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REVIEW

Drug metabolism in early infancy: opioids as an illustration

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ABSTRACT

Introduction: Drug dosing in infants frequently depends on body weight as a crude indicator for maturation. Fentanyl (metabolized by Cytochrome P450 3A4) and morphine (glucuronidated by UDP-glucuronosyltransferase-2B7) served as model drugs to provide insight in maturation patterns of these enzymes and provide understanding of the impact of non-maturational factors to optimize dosing in infants.

Areas covered: Systematic searches on metabolism and population pharmacokinetic (Pop-PK) models for fentanyl and morphine were performed. Pre- and post-model selection criteria were applied to assess and evaluate the validity of these models. It was observed that maturational changes have been rather well investigated, be it with variability in the maturational function estimates. The same holds true for Pop-PK models, where non-maturational covariates have also been reported (pharmacogenetics, disease state or external influences), although less incorporated in the PK models and with limited knowledge on mechanisms involved.

Expert opinion: PK models for fentanyl and morphine are currently available. Consequently, we suggest that researchers should not continue to develop new models, but should investigate whether collected data fit in already existing models and provide additional value concerning the impact of (non)-maturational factors like drug-drug interactions or pharmacogenetics.

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1. Introduction

The successful use of a drug in the clinical setting depends on the availability of an appropriate drug dosing regimen that results in maximal therapeutic efficacy, without sub- or toxic plasma concentrations, and a minimal amount of side effects. In early infancy, measuring efficacy and detecting adverse drug reactions or toxicity (safety) are currently still very difficult. The pharmacokinetic (PK) profile of a drug can hereby be considered as a first crucial step to subsequently determine and explore efficacy and safety in infants.

The physiologic maturation during infancy commonly affects the PK profile. This includes the maturation of drug metabolizing enzymes (DMEs). This within population maturation further adds to the differences and discrepancies in physiology between early infancy and adults. These physiological changes between and within populations have been previously and extensively discussed [1,2]. Hence, only a brief overview will be provided to illustrate its impact. Body water content is proportionally larger, body fat content is proportionally smaller in neonates in comparison to adults (impact on distribution), and liver and kidney function are not fully developed at birth, which is an important factor considering metabolism and elimination of many drugs [3,4]. Generally, the maturation of DMEs does not follow a single, uniform pattern, but displays iso-enzyme-specific maturation. In clinical

practice, drug dosing is frequently based on body weight since this parameter is often assumed as a – be it crude – marker of maturation. In neonates, where the age span is confined (0–28 days, up to 44 weeks of postmenstrual age), there is already a 10-fold variability in weight difference (0.5–5.0 kg). The same factor can also be applied to the entire pediatric population (5–50 kg). During infancy (first year of life), the body weight shows a threefold increase compared to the birth weight of a term infant. It is therefore not surprising that the extrapolation of dosing regimens from adults to neonates based on body weight alone are gross and inaccurate [5].

Most of the medications currently used in infants have not received formal approval for their use in this population or for a particular indication by the United States Food and Drug Administration or the European Medicines Agency and are consequently used 'off-label', including the absence of a dosing advice. Because of the lack of well-conducted research and the clear need for drugs in these populations, empirical guidelines and extrapolation by (adult) body weight for dosing recommendations are common practice. In recent years, a lot of progress has been made for dose selection in neonates and infants by the application of various methods such as population PK (Pop-PK) models including covariates beyond weight, or a more mechanistic approach, using physiologically-based

pharmacokinetic (PBPK) models. PBPK models hereby scale physiological parameters in combination with maturation profiles [6]. Unfortunately, the subsequent translation to labeling for neonates and infants is still very limited.

In this review, we have taken a closer look into two opioids to improve the understanding of developmental drug metabolism and other additional factors. Fentanyl and morphine were selected to illustrate the metabolic differences between neonates, infants, and adults and how these differences can be translated into dosing regimens tailored to infants. This will be preceded by background information concerning pain management in neonates (Section 1.1) (targeted indication for these drugs) as well as the patterns of enzyme maturation (Sections 1.2, 2, and 3). Those opioids were selected as both have different metabolic pathways and are transformed by different iso-enzymes. Fentanyl undergoes phase I metabolism (Cytochrome P450 3A4, CYP3A4), whereas morphine undergoes phase II (UDP-glucuronosyltransferase-2B7, UGT2B7) metabolism. Importantly, both compounds have also been studied in neonates and infants. This resulted in several Pop-PK models of these drugs, which are of great value to determine optimal dosing in infants. Since Pop-PK is considered an advancement toward evidence-based dosing in this population, the influence of maturational (often expressed by body weight) and non-maturational changes (e.g. pharmacogenetics (PG)) should be implemented as discussed in Section 4. Clinical interpretation and factors of interest (e.g. covariates, scaling) are investigated for the fentanyl and morphine PK models found in literature, in Sections 4.1 and 4.2, respectively. Pre-model selection and post-model development principles, to evaluate and categorize PK models, are proposed in Section 4.

1.1. Pain management in neonates and infants

Several decades ago, it was common practice to withhold anesthetic or analgesic agents from neonates when undergoing surgical procedures. This practice shifted, driven by anecdotal cases and pivotal studies. In 1985, such an incident resulted in raised attention for this problem, when a premature neonate (the Jeffrey Lawson case) only received muscle relaxant during cardiovascular surgery [7,8]. Two years later, the American Academy of Pediatrics stated that it was no longer ethical to perform surgery on preterm babies without anesthetics [9]. This statement co-appeared with the pivotal observations of Anand *et al.* on the relevance of opioids on outcome after surgery, but not during mechanical ventilation. These data left the medical community with the knowledge that opioids like fentanyl or morphine were indicated to improve outcome (even survival) after neonatal surgery, with the subsequent need to learn more about how to dose (PK), and how to assess the effects and safety profile (pharmacodynamics, PD) [10,11].

As mentioned earlier, the PK profile is hereby a first, but crucial step to determine and explore efficacy and safety although PD assessment in infants also has its burdens. The definition of pain is characterized as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [12].

Although neonates perceive pain, they cannot express their pain verbally while aspects like emotional experiences are difficult to apply to neonates. Moreover, neonates completely depend on others to recognize and manage their pain. The absence of behavioral responses neither ensures the absence of pain in neonates [13]. Unfortunately, an explosion of validated pain assessment instruments occurred without sufficient consideration that 80% redundancy of items exists in these tools. Moreover, all currently available tools depend on subjective hetero-assessment [14–16]. Only very recently, it has been suggested that electrophysiological measurements may provide a more objective tool to quantify pain in neonates [17]. However, this observation needs further validation, preferably in different pain models [17].

1.2. Changes in drug metabolism: enzyme maturation and non-maturational changes

From birth through adolescence and beyond, changes based on growth and development occur. In addition to overt physiological characteristics like growth or weight, more concealed processes like enzyme maturation occur during development [18]. Drug metabolism is driven by enzyme activity which transform and metabolize drugs into (in)active metabolites. These compounds will subsequently be eliminated by renal or other elimination pathways (e.g. bile). DMEs play a critical role in drug transformation needed for their elimination. Consequently, maturation of hepatic DMEs can significantly influence the variability in drug clearance throughout infancy [2].

