is allowed to vary with bodyweight, the BDE function offers maximal flexibility to capture different maturation rates at varying stages of paediatric development [11]. Typically, this exponent k has a certain value k_0 at a hypothetical bodyweight of 0 kg, after which it decreases with bodyweight sigmoidally according to a maximum effect (E_{max}) model [11]. More recently, simplified decreasing functions on the basis of a power function have been proposed when a smaller weight range is concerned (i.e. lack of data for preterm neonates) [12]. In both analyses, the BDE function proved to optimally describe the changes in clearance between neonates and adults using bodyweight without the need for a secondary age-related covariate [11, 12].

Therefore, in the current study, we analysed morphine concentration–time profiles from 475 preterm and term neonates, infants, children, adolescents and adults, with the aim of characterizing developmental changes in morphine clearance across the entire human lifespan. Given the strong evidence for a high maturation rate (exponent of 1.44) in children under the age of 3 years [4, 10], and the need to reach a plateau for the maturation rate at older age ranges with a lower value for the exponent, the recently developed BDE model was applied [11]. This analysis also allows us to study whether the changes in clearance of morphine and its metabolite can be described by the BDE function without subsequent need for additional age-related covariates.

2 Methods

2.1 Subjects

Morphine concentration–time data from a total of 475 subjects participating in eight different clinical studies [13–20] were included in the current analysis. Studies represented three age groups: neonates and young children (0–3 years), older children and adolescents (6–15 years) and adults (18–36 years) (Table 1). The studies were performed at different centres in different countries, resulting in the administration of two different morphine salts. To compare the administered doses, the amount of administered morphine base was calculated for each individual in each study.

2.1.1 Neonates and Young Children

Morphine and morphine-3-glucuronide (M3G) metabolite concentrations in 338 paediatric patients (age 0.1–1,070 days; bodyweight 0.57–16.8 kg) from six different studies [13–18] were included in our analysis. Detailed demographic and clinical information on the patients in the six studies can be found in the original publications [13–18]. Table 1 summarizes the patient demographics from these six studies.

2.1.2 Older Children and Adolescents

The study in older children and adolescents was a prospective, genotype-blinded, clinical observational study to investigate the impact of race and genotype on morphine clearance [19]. Children of all races aged 6–15 years scheduled for elective adenotonsillectomy with American Society of Anesthesiologists (ASA) physiological status 1 or 2 were included. As African-American children were found to have higher morphine clearance than Caucasian children [19], we excluded 29 African subjects from the total of 146 subjects, leaving 117 patients aged between 6 and 15 years with a bodyweight between 17.9 and 79.5 kg for our modeling analysis (Table 1).

2.1.3 Adults

This prospective study compared the analgesic effects of a bolus and short infusion of morphine in healthy male and female volunteers [20]. Twenty healthy non-obese adults were given 0.1 mg/kg intravenous bolus of morphine followed by an infusion of 0.03 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 h, after which 15 samples per individual were collected.

2.2 Pharmacokinetic Modeling

The population pharmacokinetic analysis was performed with the non-linear mixed effects modeling software NONMEM® version 7.2. (ICON Development Solutions, Ellicott City, MD, USA) using the first-order conditional estimation method with the interaction option (FOCEI). The S-PLUS interface for NONMEM® (LAP&P Consultants BV, Leiden, NL), S-Plus (version 8.1, Insightful

Table 1 Overview of the datasets used to develop the population pharmacokinetic model for parent morphine (Model I) and for parent morphine and M3G metabolite (Model II)

Age group	Population	*n*	Weight (kg)	Age	Samples (*n*)	References
Neonates and young children	Postoperative term neonates, infants and children	185	1.9–16.8	0.1–1070 days	Morphine: 618 M3G: 512	[13]
	Preterm and term neonates on artificial ventilation	63	0.56–3.87	0.1–6.7 days	Morphine: 110 M3G: 132	[14]
	Preterm neonates on artificial ventilation	41	0.64–3.55	0.1–13 days	Morphine: 88 M3G: 111	[15]
	Postoperative term neonates and infants	28	1.7–9.3	0.1–294 days	Morphine: 98 M3G: 122	[16]
	Postoperative term neonates and infants	9	2.64–8.1	1–271 days	Morphine: 16	[17]
	Term neonates and infants on artificial ventilation	12	2.2–8.7	3–354 days	Morphine: 8 M3G: 12	[18]
Older children and adolescents	Older children and adolescents after adenotonsillectomy	117	17.9–79.5	6–15 years	Morphine: 264	[19]
Adults	Healthy adults	20	56–85	20–36 years	Morphine: 300 M3G:300	[20]

M3G morphine-3-glucuronide

Software, Seattle, WA, USA), PsN, Pirana and R (version 2.14.2) were used to visualize the output and evaluate the models.

2.2.1 Structural Model

As morphine concentrations were available for all three age groups, whereas M3G metabolite concentrations were only available in neonates and young children and adults (not in older children and adolescents), two different structural models were used in our pharmacokinetic analysis.

2.2.1.1 Parent Morphine Model (Model I) A two-compartment structural model [4] was applied to the parent morphine concentration data for all three age groups depicted in Table 1.

2.2.1.2 Parent Morphine and M3G Metabolite Model (Model II) A two-compartment structural model for parent morphine and a one-compartment structural model for M3G [4] was applied to parent morphine and M3G metabolite concentration data that were available in datasets of neonates and young children and the adult population (Table 1).

2.2.2 Statistical Model

The inter-individual variability of morphine and M3G clearance and volumes of distribution was assumed to be log-normal distributed, and expressed as (Eq. 1):

$$\theta_i = \theta_{\mathrm{TV}} \times e^{\eta_i}, \eta_i \sim N(0, \omega^2) \quad (1)$$

where θ_i is the individual parameter value for the *i*th individual, θ_{TV} is the population parameter value, and η_i is a random variable from a normal distribution with mean zero and variance ω^2.

All concentration data were log-transformed in the analysis. An additive residual error model was applied on the log-transformed data, which corresponds to the proportional error on the linear scale, expressed as (Eq. 2):

$$\ln C_{ij} = \ln C_{\mathrm{pred}_{ij}} + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2) \quad (2)$$

where C_{ij} is the observed concentration of the *i*th individual at time *j* and $C_{\mathrm{pred}_{ij}}$ is the corresponding predicted concentration. ε_{ij} is a random variable from a normal distribution with mean zero and variance σ^2.

