42

Principles of clinical pharmacology applied to analgesics in children

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Summary

Analgesic dosing regimens should take into account the severity and type of pain, the therapeutic window of the drug, and also the age or developmental state of the child. Translation of these concepts to safe and effective pharmacological management of pain in neonates, infants, and children necessitates a thorough understanding of the principles of clinical pharmacology of analgesics in children. Growth, weight or size, and maturation or age evolve in children and profoundly affect the pharmacokinetics (concentration–time profile, absorption, distribution, metabolism, and excretion) and pharmacodynamics (concentration–effect profile, objective assessment) of drugs, and this is also the case for analgesics. This will result in extensive variability in dosing and effects throughout childhood, and this variability is most prominent in infancy. In addition to maturational changes, there are also nonmaturational aspects (pharmacogenetics (PGx), obesity, extreme preterm neonates, and critical illness) that should be considered to further improve dosing in every individual child.

Introduction

Clinical pharmacology aims to estimate drug-specific (side)-effects based on pharmacokinetics (PK) and pharmacodynamics (PD). PK (absorption, distribution, metabolism, and excretion (ADME)) hereby aims to describe the drug concentration over time ("what the body does to the drug") in a given compartment, like plasma, subcutaneous tissue, or cerebrospinal fluid (CSF). PD describes the link between drug concentrations and (side)-effects over time ("what the drug does to the body"). For analgesics, this can be illustrated by concentration–time profiles in plasma or CSF for PK, whilst PD covers both effects (analgesia) and side effects (sedation, bladder retention, obstipation). Besides mean or average estimates, clinical pharmacology also aims to predict and explain the extent of variability, and this is where pediatric clinical pharmacology has its specific characteristics, since between- and intrapatient variability is the key characteristic of children. This is because growth and development differences exist throughout the pediatric age span. These differences may profoundly alter the PK and PD of drugs in children (Brussee et al., 2016; Kearns et al., 2003). Weight gain, growth, and maturation hereby display collinearity but not linearity.

Historically, simple mathematic extrapolations were used to determine pediatric drug doses, either linear (kg, weight), or somewhat more advanced (body surface area, $kg^{0.75}$ weight) compared to adult weight and dose. With the progresses made in developmental pharmacology and its subsequent integration into clinical practice, it is well recognized that children are not simply "small adults," while neonates and infants are not just "small children": Drug-specific pharmacotherapy in children cannot be reduced to simple rules. For pharmacotherapy to manage pain in children, an integrated appreciation of both developmental PK (ADME) and PD should be considered. We want to provide some ADME and PD related illustrations on the relevance of such an integrated approach.

- **A:** Gastric emptying is delayed in neonates versus infants or children. This means that intestinal absorption is slower in early infancy, and this may delay the time to achieve the peak plasma concentration. This has been illustrated for, e.g., acetaminophen.
- **D:** The body composition displays maturational changes throughout pediatric life, which are most prominent during infancy. Neonates have a higher percentage of body water/weight and a lower fat/weight ratio. As a consequence, the distribution volume of acetaminophen is higher, and of propofol it is lower in early infancy.
- **D:** Plasma protein concentrations (albumin, α-1 acid glycoprotein) are lower in infants than in children or adults. Besides maturational changes, disease-related differences (sepsis and lower albumin, postoperative inflammatory response and α-1 acid glycoprotein) also occur. This may affect the unbound fraction of given drugs, like local anesthetics.
- **M:** Liver size and metabolic capacity display maturation ("ontogeny"). However, there is not just one maturational pattern as the different isoenzymes involved in drug metabolism show different developmental patterns.
- **E:** Renal elimination capacity matures with age and size, and covers both glomerular filtration rate and tubular secretion/resorption. Again, this maturation is most prominent in early infancy.

- **E:** In contrast, maturation of esterase enzymes (e.g., remifentanil degradation) is very limited and is already at adult equivalent phenotypic activity in neonates.

Major advances have been made in our understanding of the impact of maturational and nonmaturational (e.g., disease, PGx and drug–drug interactions) covariates on the clinical pharmacology patterns of most drugs, including analgesics (Brussee et al., 2017; Kearns et al., 2003). A thorough understand of these patterns is essential to safely and effectively manage pain throughout early life, from preterm neonates to adolescents (Anderson and Allegaert, 2010).

Related to developmental PD, objective scoring of pain by applying the golden standard of self-report is impossible in preverbal children (<3 years old). In an attempt to account for this, numerous pain assessment instruments have been developed showing redundancy in the items used (see section 'Metabolism of drugs').

