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Size does matter : drug glucuronidation in children

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Chapter 9

Prediction of Morphine Clearance in the Paediatric Population: How Accurate are the Available Pharmacokinetic Models?

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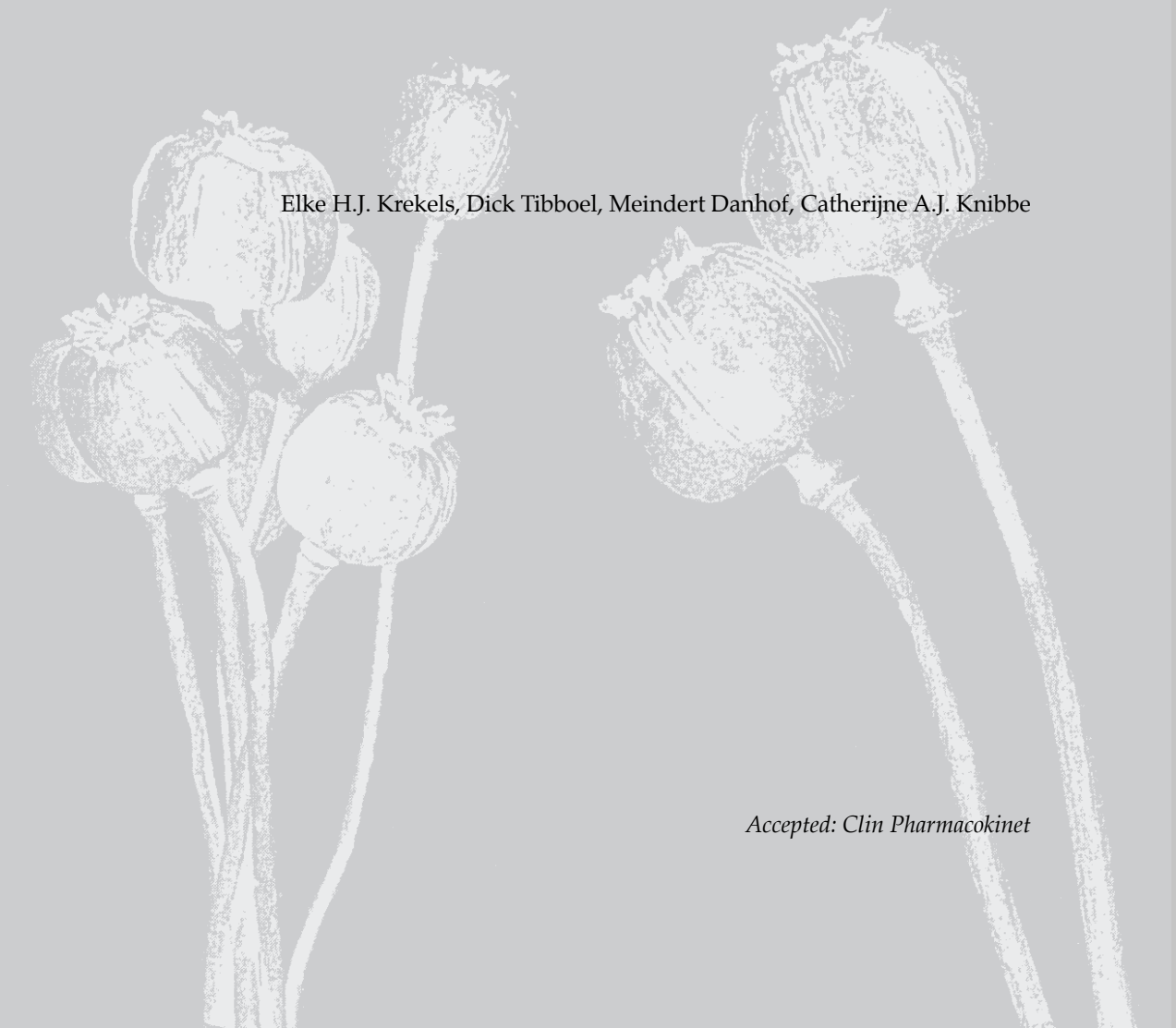

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Abstract

The pharmacokinetics of morphine in paediatrics have been widely studied using different approaches and modeling techniques. In this review, we explore advantages and disadvantages of the different data analysis techniques that have been applied, with specific focus on the accuracy of morphine clearance predictions by reported paediatric pharmacokinetic models.

Twenty paediatric studies reported a wide range in morphine clearance values using traditional rather descriptive methods. Clearance values were expressed per kilogram bodyweight, while maturation in clearance was described by comparing mean clearance per kg bodyweight between age-stratified subgroups. Population modeling allows for the analysis of sparse data thereby limiting the burden to individual patients. Using this technique, continuous maturation profiles can be obtained on the basis of either fixed allometric scaling or comprehensive covariate analysis. While the models based on fixed allometric scaling resulted in complex maturation functions, all three paediatric population models for morphine yielded quite similar clearance predictions. The largest difference in clearance predictions between these three population models occurred in the first months of life, particularly in preterm neonates. Morphine clearance predictions by a physiologically-based pharmacokinetic model were based on many continuous equations describing changes in underlying physiological processes across the full paediatric age-range, and resulted in similar clearance predictions as well. Preterm neonates could however not be integrated in this model.

In conclusion, the value of paediatric pharmacokinetic models is mostly dependent on clearance predictions and population concentration predictions, rather than on the individual description of data. For most pharmacokinetic models however, the assessment of model performance was very limited and for only one model was the accuracy of morphine clearance predictions as well as population concentration predictions confirmed by formal evaluation and validation procedures.

9.1 Background

Dosing guidelines for children have originally been scaled from adult doses using functions related to body size (i.e. bodyweight). After years of clinical experience, these dosing guidelines are often formalized in (national) formularies. Research necessary to develop evidence-based, rather than consensus-based dosing algorithms for the paediatric population is complicated by practical, ethical, and legal constraints. However, advances in pharmacokinetic and pharmacodynamic analyses and the enormous increase in computing capacities of processors over the past few decades have opened up new possibilities in data analysis and data aggregation yielding novel opportunities for paediatric pharmacological investigations.

Morphine is commonly prescribed for the paediatric population in hospital settings. Morphine clearance, its variability, and the maturation in this parameter have been extensively studied across the paediatric population. This has lead to the publication of a wide range of paediatric morphine clearance values, obtained with traditional methods as well as with the new computing-intensive modeling methodologies. Irrespective of the methodology used, reported clearance values should be representative for the studied population, because they provide the basis for paediatric dose adjustments and clinical decision making. Therefore, it is crucial that these values are both accurate and predictive for the next unstudied individual represented by the studied population.