As mentioned earlier, the maturation of the different DMEs is not a single, uniform pattern, but displays iso-enzyme-specific maturation. Hines *et al.* categorized the DMEs into three groups, based on different developmental patterns. The first group of enzymes (e.g. CYP3A7, sulfotransferase (SULT) 1A3/4) is expressed at the highest level in fetal life. Throughout a period of almost two years of age, their activity will decrease and possibly disappear. CYP3A5, CYP2C19 and SULT1A1 are examples of the second group of enzymes that will become more active later in life and show an increase after birth, but become more prominent in later infancy and beyond. The third group (e.g. CYP2D6, CYP3A4) displays already some ontogeny in the second and third trimester of pregnancy with a relevant increase in phenotypic activity throughout early infancy [2,19].

There are various methods to study enzyme ontogeny ranging from *in vitro* (messenger RNA transcription, enzyme expression and enzymatic activity) to *in vivo* (intrinsic hepatic glucuronidation of a probe, oxidizing processes, and metabolite concentration) methods [20]. Detailed insight in enzyme activity can be obtained by performing *in vitro* studies, although they are often restricted by the lack of tissue samples and translation to *in vivo* parameters in the clinical setting remains challenging [5]. With the use of probe drugs (compounds which are almost completely metabolized by the enzyme of interest), enzyme ontogeny can be investigated *in vivo*. However, also *in vivo* studies have their limitations with at best simultaneous collection of plasma and urine samples to estimate both formation clearance and subsequent elimination clearance [21].

Besides developmental changes, genetics may also affect DMEs maturation and influence the phenotypic variability in drug response. Genetic polymorphisms in DMEs, transporters or receptors may result in their activity to be enhanced, diminished or unaltered, resulting in marked inter-individual variability in PK and PD [22,23]. Genetic polymorphisms may influence the risk of adverse effects. CYP3A4 is the most dominant enzyme and the large inter-individual variation in activity has suggested inheritance [24]. CYP3A4 is one of four genes (CYP3A4, CYP3A5, CYP3A7, and CYP3A43) which are located on chromosome 7 and are part of the cytochrome P450 3A gene family. More than 30 single nucleotide polymorphisms (SNPs) have been described in CYP3A4 gene. Although variations in PG exhibit a clear influence in adults, several considerations need to be taken into account in neonates. When there is still low phenotypic enzyme activity, the additional impact of PG driven reduction will be limited, as illustrated for CYP2C19 [25]. Secondly, it is insufficient to explore only PG variations initially described in adults to neonates: neonates are not just small adults [26]. This may be considered for CYP3A7, having a higher phenotypic activity in early infancy with a subsequent important drop.

Finally, the impact of genetic polymorphisms interrelates with maturational changes, but also non-maturational changes can affect the DME capacity [23]. It is not possible to provide extensive information on the impact and relevance of non-maturational variables within this review, and we refer the interested reader to recent reviews on non-maturational factors in neonates [23,27,28]. Grossly, non-maturational variables can be subdivided in inborn or acquired diseases and environmental influences. To further illustrate this, critical illness associated with inflammation results in down regulation of DMEs [27]. Perinatal asphyxia results in a decrease in renal function in neonates up to 40–50% [29,30]. Furthermore, the status of the ductus arteriosus (open/closed) has an impact on both clearance and volume of distribution. In a study investigating ibuprofen PK, a significant increase in ibuprofen clearance after

ductus closure was observed [31]. Examples of environmental factors are extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB). Both affect clearance up to the level that dose adjustments are indicated [27,28].

2. Fentanyl

2.1. Enzyme maturation

Fentanyl is a μ -opioid receptor agonist with rapid onset and is many times more potent compared to morphine. Fentanyl is metabolized by CYP3A4, which is primarily responsible for oxidation of drugs in order to make them more polar and facilitate elimination processes. The CYP3A subfamily is expressed in various tissues, but is most abundant in the liver [32,33]. Less than 8% (intravenous administration) of fentanyl is eliminated unchanged, mostly by urine and to a lesser extent in the stool, while 80% of the dose is recovered as metabolites. Fentanyl is mainly metabolized through N-dealkylation by CYP3A4 to its inactive metabolite, norfentanyl. Two minor routes, responsible for metabolism, are amide hydrolysis to despropionylfentanyl and terminal methyl hydroxylation to hydroxynorfentanyl [34,35]. To gain insight in the CYP3A4 ontogeny and its enzyme activity, Strougo *et al.* investigated the accuracy of maturational scaling approaches as published by Edginton *et al.*, Johnson *et al.*, and Bjorkman *et al.*, respectively [36–38]. Edginton *et al.* used data derived from *in vitro* and *in vivo* studies, whereas Johnson *et al.* and Bjorkman *et al.* used solely *in vitro* data. It was found that in neonates <10 days, a twofold difference with was observed between the three maturation functions. In all age groups, it was observed that the maturation of CYP3A seemed at adult levels above the age of 5 years. In addition, simulations illustrated that the contribution of CYP3A7 is predominantly relevant in children <3 months [6].

Discrepancies can be observed on the time points when enzyme activity is at adult levels (Figure 1) [36,39,40]. Edginton *et al.* estimated age-dependent enzyme activity values and these

Figure 1. Overview of enzyme activity in pediatric range according to percentages of adult enzyme activity (%). Data derived from literature [22,36,39,40].

were based on *in vitro* and *in vivo* clearance data gathered from literature of children from all age ranges [36]. Isoform enzyme activity was characterized for CYP3A4 and CYP3A7 by Lu *et al.* to explore the postnatal evaluation based on banked liver samples from fetus, neonates, infants, and adults [39]. Discrepancies in maturation profiles between publications can be observed (Figure 1). This may be due to different analytical methods to quantify the percentage of adult enzyme activity. Inconsistency can be observed when the ratios at one-year level are compared, as Lu *et al.* stated that the CYP3A4 enzyme activity amounted less than 50% of adult levels compared to the 100% and 120% of Edginton *et al.* and Alcorn *et al.*, respectively [36,39,40]. CYP3A7 has a fascinating maturation profile, where the enzyme activity reaches highest level in fetal period and decreases over time, almost dissipating at adult age.