2.2.3 Covariate Model

The BDE function, as shown in Eq. 3, was applied to the total morphine clearance in Model I and the formation clearance of M3G and the elimination clearance of the M3G in Model II:

$$\mathrm{CL}_i = \mathrm{CL}_{\mathrm{Std}} \times \left(\frac{\mathrm{BW}_i}{70}\right)^k, \quad k = k_0 - \frac{k_{\max} \times \mathrm{BW}_i^{\gamma}}{k_{50}^{\gamma} + \mathrm{BW}_i^{\gamma}} \quad (3)$$

in which CL_i is clearance in the *i*th individual with bodyweight BW_i; $\mathrm{CL}_{\mathrm{Std}}$ is the clearance in a standardized adult with a bodyweight of 70 kg; BW_i is bodyweight of an individual *i*; *k* is the exponent; k_0 is the value of the exponent at a theoretical bodyweight of 0 kg; $k_{\max}$ is the

maximum decrease of the exponent; k_{50} is the bodyweight at which a 50 % decrease in the maximum decrease of exponent value is attained, and γ is the Hill coefficient determining the steepness of sigmoidal decline in the exponent.

Beside the BDE function for bodyweight that was tested on the different clearance parameters, bodyweight was tested in a linear or power function on other pharmacokinetic parameters, as shown in Eq. 4:

$$\theta_i = \theta_{\text{Std}} \times \left(\frac{\text{BW}_i}{70}\right)^m \quad (4)$$

In this equation, θ_i is the parameter of ith individual with bodyweight BW_i; θ_{Std} is the parameter standardized adult with a bodyweight of 70 kg; BW_i is bodyweight of an individual i. In case of a power function, m represents the exponent value, while for a linear relationship m is fixed to 1.

The covariate was included in the model if the decrease in objective function value (OFV) was greater than 7.88 points, which corresponds to $p < 0.005$ in the Chi-square test. In addition, criteria as defined under the Model Validation section were considered.

2.3 Model Validation

The two models were validated internally using five criteria that were recently proposed for paediatric population model evaluation [5]. (i) It was checked whether the coefficient of variation (CV) of the parameter estimates either from the covariance step in NONMEM® or from stratified bootstrap resampling results was less than 50 %. (ii) The basic diagnostic plots, and particularly the plots of the observed versus population predicted concentrations stratified for age, were visually assessed for bias. (iii) The η-shrinkage calculated according to Karlsson and Savic was considered [21]. (iv) The individual and population predicted parameters were plotted against bodyweight to evaluate whether the individual predicted parameters were equally distributed around the population predicted parameters. (v) The simulation-based normalized prediction distribution error (NPDE) proposed by Brendel et al. [22] was calculated based on 2,000 simulations of the entire dataset and was evaluated visually for bias and precision.

3 Results

For the analysis, data for 475 subjects varying from preterm and term neonates to adults were available from eight different clinical studies (Table 1). Data for all 475 subjects were used in the model describing the time-course of the parent drug concentration (parent morphine model; Model I), whereas data for 358 individuals in which both morphine and M3G concentrations were available were used to describe the time-course of both morphine and M3G concentration (parent morphine and M3G metabolite model; Model II). A summary of the available datasets is given in Table 1.

A BDE model in which the exponent decreased with bodyweight in a sigmoidal manner [Eq. 3] very well described the developmental changes in total clearance of morphine (CL_T) in the parent morphine model (Model I). Similarly, a BDE model well described changes in the formation clearance of M3G ($\text{CL}_{\text{M, M3G}}$) and the elimination clearance of M3G ($\text{CL}_{\text{E, M3G}}$) across all ages in the parent morphine and M3G metabolite model (Model II). Figure 1 (upper panels) shows the post hoc estimates of total morphine clearance, formation clearance of M3G and elimination clearance of M3G versus bodyweight (η-shrinkage values being 24.9, 18.9 and 20.4 %, respectively). The lower panels in Fig. 1 show how the BDE (k) of total morphine clearance, formation clearance of M3G and elimination clearance of M3G was found to change with bodyweight. For the parent morphine model (Model I), the value of k for CL_T dropped from 1.47 (k_0) at the theoretical bodyweight of 0 kg to 0.88 ($k_0 - k_{\text{max}}$) and reached half this decrease at 4.01 kg (k_{50}) (see Table 2 for estimated parameters for the exponent k). For the parent morphine and M3G metabolite model (Model II), the value of k for $\text{CL}_{\text{M, M3G}}$ dropped from 1.56 (k_0) at the theoretical bodyweight of 0 kg to 0.89 ($k_0 - k_{\text{max}}$) and reached half this decrease at 3.89 kg (k_{50}), while the k-value for $\text{CL}_{\text{E, M3G}}$ dropped from 1.06 (k_0) to 0.61 ($k_0 - k_{\text{max}}$) and reached half this decrease at 4.87 kg (k_{50}) (see Table 3 for estimated parameters for the exponent k).

For CL_T of the parent morphine model (Model I) and $\text{CL}_{\text{M, M3G}}$ and $\text{CL}_{\text{E, M3G}}$ of the parent morphine and M3G metabolite model (Model II), no additional covariates could be identified based on visual inspection of the corresponding inter-individual variability against covariate plot and given the criteria as defined under 'Methods' (Covariate Model and Model Validation). In the parent morphine model (Model I), bodyweight was identified as a covariate in a linear equation for volume of distribution of the central compartment of morphine (V_1), volume of distribution of the peripheral compartments of morphine (V_2), and inter-compartmental clearance (Q) (Table 2). In addition, lower bodyweight normalized population values of Q and V_1 were identified for the older children and adolescents (0.071 L/kg/min and 0.66 L/kg) compared with children younger than 3 years and adults (0.027 L/kg/min and 1.16 L/kg) (Table 2). In the parent morphine and M3G metabolite model (Model II), bodyweight was identified as a covariate in a linear equation for clearance of