Morphine is predominantly eliminated through glucuronidation by UGT2B7 [1–3], thus morphine clearance directly reflects the formation of its two major metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The metabolites are cleared through renal elimination and reduced renal function may result in accumulation of the metabolites. Since M3G and M6G are considered to be pharmacologically active [4–6], the fate of the metabolites after formation through morphine glucuronidation of is of clinical importance. However, as only a limited number of publications have addressed the pharmacokinetics of the morphine metabolites in addition to the pharmacokinetics of morphine, the current review is limited to total morphine clearance.

In this review, reported paediatric morphine clearance values and the maturation in this parameter in the paediatric population are evaluated. Morphine clearance values obtained using the traditional methods will be discussed after which the focus will shift to results obtained with the more recent computing-intensive modeling approaches such as population pharmacokinetic modeling and physiologically-based pharmacokinetic modeling. General advantages and disadvantages of the different analysis approaches are explored and details of the different published pharmacokinetic morphine models are discussed. The predictive value of the models for a 'new' patient represented by the

studied population, and thus the suitability of the models for simulation purposes for a population of patients with similar characteristics as the studied population, is assessed in particular. The assessment of the accuracy of model predictions is mainly based on the visual comparison of population concentration predictions *versus* clinically observed concentrations, while the accuracy of clearance predictions is based on the Mean Prediction Errors (MPE) of the population clearance values compared to individual clearances.

9.2 Methods

Pubmed was searched in November 2011 for original research on morphine clearance in the paediatric population. The search was limited to the last 20 years, including publications from January 1991 onwards. The following key words were used: 'morphine clearance', 'morphine metabolism', 'morphine glucuronidation', 'morphine elimination', or 'morphine pharmacokinetics'. Limits were set for age to include children between 0 – 18 years. Case reports were excluded. Only studies with intravenous administration were selected, to avoid confounding issues with bioavailability in the reported clearance values. Since the pharmacokinetics of drugs in patients on extracorporeal membrane oxygenation (ECMO) may depend on various components of the ECMO circuit itself [7,8], studies in these patients were excluded as well. The obtained publications were categorized as analyzed according to 1) traditional methods, 2) population pharmacokinetic modeling, or 3) physiologically-based pharmacokinetic modeling.

9.3 Clearance Estimates Obtained With Traditional Methods

9.3.1. Traditional Methods

Traditional methods to determine pharmacokinetic drug parameters in a population rely on firstly determining individual parameter values, using either compartmental or non-compartmental analysis techniques, after which each parameter is summarized as mean and standard deviation. As such, this yields for each pharmacokinetic parameter a point estimate (mean value) for the population and a measure of variability (standard deviation). This may be useful in early drug development, when data of a very limited number of patients are available. However, since intra-individual variability, measurement error and model misspecification, cannot be distinguished from inter-

individual variability with this method, other methods are preferred to describe and quantify trends in a population when more data become available.

As the determination of individual drug clearance values with compartmental methods relies on densely sampled concentration-time profiles for each subject, this method may not always be feasible especially in the very young. Similarly, non-compartmental methods may not be feasible as they rely either on the area under the concentration-time curve, which also requires dense sampling per individual, or on imprecise measurements of steady state concentrations. Using traditional methods, the maturation patterns in drug clearance are usually studied by expressing individual clearances per kilogram bodyweight, stratifying patients into age-groups, and comparing mean clearance values per kilogram bodyweight between the age-groups. This allows for easy comparisons between studies and between age groups, but this makes findings on maturation dependent on the stratification and precludes the development of continuous maturation profiles. Additionally, it assumes clearance to scale linearly with bodyweight within the age-groups, which may be a practical approximation when the range in bodyweight within each stratum is small, but it may not accurately reflect the underlying physiological changes across the entire human life-span.

9.3.2. Morphine Clearance Determined With Traditional Methods.

Table I provides an overview of paediatric morphine clearance values obtained with traditional methods. The reported morphine clearance values in neonates with a postnatal age from 0 – 30 days range from about 0.58 ml/min/kg [9] to about 16 ml/min/kg [19], which is more than a twenty-fold difference. In infants aged 1 month to 1 year, morphine clearances were reported to range between 7.8 ml/min/kg [16] to 69.4 ml/min/kg [19,20], while in children from 1 to 18 years the range in morphine clearance was reported to vary from about 12 ml/min/kg [23] to about 60 ml/min/kg [27]. The wide ranges in reported clearance values within each age-group may in part be explained by the differences between studies in terms of patient characteristics, sampling schemes or dosing schemes, but are probably mainly caused by the relative imprecision of the applied data analysis methods. Additionally, most studies are based on a relatively small number of individuals (table I), limiting the precision of each finding.

Table I. *Overview of paediatric morphine clearance values reported over the past 20 years, obtained with traditional methods.*

Population	Age	Bodyweight [kg]	Number of patients	Morphine clearance [ml/min/kg]	Reference
term ischemic neonates (normotherm)	< 6 hr	3.3 (2.4 – 4.0)[a]	6	0.89 (0.65-1.33)[a]	Róka, *et al.* 2008 [9]
term ischemic neonates (hypotherm)	< 6 hr	3.4 (2.5 – 4.0)[a]	10	0.69 (0.58 – 1.2)[a]	
preterm neonates on artificial ventilation	< 24 hr	1.3 ± 0.38[c]	9	2.4[b]	Hartley *et al.* 1993 [10]
term and preterm neonates on artificial ventilation	< 24 hr	1.3 (0.77 – 4.0)[a]	31	2.4 ± 1.1[c]	Saarenmaa *et al.* 2000 [11]
term and preterm neonates on artificial ventilation	1 – 2 d	1.4 ± 0.6[c]	19	total: 4.6 ± 3.2[c] formation M3G: 2.5 ±1.8[c] formation M6G: 0.46 ± 0.32[c]	Barrett *et al.* 1996 [12]
preterm and term neonates on artificial ventilation	1 – 4 d	2.6 (1.3 – 3.6)[a]	19	2.55 ± 1.65[c] 2.09 ± 1.19[c]	Chay *et al.* 1992 [13]
preterm neonates	1 – 18 d	1.1 (0.6 – 1.6)[a]	8	2.82 (1.88 – 6.60)[a]	Mikkelsen *et al.* 1994 [14]
term neonates	1 – 18 d	3.4 (2.3 – 4.0)[a]	5	4.73 (1.75 – 6.61)[a]	
preterm neonates on artificial ventilation	1 – 37 d	0.88 – 1.46[d]	26	3.6 ± 0.9[c]	Barrett *et al.* 1991 [15]
preterm neonates	1.1 ± 0.3[b] wk GA 26.6 ± 0.7[b] wk	birth weight 1.0 ± 0.17[c]	10	2.27 ± 1.07[c]	Scott *et al.* 1999 [16]
	1.3 ± 0.6[b] wk GA 29.5 ± 1.3[b] wk	birth weight 1.4 ± 0.24[c]	16	3.21 ± 1.57[c]	
	6.1 ± 9.1[b] wk GA 32.5 ± 1.6[b] wk	birth weight 2.1 ± 0.41[c]	15	4.51 ± 1.97[c]	
	16.4 ± 31.6[b] wk GA 35.4 ± 4.8[b] wk	birth weight 3.3 ± 0.46[c]	7	7.80 ± 2.67[c]	
postoperative or artificially ventilated patients	1 – 7 d	-	10	8.7 ± 5.8[c]	Pokela *et al.* 1993 [17]
	8 – 60 d	-	10	11.9 ± 5.1[c]	
	61 – 180 d	-	7	28.0 ± 8.9[c]	
term neonates and infants on artificial ventilation	3 d – 11 mo	2.2 – 8.7[d]	12	23.4 ± 18[c]	Choonara *et al.* 1992 [18]