While fentanyl is metabolized by CYP3A4 in adults, the presence of an enzyme switch may be important for this analgesic in infants. It is hypothesized that drugs that are mainly metabolized by CYP3A4 in adults, are likely or potentially metabolized by CYP3A7 in neonates and young infants [6]. CYP3A7 is the major CYP isoform detected in human embryonic, fetal, and newborn liver, but decreases rapidly during the first week of life. The CYP3A7 gene is also located on chromosome 7 (identical as CYP3A4) and its nucleotide sequence is nearly 95% homologous to CYP3A4, suggesting similar functional properties [40,41]. It appears that there is a postnatal switch from fetal CYP3A7 to CYP3A4 over the first 3 months of life [6]. CYP3A7 predominates before birth and is then replaced by CYP3A4 during the first 3 months of life [6,40]. Currently, the data are still inconclusive and contradictory as Daly *et al.* suggested that substrate sharing between CYP3A7 and CYP3A4 is minimal and exogenous compounds shared between those enzymes are profoundly metabolized by CYP3A4 [42]. Therefore, it is uncertain if, for example, the available *in vivo* observations on cisapride and sildenafil disposition only indicate CYP3A4 ontogeny [43,44]. Because of this inconclusiveness, it might be important to consider the influence of CYP3A7 during preclinical studies in drug development to improve PK prediction in infants.

2.2. Non-maturational changes: PG and beyond

As mentioned earlier, the relevance of polymorphisms in neonates can be questioned when there is still low enzyme activity at birth for a given iso-enzyme (CYP3A7 is an exception and polymorphisms for CYP2D6 has been documented) [45]. Polymorphisms in CYP2C19 and CYP3A4 are not yet relevant for neonates. The CYP3A7 PG variant is especially of potential relevance during the perinatal period. However, these patterns cannot simply be translated from adults because the phenotypic CYP3A7 activity in adults is anyhow very low.

As mentioned before, CYP3A7 is an important DME in early infancy. CYP3A7 is predominantly expressed in the fetal liver. Catalytic activity of CYP3A7 is detectable as early as 50–60 days of gestation in the embryonic liver [46]. The polymorphic variant, CYP3A7*2 is an active enzyme with moderate higher-specific activity compared to CYP3A7*1 using dehydro-epiandrosterone (DHEA) [47]. Interestingly, an allelic variant of CYP3A7 has been identified in adults. In this variant, the CYP3A7 promoter has been replaced by the corresponding

region from the CYP3A4 promoter, resulting in persistent CYP3A7 expression in adults [48]. Similar to the CYP3A4 setting, neonates do not yet display high UGT2B7 enzyme expression or activity, therefore the contribution of polymorphisms can be questioned. Polymorphism of UGT2B7 influences the metabolism of norfentanyl to its glucuronide in adults. However, this is an inactive metabolite and one can question its contribution in case of accumulation (poor metabolizer) [35].

When focusing on disease related non-maturational changes beyond CYP3A4 PG, Vet *et al.* investigated the effects of inflammation in critically ill children on drug metabolism. It was documented that inflammation downregulates CYP expression and with this the capacity to metabolize drugs, which results in a (62.3%) decrease in clearance. However the use of CRP as an indicator of the amount of illness is still under debate. Equally important is the shift in disease degree over time in the days following admission (intra-patient trends). Recent pooling of this data with other data (including preterm neonates) resulted in accurate prediction from term neonates onwards. However, no accurate prediction of clearance was obtained in preterm infants, likely illustrating the complexity to disentangle maturation versus organ failure related differences [49].

An environmental related factor such as the need for ventilation illustrated that midazolam clearance in critically ill and ventilated neonates was lower compared to non-ventilated children [27,49]. Additional research showed that midazolam clearance values increased threefold during the first 5 days of ECMO [50]. Due to similar CYP3A metabolism between midazolam and fentanyl, these factors can also be of relevance for fentanyl metabolism.

3. Morphine

3.1. Enzyme maturation

Morphine produces its analgesic effect through μ_1 - and μ_2 -opioid receptors, reduces behavioral and hormonal responses, improves ventilator synchrony, alleviates postoperative pain, sedates ventilated preterm neonates and alleviates acute procedural pain [51]. Morphine target concentrations have been suggested to be 125 ng/mL, with adverse effects and toxicity at morphine concentrations beyond 300 ng/mL although such targets are highly debated [52].

Morphine undergoes phase II metabolism by glucuronidation. This is a conjugation reaction and promotes passive renal elimination by increasing the water solubility of compounds. Uridine 5'-diphosphate (UDP)-glucuronosyl-transferases (UGT) catalyze the conjugation of glucuronic acid to their substrates [40]. The UGT iso-enzyme 2B7 is responsible for the glucuronidation of morphine into two active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) and one inactive metabolite normorphine. Approximately 90% of morphine is eliminated by hepatic metabolism. The kidneys subsequently excrete these glucuronides and therefore, impaired renal function leads to accumulation of M3G and M6G [53]. M3G is the major metabolite and comprises 45–55% of the metabolites, only 10–15% is converted into the active M6G (85–96% of morphine analgesic effect) [54].

Although M3G metabolites have a lower μ -receptor binding capacity compared to M6G metabolites, and an antagonistic effect of M3G metabolites is reported by several studies [55,56]. Interestingly, clearance through morphine metabolites was increased in neonates >10 days compared to younger neonates [57]. However, even in extreme premature neonates as young as 24 weeks of gestational age (GA), glucuronidation of morphine can already be observed [1].

3.2. Non-maturational changes: PG and beyond

A single pattern of glucuronidation does not exist, due to differences in substrate specificity, variations in metabolic and elimination pathways and diversity in the development of individual (UGT) iso-enzymes. Observed variability in morphine PK in early infancy is not the only result of DMEs maturation, but is also partly determined by genetic predisposition. Polymorphism -900G>A leads to altered UGT2B7 activity which affects morphine PK in neonates. Carriers of the -900A allele had significantly lower morphine plasma concentrations compared to -900G homozygous patients [58]. A randomized controlled trial in 64 neonates showed that the combined transporters opioid receptor μ_1 (OPRM1 118A>G) and catechol-O-methyltransferase (COMT 472 G > A) genotype correlated with the need for rescue morphine [59]. All these genetic differences may partly explain why some patients need higher opioid doses and why variations are observed in adverse effects [60]. Considering disease related factors, infants who underwent cardiac surgery showed consistently lower morphine clearance compared with age-matched peers undergoing noncardiac surgery [61]. Body cooling after asphyxia decreased morphine clearance and its metabolites [62,63].

4. A closer look into Pop-PK model: where do we stand and how to select?

As mentioned earlier, Pop-PK is a useful and valuable first step toward evidence-based dosing in neonates. In the previous paragraphs, it has been illustrated that both maturational (expressed as body weight or age) and non-maturational changes (e.g. disease state) affect PK during infancy. In this paragraph we will take a closer look into the Pop-PK models and explore if maturational and non-maturational changes have been investigated or incorporated in these models for the two model drugs. Over recent years, modeling and simulations techniques have been extensively applied and have resulted in an abundance of PK models for similar drugs and populations. Although it is commonly stated that 'all models are wrong but some are useful', it is still difficult, but valuable to discriminate which ones are indeed 'more' valuable and in what scenario. As a lot of research has been conducted with drugs (e.g. morphine) in infants, it is no longer a question whether we can develop a Pop-PK model for dosing regimens. The question arises whether we should continue to design models or instead, investigate if the collected samples of our population fit to already existing models or how we can attribute to already existing models (collecting additional covariates). To do so, the quality of the models should be assessed. Although many papers and best practices have

Box 1. Pre-model selection criteria.