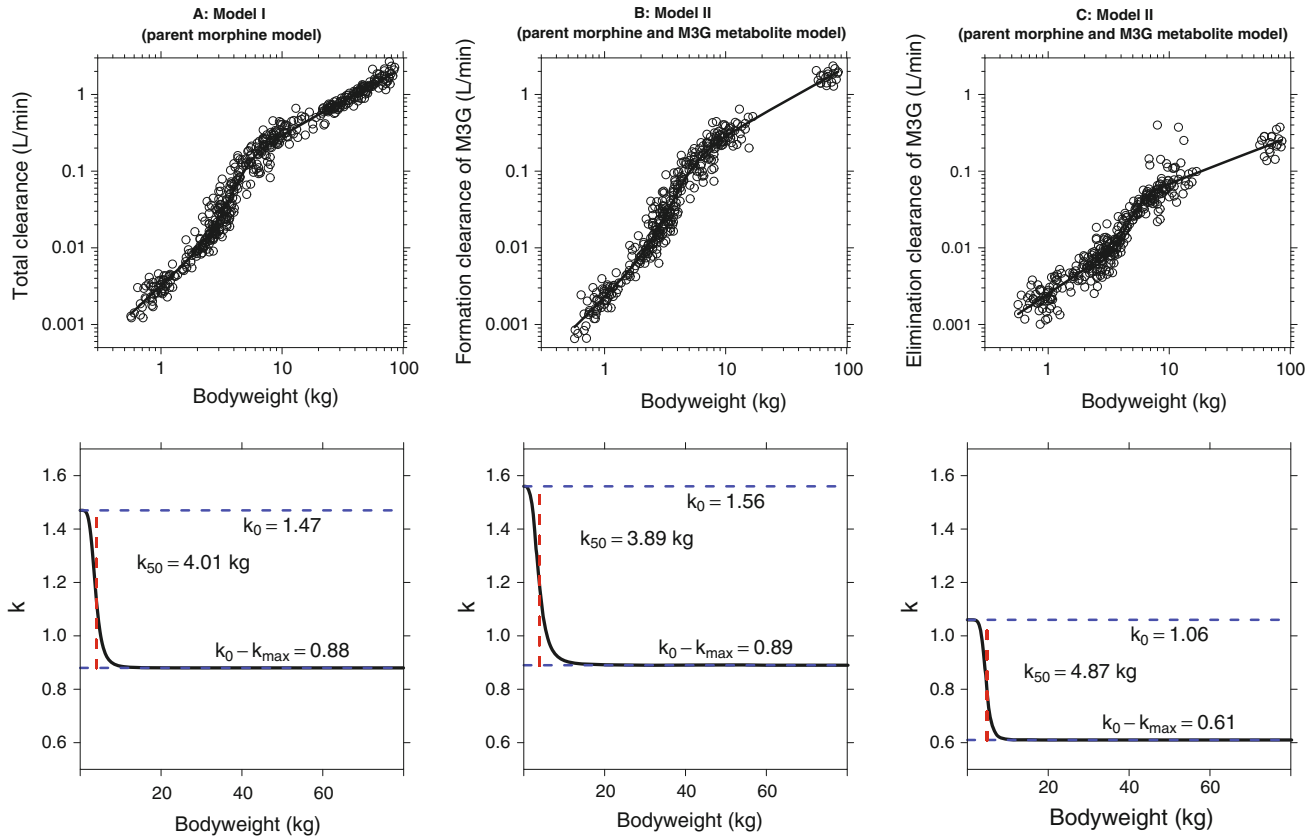

Fig. 1 Post hoc clearance values of total clearance, formation clearance of morphine-3-glucuronide(M3G), and elimination clearance of M3G and values of the corresponding bodyweight-dependent exponent (k) versus bodyweight from Model I (parent morphine model) and Model II (parent morphine and M3G metabolite model). *Upper panels, open circles* are post hoc values of total clearance (**a**), formation clearance of M3G (**b**), or elimination clearance of M3G (**c**); *solid curves* are corresponding model predicted values. *Lower panels*, k is the bodyweight-dependent allometric exponent (Eq. 3) of total clearance (**a**), formation clearance of M3G (**b**), or elimination clearance of M3G (**c**); k_0 is the value of the exponent at a theoretical bodyweight of 0 kg; k_{max} is the maximum decrease of the exponent; k_{50} is the bodyweight at which a 50 % decrease in the maximum decrease of exponent is attained; *upper blue dash line* is the reference line of k_0; *lower blue dash line* is the reference line of $k_0 - k_{max}$; *red vertical dash line* is the reference line of k_{50}

morphine through routes other than M3G (CL_0), V_1, V_2, and Q (Table 3). For the volume of distribution of M3G (V_{M3G}), a population value of 20 L was estimated, which proved in accordance with literature [23] and which was later fixed to this value in order to achieve successful minimization with a covariance step. V_{M3G} was found to vary with bodyweight, which was best described by a power function with an estimated exponent value of 0.71. In both the parent and the parent and metabolite model (Model I and Model II, respectively), no other covariates were identified on any of the other parameters based on the criteria as described in the 'Methods' section (Covariate Model and Model Validation).

Figure 2 shows that both the parent morphine model (Model I) and the parent morphine and M3G metabolite model (Model II) described the morphine and M3G concentration data in all different age groups well. The NPDE analysis as a simulation-based validation method shows that morphine and M3G concentrations in the models were normally distributed around the median prediction and that there was no trend in the NPDE versus TIME and versus the log-transformed individual predicted concentrations (Fig. 3). All parameter estimates and results of the bootstrap validation of the parent morphine model (Model I) and the parent morphine and M3G metabolite model (Model II) are listed in Tables 2 and 3, respectively.

Figure 4 illustrates that postnatal age (PNA) younger or older than 10 days, which was reported as a covariate for morphine glucuronidation clearance in a previous study in children younger than 3 years of age [4], was not a covariate for clearance in the final model of the current study.