Developmental pediatric pharmacokinetics

Dosing guidelines on analgesics in children should be guided by the general principles of developmental pharmacology. One should also consider the type and severity of pain and the age or developmental state of the child (Brussee et al., 2016; Boric et al., 2017), aiming for the claimed therapeutic window of the drug(s) involved. Only once these PK-associated aspects are sufficiently well characterized, potential developmental PD (cf. lower) can be considered. This is because most of the age-related "toxicity" can be explained by PK (ADME)-related processes. This chapter provides a more general overview of how clinical pharmacology affects the PK and PD of analgesics in children, driven by both maturational and non-maturational covariates.

As illustrated in **Figure 42.1**, the target or effect compartment of interest hereby varies. This target compartment can be peripheral tissues, the perineural or peridural space, up to the spinal canal or central nervous system (CNS). This means that PK collected in the blood compartment does not necessary reflect the concentration–effect relation well, but that a target or effect compartment (commonly reflecting the CNS concentrations) is more appropriate (Martini et al., 2011) (**Figure 42.1**). Though many studies used plasma concentrations as a biochemical marker of the effectiveness of analgesics, any relation between these concentrations and the extent of pain reduction is, at best, very poor. Even so, any analgesic still has to get into this compartment, driven by evolving ADME processes.

Absorption of drugs

Absorption describes the concentration–time pattern of a given drug after nonintravenous (IV) administration. The absorption pattern is captured by the absorption rate *(how fast?)* and the bioavailability *(how much?)*. When administered by other routes (e.g., sublingual, buccal, oral, rectal, cutaneous, and inhalational), drugs may not fully enter the systemic circulation. Compared to IV administration, a reduced percentage of the drug will enter the circulation. This is because there are barriers (e.g., skin and intestinal mucosa) that obstruct, limit, delay, or alter (first-pass metabolism) the drug during passage. The proportion that enters the systemic circulation is defined as the drug's bioavailability.

When assessing the clinical relevance and safety issues related to absorption patterns, we should also consider unintended absorption (e.g., resorption of local anesthetics after perineural, and subcutaneous or cutaneous injection or application). A second aspect is the variability and related predictability of absorption. Compared to oral administration, the relative bioavailability for acetaminophen after rectal administration is, on average, 0.54 but with a significant unexplained between-individual variability (0.2–0.8) (Anderson et al., 1999). It is the higher variability that makes effective rectal acetaminophen dosing regimens more difficult than the oral route. Since absorption and bioavailability of acetaminophen suppositories are unpredictable, delayed peak plasma concentration is observed compared to oral administration, rectal administration of acetaminophen may result in subtherapeutic plasma concentrations in a significant proportion of patients. Increasing the rectal dose guidelines will result in attainment of therapeutic plasma concentrations in a large proportion of patients but at the risk of overdosing in some cases with the higher bioavailability. We should therefore be aware that the causes of the variability remain unknown and unpredictable (Anderson et al., 1999). Similar patterns have been observed for thiopentone or methohexitone, for example. The between-individual absorption and relative bioavailability variability is more extensive than with oral administration, making rectal administration less suitable for repeated administration (Anderson and Allegaert, 2010).

Besides developmental changes in absorptive surfaces, absorption is affected by different maturational covariates. For the gastrointestinal tract, this includes the rate of gastric emptying and gastric pH, the ontogeny of intestinal motility, and the development of intestinal enzymes (first-pass metabolism) and transporters related to drug disposition. Gastric emptying in neonates is not only slower than in children or adults, but is also affected by the type of feeding. In neonates intragastric pH (>4) is elevated. This decreases the bioavailability of weak acids (phenobarbital) and increases the bioavailability of acid-labile drugs (penicillin G) after oral administration. Related to first-pass metabolism, maturational differences in intestinal drug-metabolizing enzyme activity in neonates and infants may affect the bioavailability of drugs (Hines, 2013). This can alter the systemic absorption of therapeutically active metabolites of certain drugs, like tramadol (with 0-desmethyl tramadol as active metabolite).

Similar developmental changes can be considered for the skin or respiratory tract. The skin displays maturational changes in absorptive surface (body surface area/weight) and permeability, either maturational (age) or nonmaturational (burns, eczema, bullous skin diseases). Relative to adults, the stratum corneum is thinner and the skin is also more hydrated in early life. This may result in an increase in percutaneous absorption during infancy, as topically applied drugs display greater systemic exposure in infants, which may result in toxic effects if the dose administered is not age-appropriately adjusted (e.g., lidocaine–prilocaine (EMLA) cream application in neonates). The bronchial tree also displays changes in absorptive surface, permeability, and in first-pass metabolism. Neonates have increased alveolar ventilation and a smaller functional residual capacity than adults. This is because of their increased chest wall compliance. Consequently, pulmonary absorption is generally faster in neonates (Anderson and Allegaert, 2010).