Model selection

1. Population (demographic characteristics)
2. Data
 - a. Single/multicenter
 - b. Pro-/retrospective collection
 - c. No. of subjects
 - d. No. of concentration measurements
 - e. Time of concentration measurements
3. Administered dosage
4. Structural model and clinical relevance of included covariates
5. Parameter estimates & inter-individual variability
6. Graphical representation
7. Validation method

been published on model development and evaluation of models, this is not yet the case for model selection [64,65]. In Box 1 and 2 pre- and post-model selection criteria are provided. These will be applied to our two model drugs, fentanyl and morphine [65].

Considering the two model drugs, fentanyl and morphine, a systematic PubMed search (compound AND 'Pharmacokinetics' [Mesh] OR 'population' [Mesh] AND 'infant' [Mesh] OR 'newborn' [Mesh] OR 'child' [Mesh] OR 'pediatric' [Mesh]) was conducted on 29th of September 2017 to collect available PK models in neonates and infants. Fentanyl and morphine were used as compound Medical Subject Headings search term. In addition, references were examined and a supplementary search was performed to ascertain no duplicates were included and no studies were missed.

When focusing on Box 1, it should be evident that as a consequence of the complex maturation profile of phase I and II enzymes during infancy, studies incorporated data derived from (pre)term neonates are favored compared to studies that extrapolated PK parameters based on, for example, allometric scaling from children or adults. Wang *et al.* observed less bias and less over-prediction of clearance when data in infants were used in model development to predict neonatal exposure [66]. Similar, preference is given to multicenter data, because of variations in population in, for example different settings, time point measurements, and comorbidities compared to single center data. Next, the sampling time of concentration measurements is crucial as this will determine how accurate research questions can be answered. For example, when interested in the absorption profile, early sampling (in the absorption phase) is required. When considering volume of

Box 2. Post-model evaluation criteria according to Krekels et al. [65].

Model evaluation

1. No. parameters & condition number
2. Numerical diagnostics (e.g. bootstrap, relative standard error (RSE))
3. Goodness-of-fit (GOF) plots
4. Eta-shrinkage for parameters which included inter-individual variability
5. Normalized prediction distribution errors (NPDEs)
6. Individual and population parameter estimates vs. most predictive covariate in model.

AQ4

Box 3. Highlights covering the key aspects of the review.

Highlights box

- Maturation and non-maturational factors can influence pharmacokinetics (PK) of opioids in infants.
- For two model drugs, fentanyl and morphine, first steps are made in investigating the maturational and non-maturational factors.
- Maturational factors suggested are weight or age (postnatal, gestational age).
- Non-maturational covariates have also been reported (pharmacogenetics, inflammation, type of surgery, extracorporeal membrane oxygenation or cardiopulmonary bypass), although these are less incorporated in PK models and there is still limited knowledge on mechanisms involved.
- As there are already quite some published Pop-PK models for both morphine and fentanyl, the first step in model-building should no longer be to develop a new model. Instead, researchers should assess new data in the context of already available literature and to extent existing Pop-PK models to investigate the influence of additional maturational and non-maturational factors.
- To enable selection of the best fitted existing Pop-PK model to do this, pre- and post-model selection criteria are needed to accurately evaluate the already existing Pop-PK models.
- Fentanyl and morphine served as model drugs to illustrate how improved knowledge on maturational and non-maturational factors reflect in part (semi)physiological mechanisms that can be applied to estimate concentration time profiles for other compounds that undergo the same metabolic pathways.

distribution, it is necessary to have knowledge about the maximum (peak) concentration and translate this into relevant sampling times. If metabolites and/or clearance values are crucial, sampling over a longer period is recommended, and simultaneous sampling of blood and urine samples may be considered [67]. Since drug clearance is in general lower in early infancy compared to adults, a longer period to collect observations to estimate clearance is warranted. When comparing studies with different structural models it is important to realize that the defined structural model not only depends on the drug characteristics, but also on sampling time points. In early infancy, age and weight (which are highly correlated) are commonly included as significant covariates in Pop-PK models. During model development or evaluation, the relevance of included covariates should be checked for clinical applicability. For instance, the added value of height or certain test score included in a PK model in the neonatal population for a drug can be questioned, when these measurements (height/test scores) are not applied in clinical practice or are inaccurate. Finally, considering the evaluation of models, many graphical and numerical diagnostics have been assessed, such as goodness of fit plots (GOF, e.g. conditional weighted residuals (CWRES) over time, individual predictions (IPRED) vs. observed concentrations (OBSER)) in which can be stated whether the model can accurately describe the data or whether a trend can still be observed. The reliability of the estimated PK-parameters can be expressed in residual standard error (RSE) analysis. Normalized prediction distribution errors (NPDE), and bootstrap analysis are ways to internally validate your model.

An overview of post-model evaluation criteria are proposed by Krekels *et al.* [65] and are included in Box 2. Using external datasets for validation is favored compared to the use of only internal validation, because of aforementioned arguments concerning data collection in a single- or multicenter manner.

4.1. Fentanyl

Twenty-seven publications were retrieved using the Pubmed search, but many studies were not included since the studies were not Pop-PK studies. Together with an additional search, six Pop-PK studies were analyzed (Table 1). Variations were observed in the fentanyl dose across studies. In four studies, neonates were included (range 1–71 days) with weight ranging between 1.4 kg and 4.0 kg [68–71]. Two studies included only infants and children (range 1 month–4.5 years) with weight ranging between 3.7 kg and 17.3 kg [72,73]. Only one study included neonates, infants, children, and adolescents, although the total number ($n = 13$) of included subjects was limited [70]. Intravenous bolus administration was used in most studies ($n = 5$) followed by continuous infusion ($n = 2$), whereas one study applied only continuous infusion [68].

Focusing on the PK models, it was observed that covariates such as postnatal age (PNA) and weight (by allometric scaling) are implemented in the models. In none of the PK models maturational profiles according to CYP enzyme profiles or polymorphisms are incorporated or explored. Non-maturational aspects such as mechanical ventilation, cardiac surgery or drug–drug interactions with fentanyl have been investigated, but clear differences between patient groups are lacking and cannot be derived based on these results. Focusing on the PK parameters, clearance and distribution volume appeared to be higher in neonates compared to children and adults, which is possibly due to increased hepatic blood flow (normalized to weight) [70,74]. Clearance estimates are different between population groups for different studies (Figure 2). Allometric scaling is used with the standardized factor of 0.75 in only one study [72]. Only Santeiro *et al.* found a significant correlation between clearance and PNA [68]. In all studies, a two-compartmental model was defined as the most appropriate model structure to describe the PK profile of fentanyl. Except for the study of Santeiro *et al.* a one-compartmental model was identified, likely due to sparse and late sampling [68]. Pop-PK models were often not (sufficiently) validated in the early years of applying modeling techniques. Only van Driest *et al.* performed bootstrap analyses and generated goodness-of-fit plots to evaluate the predictability of the developed model [72]. Other studies have not performed any validation methods, which can question the translatability of the models.