postoperative term neonates and infants, non-cardiac surgery	1 – 7 d	7.3 ± 5.0[c]	10	9.8 (6.3 – 16)[a]	Lynn *et al.* 2000 [19]
	8 – 30 d		4	13.3	
	31 – 90 d		14	23.9 (16.7 – 33.3)[a]	
	91 – 180 d		25	32.3 (18.5 – 52.1)[a]	
	181 – 365 d		30	38.1 (18 – 69.4)[a]	
postoperative term neonates and infants, non-cardiac surgery	1 – 7 d	6.6 ± 2.0[c]	4	9.2 (6.3 – 10.4)[a]	Lynn *et al.* 1998 [20]
	31 – 90 d		6	25.3 (21.7 – 33.3)[a]	
	91 – 180 d		6	31.0 (18.9 – 59.5)[a]	
	181 – 380 d		10	48.9 (34.7 – 69.4)[a]	
postoperative patients, non-cardiac surgery	3 – 12 mo	8.1 ± 1.0[c]	6	19.8 ± 5.9[c]	Haberkern *et al.* 1996 [21]
postoperative term neonates and infants	1 – 7 d	3.2 (2.5 – 3.6)[a]	9	5.5 (3.2 – 8.4)[a]	McRorie *et al.* 1992 [22]
	8 – 30 d	3.9 (3.2 – 4.6)[a]	5	7.4 (3.4 – 13.8)[a]	
	31 – 90 d	4.3 (3.5 – 5.2)[a]	7	10.5 (9.8 – 20.1)[a]	
	91 – 180 d	5.1 (4.3 – 8)[a]	11	13.9 (8.3 – 24.1)[a]	
	181 d – 2.5 y	7.2 (5.5 – 13.8)[a]	17	21.7 (5.8 – 28.6)[a]	
post-operative patients, cardiac surgery	8 mo – 7 yr	-	21	19.2 ± 7.0[c]	Dagan *et al.* 1993 [23]
patients with leukemia	1.4 – 15.9 yr	20.0 (9.3 – 54.5)[a]	17	35[b] [ml/min]	Hain *et al.* 1999 [24]
patients with cancer	2.6 – 16.42 yr	32.4 ± 21.4[c]	7	24.8[b]	Mashayekhi *et al.* 2009 [25]
patients with sickle cell disease	5 – 17 yr	34.6 ± 7.6[c]	11	1600 ± 700[c] [l/min]	Kopecky *et al.* 2004 [26]
patients with sickle cell disease	6 – 19 yr	-	18	35.5 ± 12.4[c] 34.4 ± 14.3[c]	Dampier *et al.* 1995 [27]
patients with sickle cell disease	pre-pubertal children	14 – 72[d]	11	40.4 ± 10[c]	Robieux *et al.* 1992 [28]
	pubertal children		5	37.1 ± 9[c]	
	post-pubertal children		8	28.0 ± 11[c]	

[a] median (range), [b] mean, [c] mean ± SD, [d] range
hr = hours, d = days, wk = weeks, mo = months, yr = years, GA = gestational age

9.4 Clearance Estimates Obtained With Population Modeling

9.4.1. Population Modeling

Increases in computing power now allow for the analysis of concentration-time measurements from a population as a whole while considering individuals as constituents of this population. This method is called population or non-linear mixed effects modeling. As long as data are sufficiently informative, population modeling can be used for the analysis of dense, sparse, and/or unbalanced data. This is especially beneficial for the vulnerable paediatric population as it allows for the analysis of a limited number of blood samples per patient and for the analysis of data obtained during routine clinical practice. Additionally, it may allow for the meta-analysis of data from multiple studies with different designs, thereby reducing the burden for individual paediatric patients. A proper covariate analysis does however require information on the same set of covariates in each individual dataset. Since data from various sources can be analyzed simultaneously, the precision of the findings may also increase.

Population modeling can also distinguish inter-individual variability from intra-individual variability, measurement error, and model misspecification. By identifying which patient characteristics (e.g. age, bodyweight, gender, race, genetics, disease status) are predictors of the inter-individual variability in model parameters, trends in the population can be identified and quantified. These predictors are known as covariates and the relationship between a covariate and a model parameter is known as covariate relationship. Typically, population pharmacokinetic modeling relies on outcome measures and information on covariates. Concentration data for pharmacokinetic models can be obtained relatively easily from blood samples. Covariate relationships in the population models generally include patient information that can be obtained from medical records or from routine clinical measurements. An important feature of population pharmacokinetic modelling is that it allows for the identification of continuous maturation profiles that do not depend on stratifications and that, when pharmacodynamic relationships remain constant with age, the covariate relationships describing this maturation can be directly used as the basis of evidence-based dosing algorithms. Since steady state drug concentrations are solely dependent on drug clearance and peak concentrations heavily dependent on distribution volume, the covariate relationships for these parameters can be directly incorporated in the algorithms of paediatric maintenance or loading doses respectively. However, since the use of sparse data may increase the risk of drawing wrong conclusions, population models require an advanced level of evaluation and validation before a model can be accepted [29].

One of the approaches that can be applied for paediatric population covariate modeling is fixed allometric scaling [30]. Using this approach, bodyweight is included *a priori* in the model as a covariate on clearance (*Cl*) according to the following allometric equation:

$$Cl = a \cdot (BW_i / 70)^b$$

in which BW_i is the bodyweight of the individual paediatric patient in kg, that is normalized to an average adult bodyweight of 70 kg and the value of the exponent *b* is fixed to 0.75 for clearance. The value of *a* that represents the magnitude of clearance in adults, is estimated. This fixed allometric equation describes the influence of changes in body size on drug clearance and on average predicts paediatric drug clearances with a fair degree of accuracy in children older than five years [31]. In younger children the allometric equation is augmented with an age-based function called 'maturation model', to describe the remaining influence of developmental changes on drug clearance. Additional covariate relationships that reflect the influence of altered function of elimination organs (i.e. liver or kidneys) may be incorporated as well [30].