4 Discussion

Morphine is metabolized mainly through glucuronidation mediated by the enzyme uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), which was reported to be expressed at very low levels in early life [24–26]. In the past, several models have been developed to describe the

Table 2 Parameter estimates of the parent morphine model (Model I)

Parameter	Estimated value	Bootstrap[a]
Fixed effect		
CL_T (L/min)	$CL_T = TVCL_T \cdot (BW/70)^k$	
$TVCL_T$ (L/min·70 kg)	1.62 (5.3 %)	1.63 (6.1 %)
k	$k = k_0 - k_{max} \cdot BW^\gamma / (k_{50}^\gamma + BW^\gamma)$	
k_0	1.47 (3.7 %)	1.47 (5.8 %)
k_{max}	0.59 (4.7 %)	0.59 (9.3 %)
k_{50} (kg)	4.01 (3.9 %)	4 (4.1 %)
γ	4.62 (9.5 %)	6.4 (88.5 %)
Q (L/min)	$Q = TVQ \cdot (BW/70)$	
TVQ (L/min·70 kg)		
Pop $\neq$ 2	1.9 (9.6 %)	1.95 (11.9 %)
Pop = 2	0.5 (19 %)	0.49 (16.1 %)
V_1 (L)	$V_1 = TVV_1 \cdot (BW/70)$	
TVV_1 (L/70 kg)		
Pop $\neq$ 2	81.2 (7.8 %)	79.16 (6.4 %)
Pop = 2	46 (5.1 %)	45.44 (3.8 %)
V_2 (L)	$Vp = TVV_2 \cdot (BW/70)$	
TVV_2 (L/70 kg)	128 (8 %)	129.91 (7.2 %)
Inter-individual variability		
ω^2 (CL_T)	0.16 (6.9 %)	0.156 (12.9 %)
ω^2 (V_1)	0.25 (27.5 %)	0.24 (43.6 %)
Residual error		
σ^2	0.19 (8.7 %)	0.19 (7.7 %)
σ^2 for time >1900 min	0.46 (113.2 %)	0.79 (76.9 %)

BDE bodyweight-dependent exponent, *BW* bodyweight in kilograms, CL_T total morphine clearance, k BDE on BW for total clearance, k_{max} maximum decrease of the exponent, k_0 BDE at the theoretical bodyweight of zero, k_{50} the BW at which a 50 % decrease in the maximum decrease of exponent is attained, *Pop = 2* population of older children and adolescents, *Pop ≠ 2* population of neonates and young children or adults, Q inter-compartmental clearance, $TVCL_T$ CL_T normalized to BW value of 70 kg; TVQ Q normalized to BW value of 70 kg, TVV_1 V_1 normalized to BW value of 70 kg, TVV_2 V_2 normalized to BW value of 70 kg, V_1 volume of distribution of the central compartment of morphine, V_2 the volume of distribution of the peripheral compartment of morphine, γ the Hill coefficient determining the steepness of sigmoidal decline in the exponent, ω^2 variance of the normal distribution that quantifies the inter-individual variability on the designated parameter according to Eq. 1, σ^2 variance of the normal distribution that quantifies the residual error of the morphine observations according to Eq. 2, σ^2 *for time >1,900 min* variance of the normal distribution that quantifies the residual error of extra additive error for concentrations of morphine when the time after dose is beyond 1,900 min [4]

[a] Bootstrap mean and coefficient of variation percentage

changes in glucuronidation clearance of morphine and to predict its clearance in children for the purpose of dosing guidance [2–4]. Among those models, a model was developed for paediatric patients aged less than 3 years, including preterm and term neonates [4], in which an allometric exponent value of 1.44 for morphine clearance was identified. Additional extensive investigations confirmed this finding using external data [10] and data from another UGT2B7 substrate [27]. Upon these studies, the allometric exponent of 1.44 for UGT2B7-mediated glucuronidation in children under the age of 3 years was proposed to be a system-specific parameter reflecting the maturation of the UGT2B7 enzyme in humans [27, 28]. The current study confirms not only the validity of the exponent value as high as 1.44 in neonates and young infants given the estimated exponent at a hypothetical bodyweight of 0 kg of 1.56 in this study, but also provides a basis for extrapolation to older age ranges by the quantification of the maturation of glucuronidation across the entire paediatric age range with the estimation of a lower exponent for higher bodyweight ranges.

In this study, we successfully scaled morphine clearance from preterm and term neonates to infants, children, adolescents and adults using an allometric function, in which the exponent (k) was allowed to vary with bodyweight in a BDE function (Eq. 3). In both Model I and Model II of our study, the BDE function was able to capture the changes in the clearance parameters (total morphine clearance, formation of M3G, and elimination of M3G), despite the fact that they were highly nonlinear in nature (Fig. 1, upper panels). According to Karlsson and Savic [21], diagnostics based on the empirical Bayes estimates (EBE) should be assessed in combination with corresponding η-shrinkages as they may distort covariate relationships. Based on a simulation study, it was reported that EBE-based diagnostics generally lose their power, with false indications starting to appear at a level of 20–30 % [29]. In our study, the η-shrinkages of total clearance, formation clearance of M3G and elimination clearance of M3G were all below 25 %, which is on the border of what is acceptable. In addition, both the age-stratified goodness-of-fit diagnostic plots (Fig. 2) and simulation-based NPDE diagnostics (Fig. 3) demonstrate good population and individual prediction performance of the final BDE models for concentrations of morphine and its M3G metabolite. Based on these results, it is concluded that the BDE model allows for the description of maturational changes in morphine glucuronidation clearance using a single continuous function, which has not been possible in previous attempts based on the use of allometric equations with single exponents [2–5].