To conclude, the vast majority of investigated models did not yet used validation or evaluation methods, except for van Driest *et al.* [72]. In future studies, these data can be converged in order to generate large multicenter datasets and in the end perform external validation. It may be beneficial to investigate the maturational changes (enzyme activity) and non-maturational changes (genetics, disease condition) and link these to the PK fentanyl profile. For example, for inflammation – as fentanyl and midazolam are both CYP3A substrates – collected data on fentanyl concentrations can be applied in the published midazolam model to explore if this model also describes fentanyl concentrations accurately [75].

4.2. Morphine

In total 53 studies were retrieved using the Pubmed search. After screening and additional searches, 13 publications were

Table 1. Overview population pharmacokinetic information on fentanyl in pediatric population-ordered chronological by year of publication.

N	Population	Age	Weight	Dose	Route	CL	V _c	V _{ss}	CMT	Allometric scaling/ covariates	No. of samples	Validation	Remarks	Year	Ref.
121	Infants	5.1 ms [1–21.8] ^a	6.1 kg [3.7–9.9] ^a	67 µg/kg per day [40–100] ^a	i.v. bolus + cont. inf.	36.3 L/h/70 kg	437 L/70 kg	/	2	Yes: factor 0.75	1079	GOF, bootstrap	Patients < 40 kg included in model	2016	[72]
93	Infants, children	8.1 ms [3.7–35] ^a	7.6 kg [5.1–12.8] ^a	63 µg/kg per day [39–90] ^a	i.v. bolus	38.9 L/h/70 kg	298.2 L/70 kg	/	2	Yes: factor 0.75	1079	GOF, bootstrap	Only bolus iv. Included model	2016	[72]
7	Neonates	16 ds (9) ^b 32 wks GA (4) ^b	1.88 kg (1.12) ^b	1.28 µg/kg/h (0.58) [0.53–1.9] ^b	Cont. inf.	1154 mL/kg/h (494) [565–2000] ^b	/	17 L/kg (9) [10.1–30.3] ^b	1	CL ~ PNA (r = 0.8)	5 per patient	None	Mechanical ventilation	1997	[68]
14	Neonates	18.3 ds [1–71 ds] ^b	2.7 kg [1.9–3.9] ^b	54.1 µg/kg (2.3) ^b	2 min i.v.	22.4 mL/kg/min [9–32.8] ^b	/	8.3 L/kg [4.8–11.9] ^b	2/3	No	23 samples/12 h per patient	None	No CL measurements (n = 2)	1988	[69]
14	Neonates	6 ds (3.2) [0–49] ^c	2.9 kg (0.2) [1.4–4] ^c	10–50 µg/kg	1–3 min. i. v.	17.67 mL/kg/min (4.08) [3.4–47.4] ^c	1.37 L/kg (0.33) [0.1–2.68] ^c	4.95 L/kg (0.95) [1.34–13.46] ^c	2	No	8/18 h per patient	None	Myelomeningocele, patent ductus arteriosus	1986	[71]
2	Neonates	1 ds (0) ^b	3.18 kg (1.1) ^b	30.3 µg/kg (16) ^b	2–10 min i. v. bolus	16.2 mL/kg/min (2.59) ^b	1.73 L/kg (1.1) ^b	5.94 L/kg (1.47) ^b	2	No	13 per 8 h	None	None	1984	[70]
2	Infants	7 ms (0.056) ^b	5.95 kg (1.2) ^b	19.1 µg/kg (14.5) ^b	2–10 min i. v. bolus	18.1 mL/kg/min (1.41) ^b	0.93 L/kg (0.14) ^b	4.45 L/kg (1.64) ^b	2	No	13 per 8 h	None	None	1984	[70]
6	Children	3.17 yrs (0.68) ^b	17.3 kg (3.39) ^b	10.0 µg/kg (3.07) ^b	2–10 min i. v. bolus	11.5 mL/kg/min (4.19) ^b	0.8 L/kg (0.42) ^b	3.06 L/kg (1.02) ^b	2	No	13 per 8 h	None	None	1984	[70]
3	Adolescents	12 yrs (1.73) ^b	58.3 kg (13.3) ^b	4.34 µg/kg (1.22) ^b	2–10 min i. v. bolus	7.05 mL/kg/min (1.24) ^b	0.28 L/kg (0.15) ^b	1.92 L/kg (1.04) ^b	2	No	13 per 8 h	None	None	1984	[70]
10	Infants, children	19 ms [5 ms–4.5 yrs] ^b	8.6 kg [4.4–12.2] ^b	50 µg/kg + 0.15 µg/kg (n = 4) or 0.3 µg/kg (n = 6)	1 min. i.v. bolus & cont. inf.	12.8 mL/kg/min (7.3) ^b	1.385 L/kg (0.875) ^b	/	2	Missing	Missing	Missing	Cardiac surgery with CPB	1984	[73]

n: number of patients included in analysis; CL: clearance; V_c: volume of distribution central compartment; V_{ss}: volume of distribution at steady-state; CMT: compartments; no.: number; ref.: reference; GA: gestational age; PNA: postnatal age; PMA: postmenstrual age; CV: coefficient of variation; i.v.: intravenous; cont. inf.: continuous infusion; ds: days; wks: weeks; ms: months; yrs: years; kg: kilogram; min: minutes; h: hour; GOF: goodness-of-fit plots; CPB: cardiopulmonary bypass.

a: median [interquartile range]

b: mean (SD) and/or [range]

c: mean (SEM) and/or [range]

d: median and/or [range]

Figure 2. Clearance values (mL/kg/min) for fentanyl for four different population groups derived from literature [68–73].

considered eligible and included in the analysis (Table 2). Population groups were considerably larger compared to the fentanyl studies. Four studies only included neonates [62,76–78] and four studies consisted of data solely based on children [79–82]. Five Pop-PK models were based on data of combined population groups (neonates, infants, children, and adolescents) [83–87]. Differences can be observed in route of administration, although intravenous administration is mostly used in neonates and infants. In older children, orally administered morphine is more common [76].

Morphine clearance correlates positive with postconceptional age and quadruples between 27 and 40 weeks postconceptional age, thereby necessitating corresponding increase in morphine dose to maintain effective analgesia [1]. Morphine glucuronidation is reduced by half in neonates with a PNA <10 days, independent of GA [88]. Although postmenstrual age (PMA) defines glucuronosyl transferase activity, transition from intrauterine to extrauterine environment (PNA) accelerates glucuronidation [89]. Scaling is implemented in 10 Pop-PK models with factors ranging from 0.75 to 1.44. Glomerular filtration rate correlated with morphine metabolite formation [87]. No consistency is found in the structural models. One-, two-, and three-compartmental models are observed, reflecting differences in sample times. Discrepancy can be observed in clearance values, whereas 10 studies reported morphine values, per kg or scaled (allometric, per 70 kg) [62,76–80,83,84,86,90], three studies reported morphine elimination clearances as elimination clearance of the metabolites (M3G and M6G) values [81,82,85].