The fixed allometric scaling approach is frequently applied, despite theoretical and data-driven studies challenging the hypothesis that the allometric equations accurately describe the influence of body size on pharmacokinetic processes [32–39]. Additionally, with the inclusion of bodyweight, part of the influence of age is included as well, due to the strong correlation between bodyweight and age in the paediatric population. This makes the maturation model a mathematical residue of the influence of age that remains after the inclusion of the correlated covariate bodyweight, rather than a descriptor of maturation *per se*. Moreover, since bodyweight and age are included without formal testing for significance, there is a risk of over-parameterizing the models, leading to imprecise parameter estimates. Finally, special attention is required for the interpretation of these models. Due to the separation of the influence of body size (expressed by bodyweight) and maturation (expressed by age), the statement that maturation is completed at a certain age does in this context not mean that absolute clearance has reached adult values, as body size is usually still increasing. Misinterpretation of such results can lead to over-dosing when used for paediatric dose adjustments, and therefore the expression of the pharmacokinetic parameters per 70 kg may be unwarranted particularly in neonates.

Another approach in paediatric population pharmacokinetic modelling is the application of a comprehensive covariate analysis, in which all potential covariates for pharmacokinetic parameter are tested in various relationships and are included into the model based on statistical significance. This procedure can be used to identify demographic factors or

co-morbidities that significantly influence drug clearance. In the paediatric population it can also be used to identify covariate relationships that describe functional maturational changes in drug clearance [40]. The paediatric covariate relationships, are usually based on bodyweight, age or a combination of both, and may vary in nature (e.g. exponential or linear). It should be noted however that these covariate relationship are empirical and that bodyweight or age should not be regarded as the drivers of the observed changes in drug pharmacokinetics, but as surrogate descriptors of the net changes in the underlying physiological system. The descriptive nature of these covariate relationships explicitly precludes extrapolations outside the covariate range in the learning dataset.

9.4.2 Morphine Clearance Determined With Population Modeling

9.4.2.1. Bouwmeester *et al.* (2004)

The model by Bouwmeester *et al.* [41] comprises morphine as well as its two main metabolites M3G and M6G. The model is based on data from 184 term neonates to infants up to the age of three years from Van Dijk *et al.* [42].

The Bouwemeester-model was developed using fixed allometric scaling principles described in section 9.4.1. The maturation model for the formation of morphine glucuronides was an exponential model based on postnatal age and serum bilirubin concentrations were included as a covariate on morphine glucuronidation. The set of equations below shows how total morphine clearance is described by the Bouwmeester-model:

$$Cl_{tot} = Cl_{M3G} + Cl_{M6G} + Cl_R$$

$$Cl_{M3G} = 64.3 \cdot (BW_i / 70)^{0.75} \cdot (1 - 0.834 \cdot EXP(-PNA \cdot (\ln 2 / 88.3))) \cdot EXP(C_{bili} \cdot -0.00203)$$

$$Cl_{M6G} = 3.63 \cdot (BW_i / 70)^{0.75} \cdot (1 - 0.834 \cdot EXP(-PNA \cdot (\ln 2 / 88.3))) \cdot EXP(C_{bili} \cdot -0.00203)$$

$$Cl_R = 3.12 \cdot (BW_i / 70)^{0.75}$$

In these equations, Cl_{tot} is total morphine clearance in l/h, Cl_{M3G} and Cl_{M6G} are the formation clearance of M3G and M6G in l/h, and Cl_R is the residual clearance through alternative pathways in l/h. BW_i is the bodyweight of the individual paediatric patient in kg, PNA is the postnatal age in days, and C_{bili} is the serum bilirubin concentration in μmol/l. Total morphine clearance is 71.1 l/h/70kg$^{0.75}$, and from the maturation model it can be derived that the adult value of morphine glucuronidation is reached between the age of 6 to 12 months. Absolute morphine glucuronidation is however still increasing after that age, as a result of changes in bodyweight, which is described by the allometric function.

Model performance was corroborated by plots of the ratio of observed and individual morphine and metabolite concentrations *versus* time, which showed limited bias. Results of other diagnostics, in particular plots of population predicted concentrations *versus* observed concentrations, were not reported. More recently, this model has been evaluated by our group using both the learning dataset and external datasets (Chapter 8). With a condition number of 10698 the model was shown to be over-parameterized, resulting in imprecise parameter estimates that caused the bootstrapped parameter value for a number of parameters to deviate more than 10% from the originally reported values. Plots of predicted concentrations *versus* observed concentrations revealed accurate individual concentration predictions, suggesting that morphine concentrations can be described accurately when at least one observation per individual is available, although high shrinkage values render the diagnostics based on individual predictions to be potentially misleading. Population concentration predictions were found to be biased. This suggests that model-based concentration predictions based on age, weight, and bilirubin concentrations of a child alone are inaccurate. Additionally, simulation-based diagnostic showed bias towards over-prediction of morphine concentrations in the population as a whole. The cause of this bias was diagnosed to originate from structural model misspecification, since plots of individual and population parameter estimates *versus* the primary covariate bodyweight revealed that the covariate relationships describe the maturational changes in model parameters with bias, which was reflected in MPEs for the predictions of total morphine clearance in the external dataset of 86% and -27% in term neonates and toddlers respectively. A claimed advantage of the application of fixed allometric scaling principles is that it allows for predictions outside the studied age-range, however clearance predictions in preterm neonates were found to have an MPE of 192% (Chapter 8), while clearance predictions in older children have never been assessed.

9.4.2.2. Anand *et al.* (2008)

The population pharmacokinetic model by Anand *et al.* [43] was based on morphine concentrations obtained from 875 preterm neonates as well as on the data from the 184 term neonates and infants from Van Dijk *et al.* [42] that were previously analyzed by Bouwmeester *et al.*. The pharmacologically active morphine metabolites were not included in this model.