Distribution of drugs

The volume of distribution (l/kg or l) is a theoretical measure of the extent to which a drug distributes in the intravascular compartment,

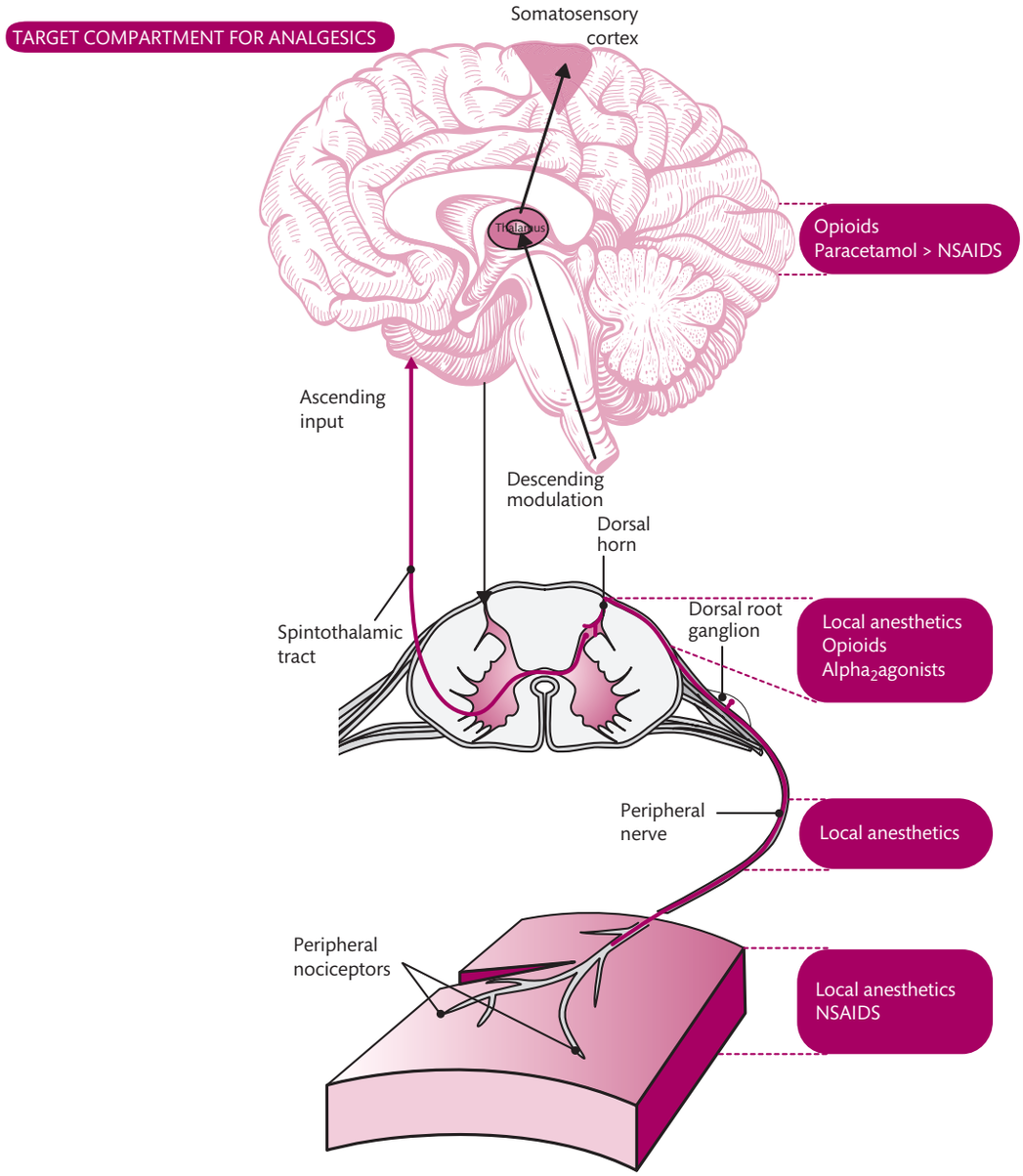

Figure 42.1 When assessing the relevance of clinical pharmacology (pharmacokinetics, pharmacodynamics), collecting data in the plasma compartment does not necessary reflect the target or effect compartment, as illustrated for different analgesics, like local anesthetics or analgesics that have their effects in the peripheral tissues or the central nervous system.

NSAIDs, nonsteroidal anti-inflammatory drugs.