The parameter values of the BDE function, i.e. k_0, k_{max}, k_{50} and γ, were found to be similar for total morphine clearance (parent morphine model; Model I) and formation clearance of M3G (parent morphine and M3G metabolite model; Model II). This result can, in our opinion, be

Table 3 Parameter estimates of the parent morphine and morphine-3-glucuronide (M3G) metabolite model (Model II [based on morphine and M3G concentrations])

Parameter	Estimated value	Bootstrap[a]
Fixed effect		
$CL_{M,\ M3G}$ (L/min)	$CL_{M,\ M3G} = TVCL_{M,\ M3G}\cdot(BW/70)^{k}$	
$TVCL_{M,\ M3G}$ (L/min·70 kg)	1.67	1.66 (5.2 %)
k of $CL_{M,\ M3G}$	$k = k_0 - k_{max}\cdot BW^{\gamma}/\ (k_{50}{}^{\gamma} + BW^{\gamma})$	
k_0 of $CL_{M,\ M3G}$	1.56	1.56 (4.1 %)
k_{max} of $CL_{M,\ M3G}$	0.67	0.67 (6.8 %)
k_{50} of $CL_{M,\ M3G}$ (kg)	3.89	3.91 (3.8 %)
γ of $CL_{M,\ M3G}$	3.61	3.94 (21 %)
$CL_{E,\ M3G}$ (L/min)	$CL_{E,\ M3G} = TVCL_{E,\ M3G}\cdot(BW/70)^{k}$	
$TVCL_{E,\ M3G}$ (L/min·70 kg)	0.23	0.22 (7.1 %)
k of $CL_{E,\ M3G}$	$k = k_0 - k_{max}\cdot BW^{\gamma}/(k_{50}{}^{\gamma}+ BW^{\gamma})$	
k_0 of $CL_{E,\ M3G}$	1.06	1.07 (9 %)
k_{max} of $CL_{E,\ M3G}$	0.45	0.45 (11.8 %)
k_{50} of $CL_{E,\ M3G}$ (kg)	4.87	4.68 (6.4 %)
γ of $CL_{E,\ M3G}$	6.84	9.49 (78.3 %)
CL_0 (L/min)	$CL_0 = TVCL_0\cdot(BW/70)$	
$TVCL_0$ (L/min·70 kg)	0.06	0.06 (40.3 %)
Q (L/min)	$Q = TVQ\cdot(BW/70)$	
TVQ (L/min·70 kg)	4.2	4.12 (4.9 %)
V_1 (L)	$V_1 = TVV_1\cdot(BW/70)$	
TVV_1 (L/70 kg)	29.3	27.67 (13.5 %)
V_2 (L)	$V_2 = TVV_2\cdot(BW/70)$	
TVV_2 (L/70 kg)	155	155.29 (7.1 %)
V_{M3G} (L)	$V_{M3G} = TVV_{M3G}\cdot(BW/70)^{p}$	
TVV_{M3G} (L/70 kg)	20 FIX	20 FIX
p	0.71	0.71 (6.2 %)
Inter-individual variability		
ω^2 $CL_{M,\ M3G}$	0.20	0.20 (15 %)
ω^2 $CL_{E,\ M3G}$	0.19	0.18 (20.5 %)
ω^2 CL_0	0.07	0.26 (173.3 %)
ω^2 V_1	0.51	0.47 (26.4 %)
ω^2 V_2	0.31	0.31 (43.6 %)
ω^2 V_{M3G}	0.37	0.39 (37.7 %)
Residual error		
σ^2 additive morphine	0.20	0.19 (8.1 %)
σ^2 additive M3G	0.14	0.13 (10.1 %)
σ^2 for time >1,900 min	1.85	1.92 (32.5 %)

BDE bodyweight-dependent exponent, *BW* bodyweight in kilograms, $CL_{E,\ M3G}$ elimination clearance of morphine-3-glucuronide, $CL_{M,\ M3G}$ formation clearance of morphine-3-glucuronide, CL_0 clearance of morphine via other elimination routes, k BDE of BW $CL_{M,\ M3G}$ or $CL_{E,\ M3G}$, k_{max} maximum decrease of the exponent, k_0 BDE at the theoretical BW of zero, k_{50} the BW at which a 50 % decrease in the maximum decrease of exponent is attained; *M3G* morphine-3-glucuronide, p exponent value of the power function of BW for V_{M3G}, Q inter-compartmental clearance, $TVCL_{E,\ M3G}$ $CL_{E,\ M3G}$ normalized to BW value of 70 kg, $TVCL_{M,\ M3G}$ $CL_{M,\ M3G}$ normalized to BW value of 70 kg, $TVCL_0$ CL_0 normalized to BW value of 70 kg, TVQ Q normalized to BW value of 70 kg, TVV_{M3G} V_{M3G} normalized to BW value of 70 kg, TVV_1 V_1 normalized to BW value of 70 kg, TVV_2 V_2 normalized to BW value of 70 kg, V_{M3G} volume of distribution of the M3G, V_1 the volume of distribution of the central compartment of morphine, V_2 the volume of distribution of the peripheral compartment of morphine, γ is the Hill coefficient determining the steepness of sigmoidal decline in the exponent, ω^2 variance of the normal distribution that quantifies the inter-individual variability on the designated parameter according to Eq. 1, σ^2 variance of the normal distribution that quantifies the residual error of the morphine or M3G observation according to Eq. 2, σ^2 *for time >1,900 min* variance of the normal distribution that quantifies the residual error of extra additive error for concentrations of morphine or M3G when the time after dose is beyond 1,900 min [4]