The Anand-model continued to build on the concepts introduced in the publication by Bouwmeester *et al.* Fixed allometric scaling was augmented by a maturation model, in which the best fit was obtained with a sigmoidal model based on postmenstrual age, compared to an exponential model. Covariates based on organ function (i.e. serum bilirubin concentrations to reflect hepatic function) were not included,

but a scaling factor to adjust morphine clearance in preterm neonates in comparison to term neonates was included. There is some ambiguity on which parameter this fraction for preterm neonates is applied, as both the standard adult value of morphine clearance and the postmenstrual age at which half the allometric adult value of morphine clearance is reached, are mentioned. Most probably, the preterm factor was applied to the standard value of morphine clearance, indicating that morphine clearance in preterm neonates is 61% of the clearance in term neonates. This reduction remains constant throughout the full age-range described in the model. The equations below show how total paediatric morphine clearance is described by the Anand-model:

$$Cl_{tot,term} = 84.2 \cdot (\frac{BW_i}{70})^{0.75} \cdot (\frac{PMA^{3.92}}{PMA^{3.92} + 54.2^{3.92}}) \text{ or}$$

$$Cl_{tot,preterm} = 51.4 \cdot (\frac{BW_i}{70})^{0.75} \cdot (\frac{PMA^{3.92}}{PMA^{3.92} + 54.2^{3.92}})$$

In these equations, $Cl_{tot,term}$ and $Cl_{tot,preterm}$ represent total morphine clearance in l/h in term and preterm patients, respectively, BW_i is the bodyweight of the individual paediatric patient in kg, and *PMA* is the postmenstrual age in weeks. According to the maturation model, half the standard adult value of morphine clearance is reached at a postmenstrual age of 54 weeks. Around the postnatal age of one year, the influence of the maturation models becomes negligible, after which the increase in absolute clearance is described solely by bodyweight in the allometric equation.

In terms of model evaluation and validation procedures, diagnostics based on individual as well as population concentration predictions are reported, although due to their layout it is difficult to assess the accuracy of the predictions from these plots. No other results on model evaluation and validation were reported. The Anand-model was further evaluated by Mahmood using external data [44]. The MPE in total morphine clearance ranged between 8% in preterm neonates, 19% in term neonates, and 21% in toddlers between one week and two months of age, while the MPE was 1.5% in toddlers between two to ten months of age. The MPE in clearance predictions in children between the age of 3 to 5 years, which was older than the age-range in internal dataset, was 17%.

9.4.2.3. Knibbe *et al.* (2009)

The model by Knibbe *et al.* (Chapter 3) was also based on data from the 184 term neonates and infants of Van Dijk *et al.* [42]. Additionally data from Simons *et al.* on 64 preterm and term neonates [45] were added. Both morphine and its main metabolites were included in the model.

Model development of the Knibbe-model was based on a comprehensive covariate analysis. Bodyweight, bodyweight at birth, body surface area, sex, postnatal age, postmenstrual age, serum bilirubin concentration, creatinine clearance, mechanical ventilation, surgery *versus* non-surgery and type of surgery were investigated as potential covariates on clearance in equations of various forms. Differences in morphine glucuronidation were best described by a bodyweight-based exponential equation with an estimated exponent of 1.44. Within this equation the formation clearance of the morphine glucuronides was found to be reduced in neonates younger than ten days. This discontinuity did not result from stratification of the data, but from the observed differences in morphine clearance between young neonates and older patients after inclusion of the bodyweight-based covariate relationship. Compared to inclusion of age in a continuous relationship or to age cut-points at 3, 7, 14 or 21 days, inclusion of a discontinuity at the postnatal age of ten days provided the best mathematical description of this observed difference according to predefined statistical criteria. Physiologically a rapid but continuous change is however more probable. Clearance through pathways other than glucuronidation was found to be not significant and therefore not included in the model. The set of equations below shows how total morphine clearance is described by the Knibbe-model.

$$Cl_{tot} = Cl_{M3G} + Cl_{M6G}$$

$$Cl_{M3G(d<10)} = 3.48 * BW_i^{1.44} \quad \text{or} \quad Cl_{M3G(d>10)} = 8.62 * BW_i^{1.44}$$

$$Cl_{M6G(d<10)} = 0.426 * BW_i^{1.44} \quad \text{or} \quad Cl_{M6G(d>10)} = 0.67 * BW_i^{1.44}$$

In these equations Cl_{tot} is total morphine clearance in ml/min, Cl_{M3G} and Cl_{M6G} are the formation clearance of M3G and M6G in ml/min with different values for neonates younger than ten days and older patients, and BW_i is the bodyweight of the individual paediatric patient in kg.

The model was evaluated using various methods with the learning dataset and later also with external datasets (Chapter 4). With a condition number of 293 the model was found to be not over-parameterized, which resulted in precise parameter estimates causing the bootstrapped parameter values also to be within 10% of the originally reported value for all parameters. Plots of individual predicted morphine concentrations *versus* observed concentrations were minimally biased, although the value of diagnostics based on individual predictions is limited due to high shrinkage. Population predicted concentrations showed limited bias. Simulation-based diagnostics further confirmed that the model could accurately predict morphine concentrations based on bodyweight and age alone in children under the age of three years that, similar to the patients in the learning dataset had undergone major non-cardiac surgery or were mechanically

ventilated. Additionally, it was confirmed that covariate relationships describe individual parameter values accurately, with MPEs for total morphine clearance in the external datasets of 17% for preterm neonates and 30% for term neonates and toddlers (Chapter 4). The exponential increase in morphine clearance with bodyweight explicitly precludes this model from making clearance predictions in children older than three years.

Table II summarizes the details of the pharmacokinetic population models discussed above. For comparison, table III lists the absolute clearance values and clearance values per kg bodyweight for nine hypothetical patients, predicted by each of these three population models. The largest differences in predicted morphine clearance values between the models are observed at the extremes of the age-ranges of the models, with a difference of almost a factor 2 in the first month of life and around a 30% difference at the age of three years. Particularly large differences were found for preterm neonates aged 1 day to 2 weeks, and term neonates aged 2 weeks.

Table III. *Overview of morphine clearance predicted by the three population pharmacokinetic models for morphine in children with normal hepatic function.*