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and migrates to extravascular compartments. These shifts to and from extravascular compartments can depend on passive processes (binding to plasma proteins or erythrocytes, permeability) or active processes (transporters). Besides the chemical characteristics of a given drug (e.g., molar weight and lipophilicity), the volume of distribution will be affected by population-specific characteristics, either developmental or nondevelopmental (Kearns et al., 2003; Allegaert, 2017). These characteristics relate to body composition, plasma protein content, regional blood flows, or the blood–brain barrier (BBB).

The *body composition* displays maturational changes throughout pediatric life, most prominent during infancy. Neonates have a higher percentage of body water/weight and a lower body fat/weight ratio. As a consequence, the distribution volume of acetaminophen or propofol are, respectively, higher and lower in early infancy. Similar, *plasma protein concentrations* (albumin, α-1 acid glycoprotein) are lower in infants than in children or adults. These lower amounts of total circulating plasma proteins result in a higher free fraction or concentration of drugs. This affects the availability of the active drug (PD) and its subsequent elimination (PK). Other

age-related physiological changes, such as differences in *organ perfusion or regional blood flow*, and permeability of cell membranes can also alter drug binding and distribution. Besides maturational changes, disease-related differences (e.g., renal impairment and edema, sepsis and lower albumin, postoperative inflammatory response and increase in α-1 acid glycoprotein, whole-body hypothermia affects regional organ perfusion, hyperbilirubinemia, and competitive binding to albumin) also occur. These factors may also affect the distribution or unbound fraction of given drugs.

The *BBB* is based on a network of tight junctions to reduce paracellular (passive) diffusion of drugs between the CNS and the blood compartment. This barrier function is further secured by active transcellular transporter mechanisms, like P-glycoprotein 1 (P-gp). P-gp, also known as multidrug resistance protein 1 or adenosine triphosphate-binding cassette subfamily B member 1, or cluster of differentiation 243, is a transporter protein located in the cell membrane. It acts as an efflux transporter to pump many compounds, including drugs, out of the CNS back to the blood compartment. Both the tight junctions, as well as P-gp expression and activity, display maturation, which is most prominent in early infancy with more permeable meninges. This means that the ratio of the plasma/CSF for opioids, for example, may be different in (pre)term neonates than in children, and may explain the higher sensitivity to opioids in this subpopulation. The amount of opioid that an infant brain is exposed to is, in part, dependent on the maturity of the BBB. For example, neonates are more sensitive to the respiratory effects of morphine and meperidine than older children and adults, and the greater permeability of the neonatal CNS to opioids is one contributing factor.

The clinical relevance of the maturational differences in distribution volume mainly relate to peak concentration or the time needed to reach the steady state or target concentration, pending on the PD of the drug. In the setting of a high distribution volume and the need to reach a target concentration for a given effect, a loading dose should be considered. This is illustrated in **Figure 42.2** for the acetaminophen concentration–time profiles in a term neonate when either a loading dose (20 mg/kg) or not is administered before the maintenance dose (10 mg/kg). Using a loading dose, the median target plasma acetaminophen concentration is attained much faster.

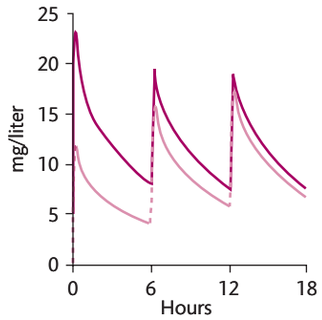

Figure 42.2 The concentration profile in a term neonate given either an acetaminophen loading dose (20 mg/kg, black continuous line) or not (gray continuous line), followed by a maintenance dose of 10 mg/kg every 6 hours. Both approaches finally result in a median target concentration of acetaminophen of 9–11 mg/l, but this target is reached sooner when a loading dose is administered.

Source: Reproduced courtesy of Karel Allegaert, Sinno Simons, and Dick Tibboel, all of Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands.

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Metabolism of drugs

Drug clearance is the volume of fluid that is completely cleared of a specific drug through either metabolism or elimination (cf. lower) for a given unit of time. It reflects the elimination capacity from the body for a given drug, and hereby reflects the average steady state or median concentration achieved with a maintenance dose. The biological purpose of drug metabolism is to convert drugs into more polar, water-soluble drugs to facilitate subsequent elimination by bile or urine. However, some metabolites (e.g., codeine to morphine, tramadol to O-desmethyl tramadol, midazolam to its glucuronide, morphine to its glucuronides, and acetaminophen to oxidative metabolites) have PD (side)-effects. Metabolic clearance is not only related to drug-specific characteristics, but also to developmental covariates, like the regional (hepatic) blood flow or the intrinsic isoenzyme-specific capacity, contribute to drug-specific clearance. The major site of drug metabolism is the liver, though the first-pass effect is also driven by intestinal drug metabolism, whilst other organs like the lungs, kidneys, blood cells (e.g., esterase function) or the CNS may also have relevant drug-specific metabolic capacity.