[a] Bootstrap mean and coefficient of variation percentage

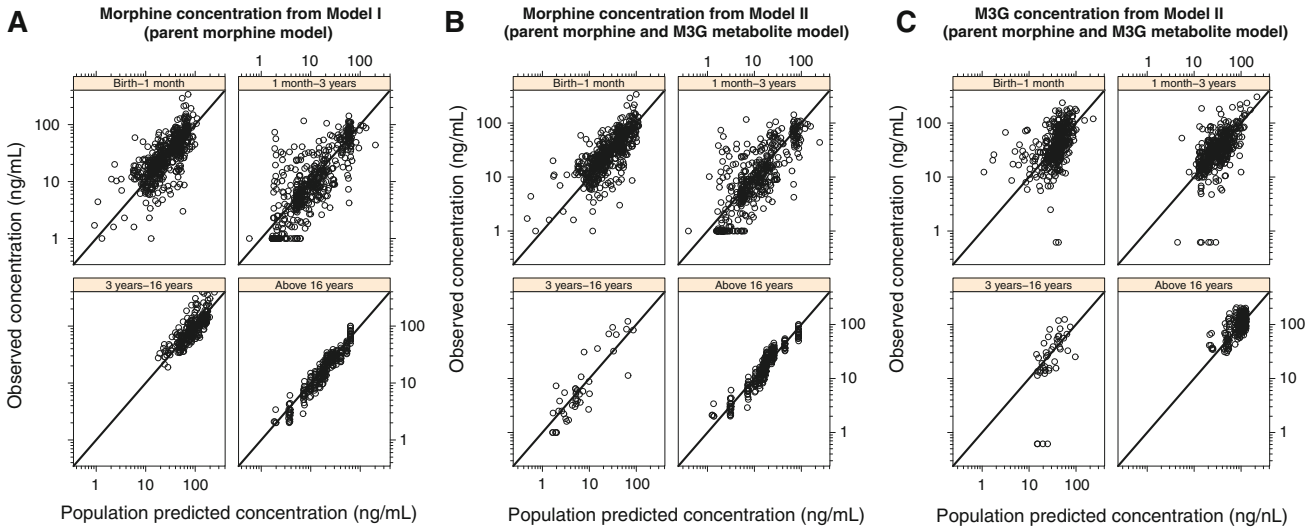

Fig. 2 Age-stratified observed versus population predicted log-transformed concentrations of morphine from Model I (parent morphine model) and of parent morphine and morphine-3-glucuronide (M3G) metabolite from Model II (parent morphine and M3G metabolite model)

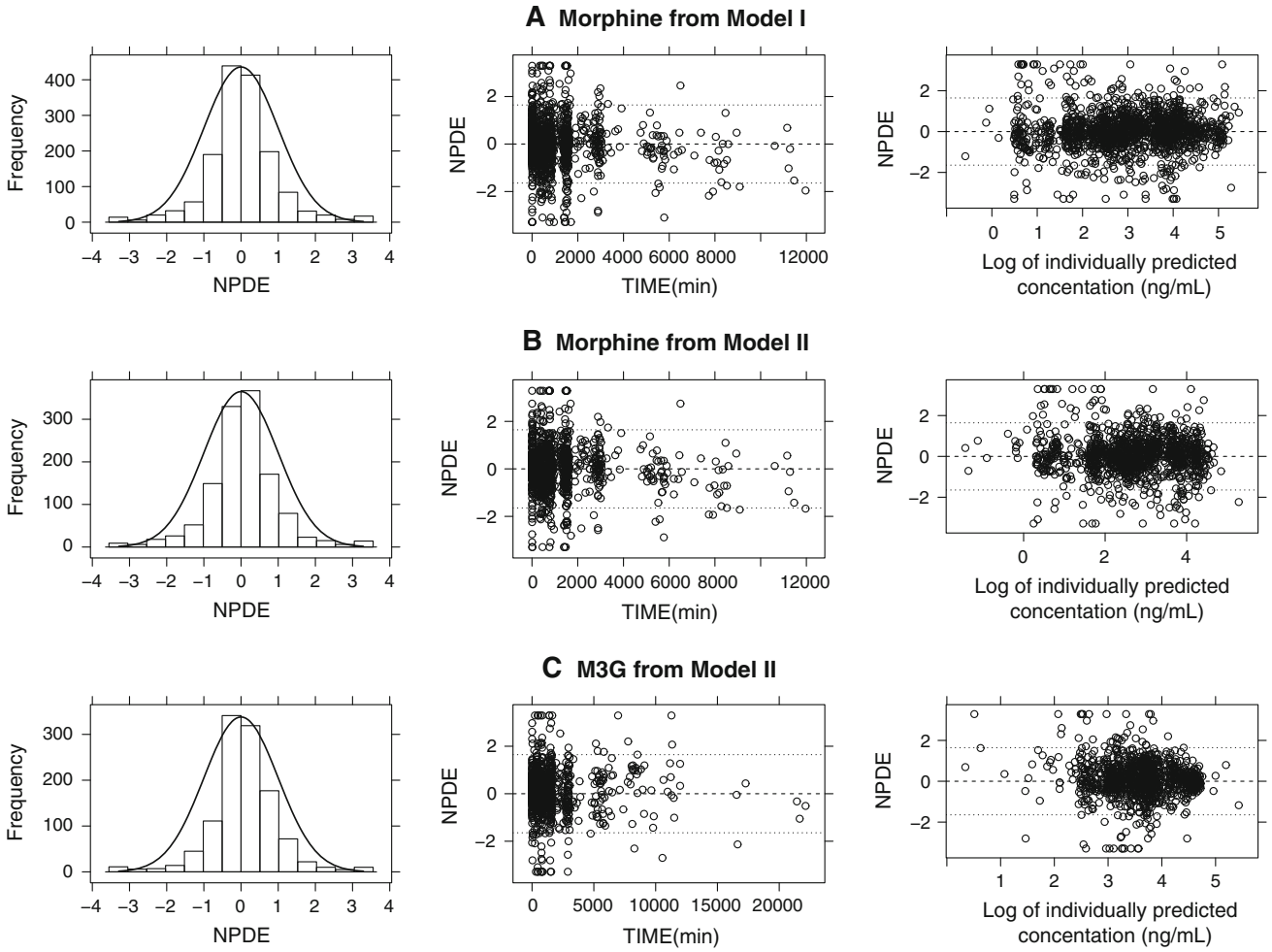

Fig. 3 Normalized prediction distribution error (NPDE) results of morphine concentrations from Model I (parent morphine model) and parent morphine and morphine-3-glucuronide (M3G) metabolite concentrations from Model II (parent morphine and M3G metabolite model)