	Clearance prediction by the Bouwmeester-model [41]	**Clearance prediction by the Anand-model** [43]	**Clearance prediction by the Knibbe-model (Chapter 3)**
preterm neonate 1 day, 0.5 kg (GA 32 wk)	n.a.	2.37 ml/min 4.73 ml/min/kg	1.44 ml/min 2.88 ml/min/kg
preterm neonate 2 weeks, 1.0 kg (GA 34 wk)	n.a.	4.90 ml/min 4.90 ml/min/kg	9.29 ml/min 9.29 ml/min/kg
term neonate 1 day, 3.5 kg (GA 38 wk)	26.2 ml/min 7.47 ml/min/kg	29.5 ml/min 8.44 ml/min/kg	23.7 ml/min 6.78 ml/min/kg
term neonate 2 weeks, 4 kg (GA 40 wk)	39.5 ml/min 9.88 ml/min/kg	38.2 ml/min 9.56 ml/min/kg	68.4 ml/min 17.1 ml/min/kg
infant 3 monts, 6 kg	114 ml/min 19.0 ml/min/kg	98.0 ml/min 16.3 ml/min/kg	123 ml/min 20.4 ml/min/kg
infant 6 months, 7.5 kg	179 ml/min 23.9 ml/min/kg	173 ml/min 23.0 ml/min/kg	169 ml/min 22.5 ml/min/kg
infant 1 year, 10 kg	263 ml/min 26.3 ml/min/kg	287 ml/min 28.7 ml/min/kg	256 ml/min 25.6 ml/min/kg
infant 2 years, 13 kg	334 ml/min 25.7 ml/min/kg	388 ml/min 29.9 ml/min/kg	373 ml/min 28.7 ml/min/kg
infant 3 years, 17 kg	410 ml/min 24.1 ml/min/kg	482 ml/min 28.4 ml/min/kg	549 ml/min 32.3 ml/min/kg

GA = gestational age

Table II. *Details of the three paediatric population pharmacokinetic models on morphine.*

Model	**Bouwmeester *et al.*** **2004** [41]	**Anand *et al.*** **2008** [43]	**Knibbe *et al.*** **2009 (Chapter 3)**
Population and number of patients	- 184 term neonates to infants of three years [Van Dijk *et al.* [42]]	- 184 term neonates to infants of three years [Van Dijk *et al.* [42]] - 875 preterm neonates	- 184 term neonates to infants of three years [Van Dijk *et al.* [42]] - 64 preterm and term neonates [Simons *et al.* [45]]
Age in overall dataset	PNA: 195 (0 - 1070)[a] days	Preterm neonates: PNA: 0.27 (0 – 2.84)[a] weeks PMA: 27.4 (0.42 – 2.4)[a] weeks Term neonates and infants: PNA: 195 (0 - 1070)[a] days	PNA: 33 (0 – 203)[b] days PMA: 41.9 (35.6 – 62.6)[b] weeks
Bodyweight in overall dataset	5.9 (1.9 – 16.8)[a] kg	Preterm neonates: 1.04 (0.42 – 2.44)[a] kg Term neonates and infants: 5.9 (1.9 – 16.8)[a] kg	3.5 (2.2 – 7.0)[b]
Pharmacologically active metabolites	Included	Not included	Included
Covariate modeling	Fixed allometric scaling principles, including covariates *a priori*.	Fixed allometric scaling principles, including covariates *a priori*.	Comprehensive covariate analysis, inclusion of covariates based on statistical criteria.
Model	- Fixed allometric equation for size. - Age-based exponential equation for maturation. - Bilirubin serum concentrations for organ function.	- Fixed allometric equation for size. - Age-based sigmoidal equation for maturation. - Fraction of clearance values in preterm compared to term neonates.	- Bodyweight-based exponential equation with estimated exponent of 1.44. - Reduction of glucuronidation in neonates younger than 10 days.
Internal model evaluation and validation by authors	- Observed/individually predicted concentration *versus* time. - Individual parameter values and covariate relationships describing population parameter values *versus* included covariates.	- Observed *versus* individual predicted concentration. - Observed *versus* population predicted concentration. - Observed/individually predicted concentration *versus* time. - Observed/population predicted concentration *versus* time. - Individual parameter values and covariate relationships describing population parameter values *versus* included covariates.	- Observed *versus* population predicted concentration. - Observed *versus* individual predicted concentration. - Weighted residuals *versus* various covariates. - Simulation based diagnostics (NPDE) - Individual parameter values and covariate relationships describing population parameter values *versus* most predictive covariate.

External evaluation and validation by authors	None.	None.	In separate publication (Chapter 4): - 120 new patients, from preterm neonates to 1 year old infants [18,19,46,47]. - Refit using all data, and bootstrap. - Observed *versus* population predicted concentrations. - Simulation based diagnostics (NPDE). - Investigation of covariate relationships using subpopulations. - Also confirmed predictive value in neonates on ECMO treatment [48–50].
Model evaluation and validation by others than the authors of the original publication	Krekels *et al*. (Chapter 8) using internal data and data from 153 external patients [18,19,45–47], from preterm neonates to 1 year old infants. - Bootstrap using internal dataset. - Observed *versus* population predicted concentrations. - Simulation based diagnostics (NPDE). - Individual and population parameter values *versus* most predictive covariate. - Mean percentage error and root mean square error in clearance predictions. - Condition number (as measure for over-parameterization).	Mahmood et al. [44] using data from 147 external patients [10,12–15,17,18,51–53] from preterm neonates to 5 year old infants: - Percentage error, mean percentage error and root mean square error in clearance predictions. - Population predicted *versus* observed concentrations.	-
Conclusion of all evaluation and validation procedures	The model can accurately describe data based on at least one blood sample. In terms of predictions, the model shows an over-prediction of morphine concentrations, especially in the very young. The model is over-parameterized and parameter estimates are not precise.	The prediction error is large especially in the very young, but this reflects properties of the population not of the model. There is a small trend towards over-prediction for clearance especially in the first 3 months of life.	Model can describe and predict morphine and metabolite concentrations without bias. The parameter estimates are precise.

PNA = postnatal age, PMA = postmenstrual age, NPDE = normalized prediction distribution error, ECMO = extracorporeal membrane oxygenation, [a] = mean (range), [b] = median (inter-quartile range).

9.5 Clearance Estimates Obtained With Physiologically-Based Pharmacokinetic Modeling

9.5.1. Physiologically-Based Pharmacokinetic Modeling

In physiologically-based pharmacokinetic models, an exhaustive set of mathematical equations mechanistically describe and quantify the interaction between a drug molecule with specific physicochemical properties and the underlying physiological system. Additionally, interactions within the physiological system are described and quantified as well. These equations and the constants within these equations thereby aggregate compound-specific information with anatomical measurements and *in vitro* or *in vivo* physiological information. So while population modeling yields models for a specific drug in a specified population, physiologically-based models are more generalizable and non-specific for particular drugs.

Physiologically-based pharmacokinetic models require a wider variety of information compared to population modeling. Some of this information may be difficult to obtain, but since a substantial part of this information relates to underlying (patho)physiological processes, rather than to specific drugs, this information needs to be obtained only once. With the current gaps in our knowledge on human physiology and maturation, years of research are still required to properly describe and quantify all physiological parameters and interactions. However, the influence of some parameters or interactions on the overall drug pharmacokinetics may be negligible and with the major physiological determinants of pharmacokinetic processes currently being well described, physiologically-based models have already been proven useful to make inferences about the changes in pharmacokinetics of drugs that have not yet been studied in a particular population [54–56]. The additional research in this area is successively refining these models or extending their application to special populations.