The major pathways involved in drug metabolism are phase I or phase II reactions. Phase I mainly covers "destructive" processes and results in structural changes of the drug, whilst phase II reactions are synthetic. Phase I involved processes like hydrolysis, oxidation, hydration, or reduction. The most relevant group of isoenzymes are the cytochrome P450 (CYP) enzymes, with a major contribution of CYP3A4/5 iso-enzymes. Other relevant isoenzymes are CYP1A2, CYP2B6, CYP2C8-10, CYP2C19, CYP2D6, and CYP2E1. Phase II involves glucuronidation, sulfation, glutathione conjugation, methylation, or acetylation. The most relevant groups of isoenzymes involved are uridine diphosphate-glucuronosyltransferases (UGTs) (Hines, 2013; Kearns et al., 2003; Anderson and Allegaert, 2010).

The phenotypic drug-metabolizing capacity is affected by multiple covariates. Throughout childhood, the most obvious covariates are maturation and growth. Liver microsomal protein content (20–25 mg/g liver proteins) is low in neonates, and subsequently increases with age to reach a maximum level of microsomal protein content (40 mg/g) at about 30 years of age. However, a single pattern suggesting that any drug metabolism is low in neonates, rising throughout infancy, early childhood and prepuberty to reach adult levels in puberty is too simplistic. Compared to older children and adults, neonates and infants exhibit distinct developmental immaturity of many phase I and phase II drug-metabolizing enzymes, which can contribute to differences in clearance, in effects, or in maturational toxicity. Hines (2013) suggested three different developmental patterns for drug metabolism enzymes: High in fetal life to low or absent postnatally (Class 1); stable throughout development (Class 2); or low in fetal life to high postnatally (Class 3). This means that for a specific iso-enzyme, significant interindividual variation is observed in the timing of changes, creating isoenzyme-specific windows of rapid changes and subsequent hypervariability, either in neonates, in infants, or in later childhood. This is also of relevance when considering the clinical pharmacology of analgesics in children, as illustrated by the examples provided.

- ***Esterase***: The esterase enzyme seems to be already at an adult level of activity in early neonatal life. This means that dosing of drugs cleared by esterases such as remifentanil, propacetamol, or remimazolam will mainly be driven by allometric concepts, and will not display maturational changes.
- ***CYP2E1***: This isoenzyme matures according to a class 3 pattern (low in fetal life to high postnatally). Acetaminophen undergoes metabolic elimination by the CYP2E1 enzyme as a minor route of elimination (except in the setting of "toxic" levels) to the toxic metabolite *N*-acetyl-p-benzoquinone imine. As this isoenzyme still exhibits low phenotypic activity at delivery, acetaminophen intoxication is rather well tolerated in early neonatal life.
- ***CYP2D6***: This isoenzyme also matures according to a class 3 pattern, but with a pattern that is already evolving (50% of adult value at term gestation equivalent) in early neonatal life. This means that codeine or tramadol metabolism to morphine and 0-desmethyl tramadol, respectively, matures rather quickly.
- ***CYP3A4*:** This isoenzyme also matures according to a class 3 pattern, but with a pattern that evolves throughout infancy. This affects the maturational clearance of fentanyl or midazolam.
- ***Glucuronidation enzymes***: The ontogeny of the glucuronidation capacity relates to both postnatal and postmenstrual age or weight. This means that morphine, propofol, or acetaminophen glucuronidation is lower in the first 8–10 postnatal days of life. This may affect the metabolism of propofol (lower in the first 10 days of postnatal life), acetaminophen (sulfation > glucuronidation in neonates), or morphine (lower concentrations of morphine glucuronides in early neonatal life, which may result in age-dependent differences in (side)-effects).

Elimination of drugs

Except for specific drugs where exhalation (e.g., inhalational anesthetics) or metabolism (e.g., esterase) are the route of elimination, the most important route of elimination for most drugs is the renal route. Maturation of renal elimination capacity is a continuous process, which has already started during fetal life and is only complete at the end of childhood. Renal elimination covers both glomerular filtration rate (GFR), as well as renal tubular transport activity (both excretion and absorption) (Allegaert, 2017; Kearns et al., 2003). Intriguingly, these processes do not mature simultaneously. The GFR is 20–45 ml/min/1.73m² in the term neonate, with a subsequent progressive increase of 5–10 ml/min/1.73m²/week. During the first 2 weeks of life, there is a rapid and marked increase, which reaches its peak adult values by 8–12 months of age, when corrected for body surface area. When expressed in a weight-corrected approach (/kg), GFR relative to age is several-fold higher in toddlers than adults. Similarly, renal tubular functions (secretion, absorption) also display maturation, but with a later onset to reach adult capacity at the end of the first year of life.