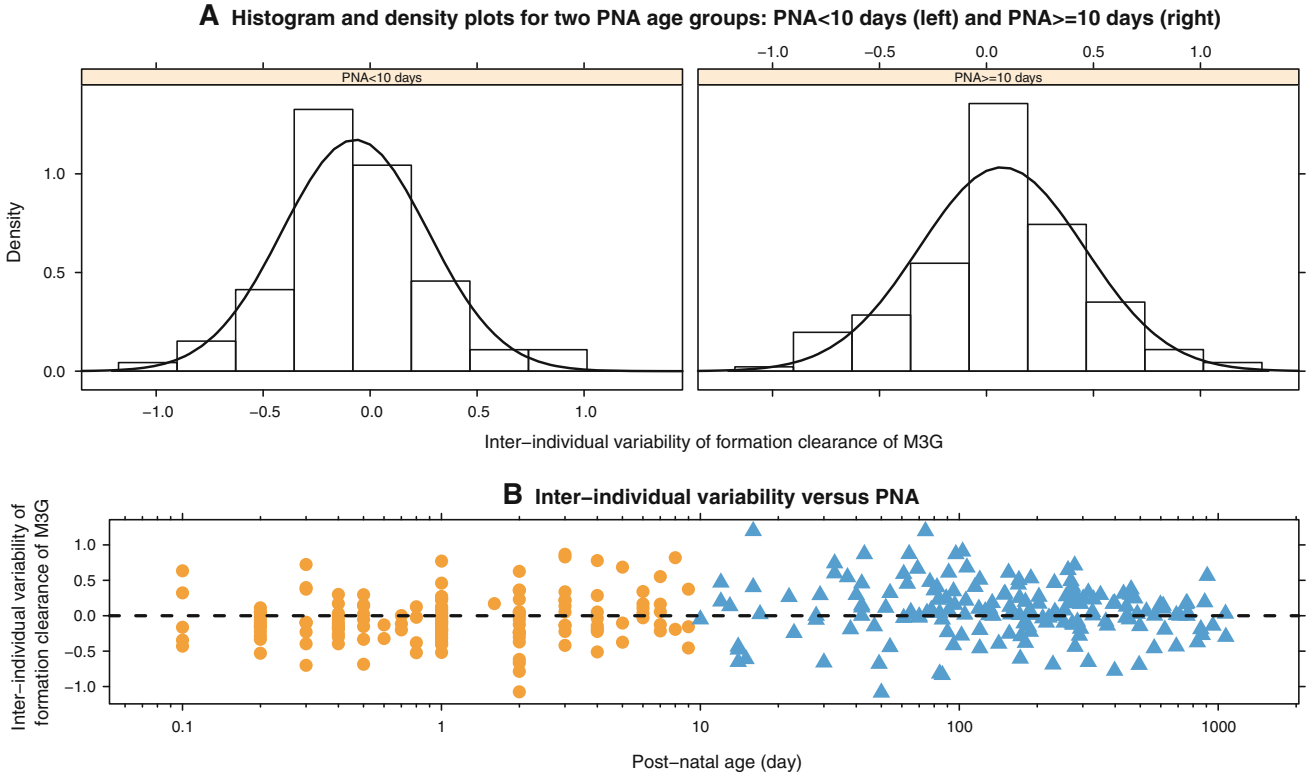

Fig. 4 Inter-individual variability of formation clearance of morphine-3-glucuronide (M3G) from Model II (parent morphine and M3G metabolite model) stratified by postnatal age (PNA) of 10 days. *Orange filled circle* PNA <10 days; *blue filled triangle* PNA ≥10 days

explained by the fact that M3G is the major metabolite of morphine, and glucuronidation of morphine is the rate-limiting step in the clearance of morphine. On the contrary, these sigmoidal equations describing the changes in the exponent *k* differed between the formation and elimination of M3G (Fig. 1, lower panel a and b vs. c). In our view, these results can be explained by differences in maturation of the glucuronidation of morphine versus the renal elimination of M3G. Even though we do not intend to enforce any physiological meaning on the parameters in the BDE function, as the aim of this analysis was primarily to most optimally describe the observations from preterm neonates to adults, this limitation does not, in our opinion, preclude studies in which the parameters of the BDE function reported for morphine glucuronidation in this study are explored for the prediction of maturational changes in clearance of morphine or other drugs that are glucuronidated. Similarly, the parameters of the BDE function for the renal excretion of the M3G metabolite can be explored for its predictive value for the maturation in excretion of other renally excreted compounds, as this approach may largely accelerate paediatric data analysis [27, 28].

Previously, for children younger than 3 years of age, PNA of less than 10 days was identified as a separate covariate for formation clearance of M3G, M6G and their corresponding elimination clearances in addition to the allometric scaling function with an exponent of 1.44 [4]. While it has been suggested before that single allometric exponent functions would not be suitable for the prediction of drug clearance in children of different age groups [6], different publications have confirmed this conclusion by reporting that an additional covariate function on the basis of an age-related covariate was needed when using single exponent functions [2–4]. In our study, we found an exponent that changed with bodyweight from an initial value at a hypothetical bodyweight of 0 kg of 1.47 and 1.56 for total clearance and formation clearance of M3G, respectively. While the initial value is in good agreement with the previously obtained value of 1.44, in the current analysis, no additional age- or weight-related covariates could be identified after inclusion of the (BDE) covariate model. From these results, it seems that the changes that were accounted for by the inclusion of the additional covariate relationship based on PNA [4] are now captured by the BDE function, in which the exponent was allowed to change with bodyweight, being of specific relevance in the youngest age ranges (Fig. 4). In this respect, Fig. 5 illustrates these findings with a graphical comparison of post hoc values for glucuronidation clearance of morphine to M3G versus bodyweight between the previous model in