Compared to fentanyl, validation methods are more often applied. Only three studies did not report any validation methods, be it limited to studies performed before 2006. All other studies applied some validation methods. NPDE, GOF, visual predictive checks (VPC), bootstrap analysis, simulations, and numerical analysis are widely applied. It is also observed that more often Pop-PK models are evaluated against predictions of previous developed models. Knosgaard *et al.*

compared five different Pop-PK models for morphine in children [77]. It is also noted that for morphine more often combined datasets are used for model building, which is encouraged.

Considering the abundance of Pop-PK models for morphine and the implementation of allometric scaling as a marker for maturational changes, it might be of interest to implement maturational profiles from DMEs. Subsequently, these can be correlated to clearance values of the metabolites. For morphine various non-maturational factors are investigated and used for model development, such as congenital heart surgery, artificial ventilation, and ECMO. In case of additional covariates of interest, it is suggested to investigate whether the parameters differ when applying data (incl. particular covariate) to a previous developed model.

5. Conclusion

Throughout infancy, maturational and non-maturational changes like genetic polymorphisms, disease state, or external influences (ECMO, hypothermia) can influence PK. Exploring the PK in this special population and its influencing factors is the first step toward an evidence-based dosing regimen. In this review, when focusing on two model drugs (morphine and fentanyl), we conclude that the maturation of a drug like morphine (metabolized by glucuronidation) is sufficiently well investigated. In contrast, for CYP3A4 metabolized compounds, like fentanyl, there is limited attention to distinguish CYP3A4 from CYP3A7 ontogeny. Age (gestational age, PNA, postmenstrual age) and weight (birth weight, current weight) obviously show collinearity. At the risk of oversimplification, it seems that glucuronidation is also driven by PNA, while cytochrome related maturation is mainly driven by weight or postmenstrual age. Compared to these maturational changes, there is still poor insight on the influence of PG and non-maturational factors. This is even more limited for fentanyl, but the knowledge obtained from midazolam studies (also a

Table 2. Overview population pharmacokinetic information on morphine in pediatric population-ordered chronological by year of publication.

N	Population	Age	Weight	Dose	Route	CL	Vd	CMT	Allometric scaling/ covariates	No. of samples	Validation	Remarks	Year	Ref.
20	Term neonates	39.1 wks GA [36–41.3] ^d	3.5 kg [1.82–5.3] ^d	40 µg/kg/6 h or 15 µg/kg/h (<48h) & 10 µg/kg/h (>48h) LD: 15 µg/kg FD: 0.06 µg/kg	Interm. (n = 10) or cont. inf. (n = 10)	0.765 L/h (48.2% CV)	4.01 L (49.5% CV)	2 CMT	AS; factor 1.23	106	Bootstrap, NPDE, simulations	Hypoxic ischemic encephalopathy	2017	[62]
20	Term neonates, infants, children	1.4 yrs [3 ds–5.4 yrs] ^b	7.8 kg [3.1–18.5] ^b	LD: 15 µg/kg FD: 0.06 µg/kg	i.v.	8.7 L/h (45% CV)	18.7 L (82% CV)	2 CMT	AS; factor 0.75 + GFR ~ metabolite formation	1080	NPDE, GOF, bootstrap	Congenital heart surgery	2016	[90]
34	Preterm and term	39.1 wks PMA (2.1) ^b 2 ds PMA (0.9) ^b	2.9 (0.4) ^b	0.08 mg/4 h Esc: 0.12, 0.16, 0.2 mg/4 h or 0.2, 0.28, 0.36 mg/3 h LD: 50–100 µg/kg	orally	75.3 L/h/70 kg	17.8 L/70 kg	3 CMT (as prior)	AS; factor 0.75 + W _{ad} 70 kg	88	NPDE, GOF, bootstrap, external model comparison	Abstinence syndrome	2016	[76]
30	Preterm neonates	F: 7.94 ds (4.67) [1–19] ^b (n = 16) M: 12.29 ds (11.28) [1–31] ^b (n = 14)	F: 0.73 kg (0.29) [0.53–1.62] ^b M: 0.86 kg (0.24) [0.61–1.4] ^b	LD: 100 µg/kg FU: 40 µg/kg/h FD: 5–10 µg/kg/h	i.v.	62.35 L/h/70 kg (8.74% SE) 69.4% BSV (15.61% SE)	105 L/70 kg (7.75% SE) 55.1% BSV (1.34% SE)	1 CMT	AS; factor 0.75 + W _{ad} 70 kg PMA ~ CL and PNA ~ metabolite elimination	206	VPC, NPDE, external model comparison	Compared with Anand, Bouwmeester, Knibbe, Wang models	2016	[77]
35	Children	Down subjects: 175 ds [127–272] ^a Controls: 155 ds [118–233] ^a	Down subjects: 6.0 kg [4.9–7.9] ^a Controls: 6.5 kg [5.5–7.2] ^a	LD: 100 µg/kg FU: 40 µg/kg/h FD: 5–10 µg/kg/h	i.v.	Formation: M3G: 0.049 (10% CV) M6G: 0.0051 (8% CV). Elimination: M3G: 0.0086 (10% CV) M6G: 0.0053 (10% CV)	4.697 L (14% CV)	2 CMT	BW on formation & elimination of metabolites	333	Internally (according to Knibbe <i>et al</i> [85].)	CL & V lower in cardiac surgery subjects	2016	[82]
40	Children	3.57 yrs (1.44) ^b 4.44 yrs (1.32) ^b 4.21 yrs (1.37) ^b	16.1 kg (3.5) ^b 17.97 kg (3.11) ^b 17.41 kg (4.53) ^b	0.1 mg/kg (n = 5) 0.2 mg/kg (n = 18) 0.3 mg/kg (n = 17)	orally	Formation: M3G: 0.776 M6G: 0.064 Elimination: M3G: 0.068 M6G: 0.042 L/min	4.96 L (66.25% ISV)	1 CMT	None	Unknown	VPC, bootstrap	Surgical procedures	2015	[81]
185	Term neonates, infants and children	0.1–1070 ds	1.9–16.8 kg	LD: 100 µg/kg FD: 10 µg/kg/h or 30 µg/kg/3 h	i.v. & bolus	23.14 mL/min/kg [43.9–388.7] ^f	0.657 L/kg [2.2–19.48] ^f	2 CMT	BW-based exponential model (BDE) (=exp. change with BW)	618	Numerical, diagnostic plots, shrinkage, NPDE, bootstrap	Postoperative medication	2013 (2002)	[86]
63	Preterm and term	0.1–6.7 ds	0.56–3.87 kg	LD: 100 µg/kg FD: 10 µg/kg/h	i.v. & bolus	23.14 mL/min/kg [12.9–89.55] ^f	0.657 L/kg [0.65–4.48] ^f	2 CMT	BDE model with factor 0.88–1.47	110	As above	Artificial ventilation	2013 (2003)	[86]
41	Preterm neonates	0.1–13 ds	0.64–3.55 kg	LD: 100 µg/kg FD: 10 or 15 µg/kg/h	i.v. & bolus	23.14 mL/min/kg [14.8–82.1] ^f	0.657 L/kg [0.74–4.12] ^f	2 CMT	BDE model with factor 0.88–1.47	88	As above	Artificial ventilation	2013 (2000)	[86]
28	Term neonates and infants	0.1–294 ds	1.7–9.3 kg	LD: 100 µg/kg FD: 5–10 µg/kg/h	i.v. & bolus	23.14 mL/min/kg [39.3–215.2] ^f	0.657 L/kg [1.97–10.78] ^f	2 CMT	BDE model with factor 0.88–1.47	98	As above	Postoperative	2013 (2007)	[86]

(Continued)

Table 2. (Continued).