Because of the relevance of prostaglandins on maturational GFR in early infancy, renal elimination clearance in early life can be compromised by administration of nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (–20%) or indomethacin (–40%). Similarly, maturational trends are not at the same pace for all maturational processes. The maturational differences between hepatic metabolism and subsequent renal maturation (or associated renal impairment) of its metabolites can result in accumulation of these metabolites, such as O-desmethyl tramadol (analgesia), morphine glucuronides (analgesia and side effects), or midazolam glucuronides (sedation) (Zuppa, 2012).

Nonmaturational covariates of pediatric pharmacotherapy

Besides the maturation-driven changes and differences in ADME within the pediatric age range, there is also increasing evidence of the relevance of exploring and considering nonmaturational covariates with regard to their impact on the PK analgesics. As drugs are more commonly administered to sick children, these covariates matter. To illustrate the potential relevance of such nonmaturational covariates, we highlight in the following subsections the relevance of preterm neonates and critically ill children, obese children, and PGx as covariates of pediatric pharmacotherapy.

Preterm neonates and critically ill children

Despite the increasing knowledge in the field of neonatal pain, many gaps and questions still remain. These gaps relate not only to assessment, prevention and treatment of painful procedures, but also to drug selection and dosing (Walter-Nicolet et al., 2017). The feasibility and relevance of a structured product development program in neonates (optimal study design based on preliminary data; model development; internal, external, and prospective evaluation; an individualized dosing regimen; long-term safety; PGx) has been reported for morphine, which also illustrates the feasibility of such programs (Smits et al., 2017). Acetaminophen metabolism is different in extreme preterm neonates. Compared to adults, very low exposure to glucuronide, but higher exposure to sulfate, cysteine, and mercapturate acetaminophen, metabolites was observed. Midazolam and fentanyl clearance, reflecting CYP3A4 activity, is lower and increases with age or weight. Propofol clearance reflects, in part, glucuronidation capacity, and so depends on both postmenstrual and postnatal age.

Similarly, the clinical status and treatment-related factors in the critically ill child also affect PK and, potentially, PD parameters, thereby resulting in additional intra- and interpatient variability causing differences in dose requirements. Acetaminophen disposition is altered in extracorporeal membrane oxygenation systems (Wildschut et al., 2010). Critical illness is associated with inflammation and downregulates drug-metabolizing enzyme activities, as illustrated for midazolam (up to 90% decrease in clearance) (Vet et al., 2016; Allegaert et al., 2017).

Propofol kinetics are altered in infants and in children recovering from cardiac surgery. Increased peripheral distribution volume and reduced metabolic clearance following surgery results in delayed elimination (Rigby-Jones et al., 2002).

Obese children

Increased body mass and obesity has become an increasingly common observation in children. Obviously, obesity alters body composition and physiological mechanisms, and it is reasonable to anticipate that this has important implications for drug dosing and safety. However, there is a lack of dosing guidelines for use in obese children, whilst the impact of obesity on drug safety and clinical outcomes is still poorly defined. The paucity of information needed for the safe and effective use of drugs in obese patients remains a problem (Harskamp-van Ginkel et al., 2015). This is also true for

analgo-sedatives, though some drug-specific observations became available (Anderson and Holford, 2017).

For acetaminophen, obesity results in higher clearance, with earlier and higher peak concentrations of acetaminophen cysteine and mercapturate. Whilst a higher dose may be appropriate to achieve adequate acetaminophen target concentrations, the increased CYP2E1-mediated pathway may preclude such dose adjustments. Fentanyl clearance is enhanced in adolescents with clinically severe obesity, whilst the volume of distribution is comparable. The PK of midazolam and its metabolites in overweight and obese adolescents show a marked increase in peripheral volume of distribution and a lack of influence on clearance. When compared to data in adults with obesity, a higher clearance of midazolam in obese adolescents is observed, likely due to less obesity-induced suppression of CYP3A activity.

Finally, the proposed maintenance dosing regimen for propofol uses total body weight in an allometric $kg^{0.75}$ function.

Pharmacogenetics

The concept of PGx reflects the fact that specific (side)-effects are not randomly distributed, but relate to genetically based variable expression and activity of transporters, and drug-metabolizing enzymes and/or receptors, due to polymorphisms (Matic et al., 2017). There are a multitude of genetic factors that can influence the disposition and action of a drug. These between-individual differences can also result in very different clinical responses to the same dose or concentration of a drug. This also applies to analgesics, and a PGx shortlist for implementation in clinical practice has been suggested (Matic et al., 2017).