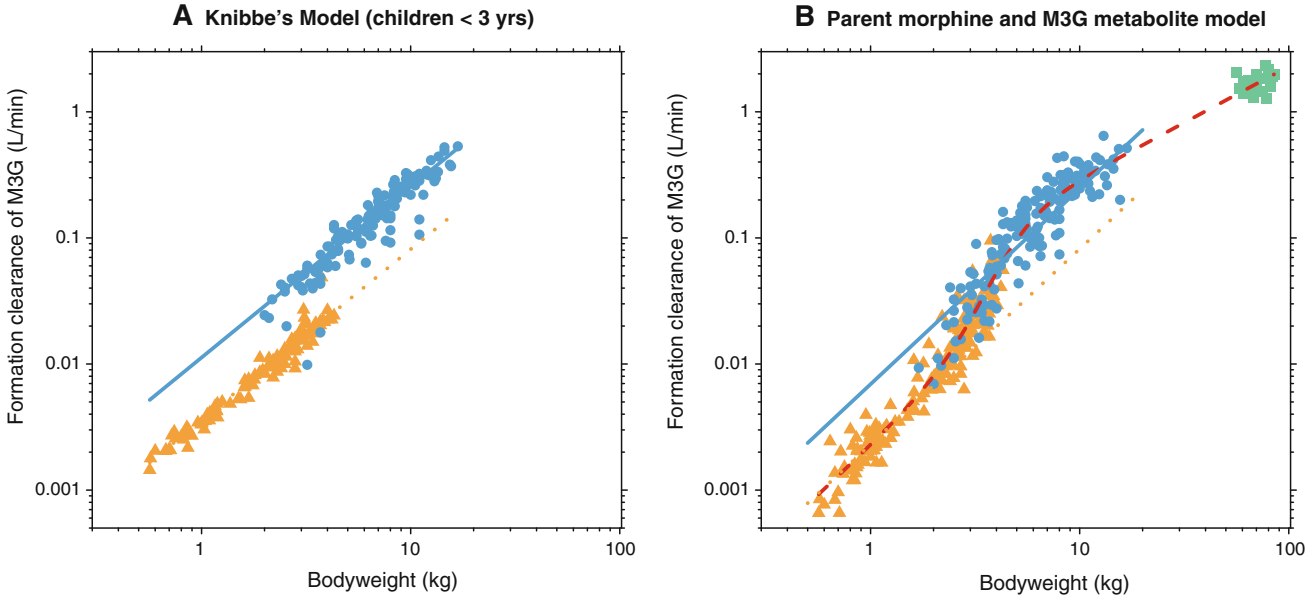

Fig. 5 Comparison of formation clearance of morphine-3-glucuronide (M3G) versus bodyweight in log-log scale between current Model II (parent morphine and M3G metabolite model) that included all age ranges except for older children and adolescents (**b**) and a previously published population model for morphine in children younger than 3 years by Knibbe et al. [4] (**a**). *BDE* bodyweight-dependent exponent, *PNA* postnatal age. **a** *Orange filled triangle* children with PNA <10 days; *blue filled circle* children with PNA ≥10 days; *orange dotted line* Knibbe's model [4] predicted clearance curve for PNA <10 days CL (L/min) = $0.00348 \times BW^{1.44}$); *blue solid line* Knibbe's model [4] predicted clearance curve for PNA ≥10 days CL (L/min) = $0.00862 \times BW^{1.44}$). **b** *Orange filled triangle* children with PNA <10 days; *blue filled circle* children with PNA ≥10 days; *green filled square* adults; *orange dotted line* simulated population clearance curve for PNA <10 days (CL (L/min) = $0.0023 \times BW^{1.56}$); *blue solid line* simulated population clearance curve for PNA ≥10 days (CL (L/min) = $0.0069 \times BW^{1.56}$); *red dash line* the BDE model predicted clearance curve of Model II in which,

$$CL_i(L/min) = 1.67 \times \left(\frac{BW_i}{70}\right)^{k_i}, \quad k_i = 1.56 - \frac{0.67 \times BW_i^{3.61}}{3.89 + BW_i^{3.61}}$$

children younger than 3 years [4] and Model II. In the figure, two parallel lines are placed with different intercepts for subjects with PNA <10 days and PNA ≥10 days at the lower end of the bodyweight range from our study (Fig. 5b), and were found to be quite similar to the patterns described by the previous model (Fig. 5a). The two simulated lines in Fig. 5b have slope values of 1.56, which corresponds with k_0 in the BDE function for $CL_{M,\ M3G}$, and can roughly describe the changes in M3G formation clearance in children in two subgroups (PNA >10 days and PNA <10 days) up to a bodyweight of 10 kg. From this figure, it seems that applying an allometric function in which the exponent is allowed to vary with bodyweight itself results in an optimal description of the varying rates of maturation of glucuronidation clearance of morphine across all age ranges without the need for additional age-based covariates.

The development of the BDE model was triggered by reports that single exponent functions are not suitable for the prediction of drug clearance in children of all age ranges [6] and the idea of using a continuous function describing clearance across a large age span without the need for an additional age-based function [11]. Besides application to propofol [11], this BDE model has been successfully applied to busulfan [12] and midazolam [30], albeit in a simplified power equation ($k = \alpha \times BW^{-\beta}$). However, in the current analysis on morphine glucuronidation clearance between preterm neonates and adults, the full sigmoidal BDE model was more appropriate. This was the result of the S-shape in the double log plot of clearance versus bodyweight (Fig. 1), which can be captured by the E_{max} function with Hill factor of the full BDE model [11], but not by the simplified function that consists of a power function [12, 30]. From these results it seems that the choice for a full BDE model, which was applied in this study and for propofol, or for a simplified BDE model, as applied for busulfan and midazolam, is related to both the age range studied and the properties of the drug. Further study of the BDE model on datasets of other drugs across the entire paediatric age range will demonstrate the cases in which the simplified or full BDE model is applicable. In any case, the choice for the final model should depend on the observed data in this data-driven approach, whereby the model with the lowest number of parameters should be chosen (the principle of parsimony).

5 Conclusions

In this study, developmental changes in total morphine clearance were described in 475 preterm and term neonates, infants, children, adolescents and adults using an allometric function, in which the exponent decreased with bodyweight in a sigmoidal manner from 1.47 for preterm neonates to 0.88 in adults, with no need to use other body size or age-based measures. Similarly, we identified values for the exponent for formation clearance of M3G to vary from 1.56 to 0.89, while these values varied from 1.06 to 0.61 for elimination of M3G. From these results, it can be concluded that an allometric function with a BDE may be of great value when scaling clearance of drugs across the entire paediatric age range.

Acknowledgments This study was performed within the framework of Top Institute Pharma project number D2-104. The work of C.A.J. Knibbe is supported by the Innovational Research Incentives Scheme (Veni grant, July 2006) of the Dutch Organization for Scientific Research (NWO). The clinical study on morphine pharmacokinetics in older children and adolescents was supported in part by USPHS Grant #UL1 RR026314 from the National Center for Research Resources, NIH and with the Place Outcomes Research Award and Translational Research Award (PI: Sadhasivam) and was supported by the Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA. The authors would like to thank Dr Richard van Lingen, Dr Caroline van der Marel, Professor Imti Choonara and Professor Anne Lynn for their willingness to share their morphine and morphine-3-glucuronide data in children in this project.

Conflicts of interest Chenguang Wang, Senthilkumar Sadhasivam, Elke H.J. Krekels, Albert Dahan, Dick Tibboel, Meindert Danhof, Alexander A. Vinks and Catherijne A.J. Knibbe declare no conflicts of interest.

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