The paediatric population can be included into this approach by integrating information on maturational changes in the physiological system into the model. Maturation of drug clearance is not defined for specific drugs, but for specific elimination routes, like glomerular filtration or biotransformation through various phase I and phase II enzymes. As morphine is mainly eliminated through hepatic glucuronidation by the UGT2B7 isoenzyme [1–3], information on ontogeny (i.e. expression and function) of this enzyme system is required, as well as maturational changes in liver size, hepatic blood flow and perfusion, plasma protein binding, and active hepatic transport mechanisms. As maturation profiles in physiologically-based pharmacokinetic models are established for all the underlying physiological changes, the developmental changes in pharmacokinetic parameters are described by a wide variety of mostly non-linear equations. This enables

the determination of pharmacokinetic parameters for drugs with specific properties in individuals for which certain key demographics (e.g. bodyweight and age) are known, which may be helpful in the development of first-in-child doses. However, the net maturation profile of pharmacokinetic parameters in a population as a whole cannot be directly derived. This complicates the establishment of evidence-based dosing guidelines from physiologically-based pharmacokinetic models.

5.2. Morphine Clearance Determined With Physiologically-Based Pharmacokinetic Modeling

9.5.2.1. Edginton et al. (2006)

The publication by Edginton *et al.* [56] is the only retrieved publication that compares overall *in vivo* morphine clearance predictions by a physiologically-based pharmacokinetic model to observed *in vivo* morphine clearances in the paediatric population. In the Edginton-model, hepatic UGT2B7 ontogeny profiles were derived from literature values of *in vivo* clearance as well as from *in vitro* determinations of enzyme activity for morphine and lorazepam. First, *in vitro* determinations of paediatric UGT2B7 enzyme activity were expressed as percentage of adult activity. This information was subsequently combined with maturational changes in the underlying physiological processes and *in vivo* adult morphine clearance values, to obtain model predicted *in vivo* paediatric clearance parameters. The *in vivo* maturation profile of morphine glucuronidation over the entire paediatric age-range was obtained by determining mean morphine clearance per kilogram of bodyweight at 17 distinct ages and generating a cubic spline of mean morphine clearance *versus* age. Available paediatric *in vivo* clearance values for morphine and lorazepam were used to further adjust the UGT2B7 ontogeny profile to provide the best visual fit of *in vivo* predicted drug clearances to the observed clearances. This yielded a bi-phasic maturation profile describing the net influence of underlying physiological changes on *in vivo* morphine clearance expressed per kilogram of bodyweight.

Optimization of the *in vivo* maturation profiles was based on visual improvement of how well the predicted profile described *in vivo* literature data, but this model fit was not numerically quantified. Age was selected as descriptor for the UGT2B7 ontogeny profile in the Edginton-model, but the ambiguity about how to quantify maturation in the first few days of life, especially comparing preterm and term neonates, could not be resolved. Therefore this model used one single clearance value for all premature neonates irrespective of postnatal or postmenstrual age. Additionally, since the maturation profile was not compared to individual clearance data, but to mean study values in stratified

age-ranges, the quality of model fit could not be assessed properly. In the manuscript, the predictive performances of the enzyme ontogeny models are tested on paediatric data from test compounds that are eliminated through multiple elimination pathways. However, this is not an ideal method to test the prediction of the clearance profiles of individual elimination routes. Alternatively, the UGT2B7 ontogeny profile was later used in a full physiologically-based pharmacokinetic model to assess the accuracy of morphine concentration predictions [55]. It was found that the predicted morphine concentrations were on average within a factor 2.06 from the observed value. However, in preterm neonates, a clear trend towards under-prediction of concentrations, and thus over-prediction of clearance, was observed.

9.6 Discussion

Morphine pharmacokinetics has been widely studied in the paediatric population, with a relatively large amount of this research being performed in children in the first few days to months of life. The majority of traditional pharmacokinetic studies in section 3 were performed in the younger age-ranges and the three population pharmacokinetic models in section 4 only included patients up to the age of three years. This is probably not only because most developmental changes occur in the early life-stages, but also because these very young patients are encountered most frequently in hospitals settings and paediatric intensive care units. Only the physiologically-based pharmacokinetic model in section 5 covers the entire paediatric age-range.

As can be seen in table I, there is a twenty-fold difference in the reported morphine clearances by traditional methods in neonates which narrows down to about a three-fold difference in older children and adolescents. The predicted clearance values by the three population models fall within the range of morphine clearance values obtained with the traditional methods. When the three population models are compared, the difference in morphine clearance predictions is most prominent in preterm neonates (which were not included in the Bouwmeester model) and in patients in the first few months of life, as illustrated in table III. The morphine clearance predictions by the Edginton-model are in the same range as the other studies as well, but an explicit relationship describing the developmental changes in morphine clearance in the paediatric population is lacking as the maturation of underlying physiologically processes instead of clearance are quantified.

The three paediatric population pharmacokinetic models for morphine discussed in section 4, were assessed for the accuracy of both their population concentration predictions and clearance predictions. The model by Knibbe *et al.* was the only model for

which accurate concentration predictions were confirmed as bias in individual as well as population concentration predicted *versus* observed concentration plots was found to be minimal. Especially the Bouwmeester-model proved to have poor population concentration predictions, while the population concentration predictions by the Anand-model were difficult to assess. With regards to MPEs of the population predictions of total morphine clearance, the error of the Bouwmeester model reached up to 85% (Chapter 8). For the Anand-model the MPE of total morphine clearance ranged between 8% and 21% [44], while for the Knibbe-model this ranged between 17% and 30% (Chapter 8). The MPEs reported for the Anand-model cannot be directly compared to the reported MPEs of the Bouwmeester-model and the Knibbe-model, as different external data were used as well as different age-ranges of the paediatric subsets and different methods to determine individual morphine clearances. These results however suggest the accuracy of total morphine clearance predictions by the Anand-model and the Knibbe-model to be in a similar range, despite the fact that the Anand-model was based on data from a larger number of preterm neonates than the Knibbe-model. This illustrates that model performance not only dependents on data density, but also on the quality of that data, showing that data should be obtained at time points that are informative for the various pharmacokinetic processes.

Concerning the physiologically-based model by Edginton *et al.*, the method to assess the model predictions was not quantitative and the visual tools were not optimal [56], making it difficult to assess the morphine clearance predictions by this model. However, morphine concentration predictions by this model were on average within a factor 2 from the observed value, which could be regarded acceptable for determining first-in-child doses or inter-drug scaling of new drugs in the paediatric population.