In addition to the earlier discussed developmental changes, genetic polymorphisms in enzymes, transporters, or receptors can also significantly influence the PK and PD responses to certain drugs. Genetic polymorphisms of isoenzymes, transporters or receptors may result in their activity being enhanced, diminished, or unaltered, resulting in marked interindividual variability in PK and PD. Genetic polymorphisms may also explain variability in the risk of adverse effects, including withdrawal or abstinence syndromes.

Drug metabolism-related polymorphisms

The impact of UGT2B7 polymorphisms on the morphine-3-glucuronide/morphine ratio following a single bolus morphine administration in preterm infants has been described. Similarly, tramadol is metabolized by O-demethylation (CYPD26) to the PD active metabolite O-desmethyl tramadol (M1). This metabolite is subsequently eliminated by renal route, whilst M1 formation is, in part, explained by age-dependent activity and CYP2D6 polymorphisms (CYP2D6 activity score).

Related to CYP2D6 polymorphisms, four phenotypic classifications have been established: Poor metabolizers; intermediate metabolizers; extensive metabolizers; or ultrafast metabolizers. In relation to codeine analgesia, metabolism of codeine by CYP2D6 to the active metabolite, morphine, is necessary to achieve an analgesic effect. Therefore, phenotypes of clinical significance are as follows.

Poor metabolizers

This polymorphism is associated with therapeutic failure, as deletion or inactive variants of CYP2D6 results in reduced formation of morphine and subsequent lack of analgesia. Approximately 5–10% of Caucasians are phenotypically classified as poor metabolizers and thus are unable to make the conversion of codeine to morphine. Consequently, they fail to elicit analgesic effects with codeine. Interestingly, the incidence of poor metabolizer status is higher in children with sickle cell anemia, explaining, in part, the common therapeutic failure of codeine in these cases during sickle cell crisis.

Ultrafast metabolizers

This polymorphism is associated with severe opioid intoxication, as individuals carrying more than two functional CYP2D6 alleles may produce an excess amount of morphine from codeine, and this will also occur faster. Approximately 1–2% of Caucasians are classified as having the ultrafast metabolizer phenotype and therefore these individuals very rapidly and readily convert codeine to morphine, resulting in approximately 50% higher plasma concentrations of morphine corresponding to severe opioid intoxication, which may result in a high incidence of CNS depression.

Severe adverse events (apnea, obstructive breathing, sudden infant death syndrome) have been observed following codeine or tramadol administration in the presence of (unknown) high CYP2D6 activity score as this will facilitate metabolism to morphine and O-desmethyl tramadol, respectively. This has also been described in the setting of maternal ultrafast metabolizer status and breastfeeding, with subsequent overexposure of morphine through breastfeeding and sedation, or even sudden infant death.

Transporter-related polymorphisms

Using the earlier mentioned tramadol disposition dataset, the impact of organic cation transporter 1 polymorphisms on M1 exposure in neonates has also been quantified. As M1 has PD relevance, this likely has clinical relevance.

Receptor and post-receptor-related polymorphisms

The combination of polymorphisms in the μ-opioid receptor and catechol-O-methyl transferase genes results in synergism as the need for rescue morphine in mechanically ventilated newborns was associated with both polymorphisms. These receptor and postreceptor-related polymorphisms are also associated with the incidence and severity of neonatal abstinence syndrome. Besides the type and amount of drug taken by the mother, the extent and timing of fetal drug exposure, drug metabolism, and elimination in both the mother and the newborn and related PGx [Catechol-O-methyl-transferase, Opioid Receptor Mu 1, epigenetic variation (Cytosine methylation of DNA CpG sites)], and also co-exposure to either nicotine or other compounds, further contributes to the phenotypic variability in incidence and severity of neonatal abstinence syndrome.

Despite the resources invested in developing the field of PGx in pediatric clinical pharmacology, at present, only a limited number of polymorphisms have been detected that outweigh the maturational effects in neonates, infants, or children. This should stimulate integrated research on both developmental pharmacology and PGx, including the interaction between both (Allegaert et al., 2017). Though variations in PGx 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 PGx-driven change will likely be limited. In the clinical setting,

aspects of PGx should at least be considered when outlier-type patterns are observed.

Developmental pediatric pharmacodynamics

It is well established that physiological development and maturation not only affects drug disposition (PK, *what the body does to the drug*), but is also of relevance when we assess the mechanism of action and the response (effects and side effects) to a drug (PD, *what the drug does to the body*). The effect of ontogeny on the interactions between a drug within the human body and the consequence of these interactions are still incompletely understood, and available observations are limited.