N	Population	Age	Weight	Dose	Route	CL	Vd	CMT	Allometric scaling/ covariates	No. of samples	Validation	Remarks	Year	Ref.
9	Term neonates and infants	1–271 ds	2.64–8.1 kg	LD: 50 µg/kg FD: as needed		23.14 mL/min/kg [61–187.4] ^f	0.657 L/kg [3.06–9.39] ^f	2 CMT	BDE model with factor 0.88–1.47	16	As above	Postoperative	2013 (2000)	[86]
12	Term neonates and infants	3–354 ds	2.2–8.7 kg	24.21 µg/kg/h ^b	i.v.	23.14 mL/min/kg [50.1–201.3] ^f	0.657 L/kg [2.55–10.09] ^f	2 CMT	BDE model with factor 0.88–1.47	8	As above	Artificial ventilation	2013 (1992)	[86]
117	Children and adolescents	6–15 yrs	17.9–79.5 kg	0.2 mg/kg bolus	i.v.	23.14 mL/min/kg [414.2–1839.6] ^f	0.862 L/kg [11.76–52.24] ^f	2 CMT	BDE model with factor 0.88–1.47	264	As above	Adenotonsillectomy	2013 (2012)	[86]
146	Children	8.77 yrs [6.0–15.87] ^d	37.25 kg [17.9–79.5] ^d	0.2 mg/kg bolus	i.v.	0.873 L/min (7% CV)	12.8 L (12.2% CV)	2 CMT	AS; factor 1.54 for V and 0.259 for CL	332	Numerical, bootstrap, NPDE, GOF	77% Caucasian 20% African American	2012	[80]
64	Preterm neonates	0.4 ds [0.2–0.7] ^a	1.18 kg [0.863–1.793] ^a	LD: 100 µg/kg + FD: 10 µg/kg/h morphine or sodium chloride	i.v. & cont. inf.	Formation M3G: 3.48 M6G: 0.426 Elimination M3G: 2.02 M6G: 1.05 mL/min/kg ^k	1.81 L (17.4% CV)	2 CMT (+ mtb.)	AS; factor 1.44 + race on CL	199	NPDE, simulations	Artificial ventilation + arterial catheter	2009	[85]
59	Term neonates	2 ds [1–6] ^a	3.15 kg [2.8–3.58] ^a	LD: 100 µg/kg + FD: 10 µg/kg/h morphine or sodium chloride	i.v. & cont. inf.	Formation M3G: 3.48 M6G: 0.426 Elimination M3G: 2.02 M6G: 1.05 mL/min/kg ^k	1.81 L (17.4% CV)	2 CMT (+ mtb.)	AS; factor 1.44	142	NPDE, simulations	Artificial ventilation + arterial catheter	2009	[85]
113	Infants	178 ds [91–315] ^a	2.857 kg [2.04–3.552]	LD: 100 µg/kg + FD: 10 µg/kg/h or 30 µg/kg/3 h	i.v. & bolus	Formation M3G: 8.62 M6G: 0.67 Elimination M3G: 2.02 M6G: 1.05 mL/min/kg ^k	1.81 L (17.4% CV)	2 CMT (+ mtb.)	AS; factor 1.44	406	NPDE, simulations	Major thoracic or abdominal surgery	2009	[85]
12	Children	863 ds [763–919] ^a	3.215 kg [2.338–3.573] ^a	LD: 100 µg/kg + FD: 10 µg/kg/h or 30 µg/kg/3 h	i.v. & bolus	Formation M3G: 8.62 M6G: 0.67 Elimination M3G: 2.02 M6G: 1.05 mL/min/kg ^k	1.81 L (17.4% CV)	2 CMT (+ mtb.)	AS; factor 1.44	45	NPDE, simulations	Major thoracic or abdominal surgery	2009	[85]
898	Preterm neonates	0.27 wks PNA [0–2.84] ^d 27.35 wks PMA [23–32] ^a	1.04 kg [0.42–2.44] ^a	LD: 100 µg/kg/1h FD: 23–26 wks: 10 µg/kg/h 27–29 wks: 20 µg/kg/h 30–32 wks: 30 µg/kg/h	i.v. & cont. inf.	84.2 L/h/70 kg (48% CV)	122 L/kg (52% CV)	1 CMT	AS; factor 0.75 W _{aid} 70 kg	1598	VPC, bootstrap, external dataset	Ventilated, endotracheal tube	2008	[78]
14	Term neonates	40 wks GA [34–42] ^e	3.2 kg [2.2–4.4] ^e	LD: 100 µg/kg + FD: 0–40 µg/kg/h	i.v.	Day 1: 1.1 mL/kg/min Day 10: 6 mL/kg/min	Day 1: 1.89 L/kg Day 10: 3.33 L/kg	1 CMT	AS; factor 0.75 W _{aid} 70 kg	328	None	Extracorporeal membrane oxygenation (ECMO)	2006	[84]

(Continued)

Table 2. (Continued).

N	Population	Age	Weight	Dose	Route	CL	Vd	CMT	Allometric scaling/ covariates	No. of samples	Validation	Remarks	Year	Ref.
184	Infants	82 ds [1–580] ^e	4.2 kg [2.5–11] ^e	LD: 100 µg/kg + i.v. & bolus FD: 10 µg/kg/h or 30 µg/kg/ 3h	i.v. & bolus	Day 1: 5.3 mL/kg/min Day 10: 7 mL/kg/min	Day 1: 0.76 L/kg Day 10: 1.33 L/kg	1 CMT	AS; factor 0.75 W_{std} 70 kg	634	None	Postoperative morphine	2006	[84]
184	0–3 year children	195 ds [0–1070] ^b	5.9 kg [1.9–16.8] ^b	LD: 100 µg/kg FD: 10 µg/kg/h + placebo/3h OR placebo inf. + 30 µg/kg/3h	i.v.	71.1 L/h/70 kg	136 L/70 kg (59.3%CV)	1 CMT	AS; factor 0.75 W_{std} 70 kg	1856	GOF	Non cardiac thoracic & abdominal surgery	2004	[83]
18	Children	6.3 yrs [1.7–9.0] ^a	34 kg [12–70] ^a	1.4 mg/kg/day [0.3–25] ^b	Orally	37.4 mL/kg/min [20.1–48.5] ^a	7.1 L/kg [4.0–8.8] ^a	1 CMT	CL ~ age	4 samples per child	None	Cancer patients	1999	[79]
22	Children	13.8 yrs [11.0–18.7]	34 kg [12–70] ^a	1.4 mg/kg/day [0.3–25] ^b	orally	21.9 mL/kg/min [16.9–26.7] ^a	4.7 L/kg [2.9–5.7] ^a	1 CMT	CL ~ age	4 samples per child	None	Cancer patients	1999	[79]