As biased clearance predictions can be harmful when used for paediatric dose adjustments or clinical decision making, we would like to emphasize that proper model evaluation and validation for all paediatric population pharmacokinetic models is of utmost importance. It should however be noted that most evaluation and validation procedure assess the accuracy of model predictions for a population as a whole. As mentioned by Mahmood [44], the inter-individual variability in paediatric morphine clearance is high, causing the prediction error in individual clearances to be high even with the most accurate population model. As a result, clinical monitoring is still important in paediatric patients on morphine treatment.

As illustrated in figure 1, population modeling and physiologically-based modeling approach the study of a drug's pharmacokinetics from opposite perspectives, and are therefore often referred to as the 'top-down' and 'bottom-up' approach, respectively. Inherent to these different perspectives is a difference in the nature of the data that are required for these models. Physiologically-based pharmacokinetic

models require a vast amount of data, which is generalizable but may not always prove to significantly influence net pharmacokinetic parameters, while population pharmacokinetic models only allow for the quantification of rate limiting processes that are not always generalizable and have to be repeated for every new drug studied in every new population. Future endeavors in paediatric pharmacology will therefore benefit from using the physiological insight and generalizability of physiologically-based models while restricting the focus to significant and rate limiting processes, as is done with population modeling. This will yield hybrid models that meet in-between the top-down and bottom-up approach and expedited paediatric model development (Chapter 6)[57].

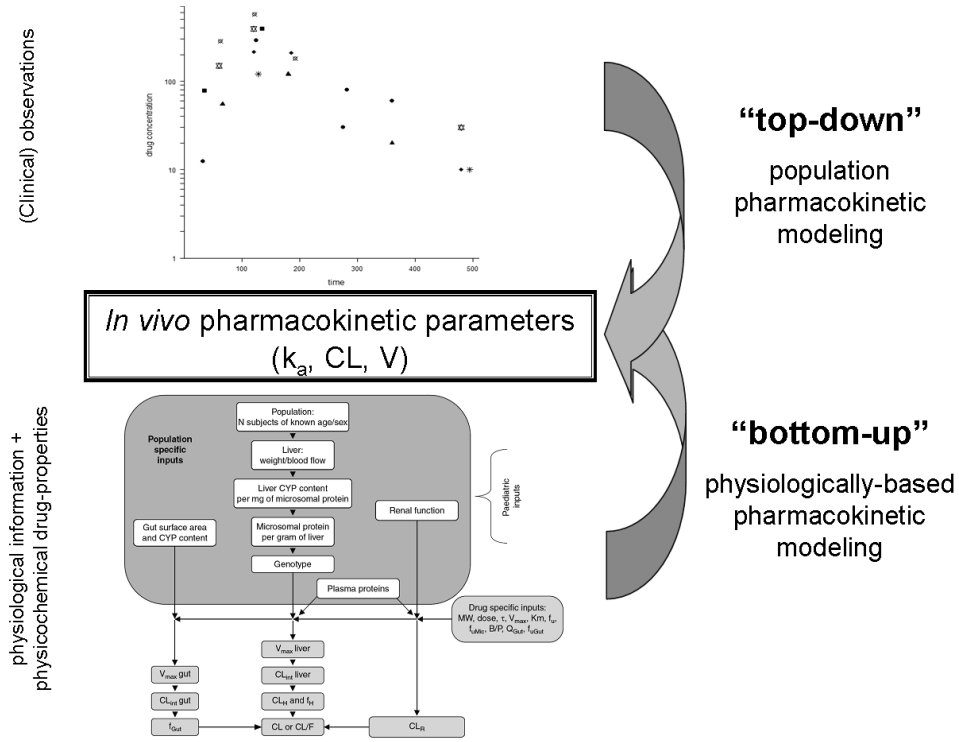

Figure 1. *Population pharmacokinetic modeling and physiologically-based pharmacokinetic modeling are often referred to as 'top-down' and 'bottom-up' approach respectively. Population modeling derives in vivo pharmacokinetic parameters from clinically observed drug concentrations, whereas physiologically-based modeling derives this information by aggregating physiochemical information of the drug with anatomical and physiological information of the biological system.*

One of the disadvantages of both population modeling and physiologically-based modeling is that they require specialized software and skilled professionals to design studies and perform the analyses. Additionally, with the mathematical equations that describe and quantify maturational changes in clearance values in the paediatric population becoming more complex, reported clearance values also become more difficult to interpret and compare. Particularly, the use of fixed allometric scaling principles in combination with age-based maturation functions [30] results in a combined function of two highly non-linear relationships for the maturation of morphine clearance in the Bouwmeester- and Anand-model. Since the analysis of data generated in population pharmacokinetic studies often yield complex covariate relationships, evidence-based dosing algorithms also grow increasingly complex. As dosing algorithms should be as simple as possible, but not simpler, special attention is required to implement these regimens in clinical practice. This may require a closer involvement of the hospital pharmacist in patient care to optimize and individualize drug dosing and to avoid dosing errors [58].

To date, most paediatric pharmacological research has focuses on drug pharmacokinetics. This is because clearance is generally believed to be the main driver of required dose adjustments in the paediatric population [59]. When pharmacokinetic models are used to derive evidence-based paediatric dosing algorithms, it is implicitly assumed that the pharmacodynamics remain constant. This assumption is acceptable when: 1) pathophysiological processes are similar in adults and children, 2) the exposure-effect relationship can be assumed independent of age based on the mechanism of action, and 3) the clinical endpoints for treatment are the same in both populations [57]. Morphine does not meet these criteria as the expression of the mu-opioid receptor may differ between age groups, and as the clinical endpoints for pain differ in adults and children. This implies that morphine pharmacodynamics needs to be studied as well, to establish age appropriate target concentrations. Future paediatric pharmacodynamic studies are therefore necessary to derive final dosing algorithms in this population that account for both pharmacokinetic and pharmacodynamic changes.

9.7 Conclusion

Traditional compartmental and non-compartmental analysis approaches, population modeling and physiologically-based pharmacokinetic modeling have been applied to study morphine clearance and the maturational changes in this parameter in the paediatric population. This has lead to a variety of reported values for paediatric morphine clearance and functions for the maturation profiles of this parameter. However, absolute predicted clearance values obtained with the different methods seem to be in good agreement, except in preterm and term born neonates and infants in the first three months of life. The predictive value of models is determined by accurate clearance predictions (quantified by MPE values) and concentration predictions (assessed in population predicted *versus* observed plots). The Knibbe-model was the only model for which accurate concentration predictions on the individual as well as population level were corroborated throughout the full age-range of the model and for both morphine and its metabolites. With regards to the prediction of total morphine clearance the Anand-model and Knibbe-model have similar accuracies, although the Anand-model did not include the pharmacologically-active metabolites.

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