n, number of patients included in analysis; CL, clearance; Vd, volume of distribution; CMT, compartments; no., number; ref., reference; GA, gestational age; PMA, postmenstrual age; interm., intermittent dose; LD, loading dose; FD, follow-up dose; F, females; M, males; ISV, inter-subject variability; CV, coefficient of variation; AS, allometric scaling; i.v., intravenous; cont. inf., continuous infusion; ds, days; wks, weeks; ms, months; yrs, years; kg, kilogram; min., minutes; h, hour; GOFs, goodness-of-fit plots; NPDEs, normalized prediction distribution errors; W_{std} , standardized weight; CV, coefficient of variation; GFR, glomerular filtration rate; Esc, escalation; VPC, visual prediction error; SE, standard error; BSV, between subject variation; BW, body weight; mtb, metabolite; CPB, cardiopulmonary bypass.

a; median [25–70 interquartile range]

b; mean (SD) and/or [range]

c; mean (SEM) and/or [range]

d; median and/or [range]

e; median [10–90 interquartile range]

f; population mean [min-max] calculated according to weight range (mL/min/kg)

CYP3A4 substrate) can provide guidance. This matters, **because** the relevance of the data go beyond the compound-specific relevance.

This is because we should use these already available datasets and published Pop PK models – also for morphine and fentanyl – to put new datasets into these perspectives. This is a very effective approach to explore additional covariates or specific subpopulations, but should be preceded by a critical assessment of the published models. To facilitate this assessment, pre- and post-model assessment criteria were provided (Box 1 and Box 2, respectively).

6. Expert opinion

In this review, fentanyl (CYP3A) and morphine (UGT) served as model drugs to illustrate how improved knowledge on maturational and non-maturational factors supports drug dosing in infants. This is of relevance for the clinical care and how to conduct studies in these populations. Researchers and clinicians should be aware that the relevance of a given dataset of concentration time points and study-specific clinical characteristics goes beyond the individual study and dataset [91]. This is because these datasets contain merged information on clinical characteristics and concentration time points, and also reflect in part (semi) physiological mechanisms that can be applied to estimate concentration time profiles for other compounds that undergo the same metabolic pathways [92]. A standard approach to size and maturation, but also for other covariates hereby provides a framework for challenging new ideas and supports a consistent method of dosing [93]. This puts merging of datasets, creation of data warehouses, and model repositories into perspective since merging data results in additional knowledge toward model informed drug development. The ddmore.eu initiative is one of the examples how this can be achieved through structured dataset collection [94]. In this review, this has been illustrated by the pooled morphine initiative (maturational estimates, including PNA) [57], the pooled midazolam initiative (maturational estimates, impact of inflammation, inaccuracy in estimates for preterm neonates) [49], and the amikacin PK on the impact of perinatal asphyxia (–40% in renal clearance) [30].

For all these examples, pooled analysis resulted in improved knowledge on the impact of maturational (age, weight) and non-maturational (e.g. clinical characteristics, inflammation, perinatal asphyxia) factors. Alternatively, knowledge gaps were highlighted, like the inaccurate in dosing prediction for midazolam in preterm neonates [30,49,57]. Similar, pooled datasets can be used as reference data to explore population-specific covariates like PG (e.g. CYP3A7, sulphation enzymes) [25], drug–drug interactions (e.g. impact of phenobarbital on glucuronidation, impact of macrolides on CYP3A4 activity, ibuprofen co-administration) [95,96], or disease characteristics (e.g. hypothyroidism, intra-patient trends during and after ECMO, perinatal asphyxia) [97,98].

This also means that datasets and PK models are relevant beyond compound-specific observations, since the model reflect maturational physiology. These (semi)physiological mechanisms can subsequently be applied to estimate

concentration time profiles for other compounds that undergo the same metabolic pathways [92]. It is reasonable to assume that PK covariate models contain system-specific information that can be used as semi-physiological functions. Quantitative functions of these maturational clearance processes can be used to develop safer and more effective dosing regimens and first dosing in infants. Its applicability has been documented for the maturation of glomerular filtration rate to predict clearance of different aminoglycosides in neonates [95] and throughout human life [99] as well as for maturation of glucuronidation, extrapolating a covariate model from morphine to zidovudine [100]. Similar, decisions on dosing can be supported by PBPK modeling. In a comprehensive literature search, the physiological information of preterm neonates to establish a PBPK model has to be summarized and implemented into the database of generic PBPK software. For subsequent assessment of its accuracy, *in vivo* datasets are compared to estimates generated by the software [96,101]. Such software programs should cover also the fast changes in time-varying physiology in early infancy, as illustrated for CYP3A4 [102].

Although the association between CYP2D6 polymorphisms and the risk for sedation following codeine or tramadol administration is PK driven [103], we should not forget that the PK profile of a drug is more commonly only a first, but crucial step to determine and explore efficacy and safety (PD) in neonates or infants: developmental PD is the next and crucial step to really improve pharmacotherapy in infants [14,15]. Besides the difficulties related to disentangle the PK and PD in the setting of the commonly used multimodal analgesia, the contribution of an integrated PK/PD analysis to further improve analgesia is hereby still hampered by the limitations of the assessment tools and the heterogeneous character of pain syndromes. Despite numerous efforts to quantify pain, finding the optimal PD marker in infant pain studies still remains a challenge [15]. Although assessment tools to manage pain in neonates and infants were developed and validated, these tools – both behavioral and physiological – for infants do not yet adequately differentiate between nociception or pain compared to (dis)stress [15]. All currently available tools depend on subjective hetero-assessment, but it has recently been suggested that electrophysiological measurements may provide a more objective tool to better quantify pain and subsequent analgesic efficacy in infants [17]. However, this observation needs further validation, preferably in different pain models [17]. Mechanisms related to procedural pain differ from pain after surgery or chronic inflammatory pain. Quantitative systems pharmacology approaches have been suggested as an approach to explore these aspects [104]. Only once we have sufficiently robust ‘biomarkers’, we can further explore aspects related to developmental PD and its covariates.

In conclusion, PK and its covariates have been described, and the prediction of the concentration-time profiles for fentanyl and morphine has been improved because better understanding of the relevant maturational and non-maturational covariates. However, this is just a first step toward more effective management of pain since these PK data should subsequently be linked with valid assessment tools (pharmacodynamics) to learn when, how and how long analgesics

should be administered to alleviate pain and to protect the outcome of infants.

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Declaration of interest

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