The observation that PD effects are different in children is very commonly made in the clinical setting, but this is frequently owing to insufficient data on developmental PK, and how to dose this drug in children. In general, the PD responses to analgesics in children have much in common with the responses in adults once the developmental PK have been fully considered. However, even after taking the PK covariates into account, developmental PD for analgesics have been observed to be related to either effects (anesthetic vapor potency) or side effects (neurocognitive outcome after neonatal exposure to analgesics) (Anderson and Allegaert, 2010).

The minimal alveolar concentration (MAC) is a measure of anesthesic vapor potency. For almost all of these vapors (e.g., halothane and isoflurane), the MAC displays maturational differences and is lower in neonates than in infants and older children. Similarly, pediatric morphine dosing regimens corrected for PK differences resulted in effective doses that prevent overdosing for neonates with a postnatal age <10 days. The fact that many neonates and infants with a postnatal age ≥10 days still require rescue medication warrants PD studies to further optimize the dosing regimens and explore maturational PD for morphine (Krekels 2014). Functionally and morphologically, the human brain is immature at birth, which contributes to the variability in opioid-related analgesia and respiratory depression. Moreover, differences in myelination, in the permeability of the BBB, or receptor expression (γ-aminobutyric acid, *N*-methyl-D-aspartate, or μ-opioid receptor ontogeny) and function underpin these maturational PD differences and may be further affected by nonmaturational covariates (e.g., trauma and meningitis). The same likely hold true for developmental toxicity.

For acetaminophen and NSAIDS, short-term safety has been documented and quantified (e.g., renal impairment), and there is active research investigating the potential association between perinatal acetaminophen or NSAID exposure and atopy, fertility, and neurobehavior.

The proposed mechanism explaining the relationship between acetaminophen exposure and atopy is related to the nonselective inhibitory action on peripheral cyclooxygenase of acetaminophen in a setting of physiologically low arachidonic acid concentrations. The major problem with these data is confounding factors. The impaired masculinization may relate to reduced fetal testicular testosterone production following fetal acetaminophen exposure. For the neurobehavioral outcome, mechanisms relate to the impact on cerebral inflammation, or specific metabolites like cannabinoids.

Animal studies have shown that neonatal exposure to stress, pain, and also opioids and anesthetics is associated with changes in the CNS, with long-term functional and behavioral impairment. These effects seem clinically less relevant in humans. A possible reason is that in patients receiving opioids in the presence of pain, opioids and anesthetics are given in balanced therapeutic dosages and with adequate monitoring of physiological parameters, in contrast to animal studies (van den Bosch et al., 2017).

Pediatric pharmacotherapy for analgesics: Integration of pharmacokinetics and pharmacodynamics

Analgesics, including both peripheral (NSAIDS or local anesthetics) and centrally (e.g., acetaminophen, morphine and related opioid drugs) acting analgesics (**Figure 42.1**), are metabolized by several enzyme systems, including sulfation, glucuronidation, oxidation, and cytochrome P450 subtypes, mainly located in the liver. Age-driven maturation of these enzyme systems in neonates and infants influences the PK properties of these agents. Besides these factors, more data on the impact of nonmaturational covariates (e.g., preterm neonates and critically ill children, children with obesity, and PGx) have been observed. Besides maturational PK, differences in PD-related responses to analgesics should be considered, though the available data on these maturational differences is still more limited. The pharmacology of drug-specific therapies is covered in more detail in other chapters, but some are briefly mentioned here.

Acetaminophen and NSAIDS

Acetaminophen and NSAIDS are frequently used to treat mild-to-moderate pain and have also antipyretic effects, whilst NSAIDS also have anti-inflammatory (peripheral) effects. With the exception of the neonatal period, the PK and PD of NSAIDS in young children are similar to adults. Though there is the potential for gastrointestinal and renal toxicities, the incidence in children is less frequent than observed in adults. Of potential relevance in the future is the recent literature that describes associations between the extent of acetaminophen or NSAID exposure in perinatal life and infancy and atopy, respiratory symptoms, and neurocognitive or behavioral issues.

IV opioids

Morphine is the most commonly used IV opioid in neonates, infants, and children, as it provides potent analgesia, but age-related differences in both PK and PD responses during development pose challenges for selection of an appropriate dose. As the sensitivity of the CNS to morphine is increased in neonates, a lower initial dose of morphine is recommended, which is then titrated against individual response. In addition, the elimination half-life of morphine is more than twice as long as that observed in adults owing to the immaturity of the neonate's hepatic enzyme system. Morphine clearance increases and by 1 year of age the ratio of plasma to CSF morphine concentration is comparable to that of adults.

These drugs are commonly used as part of multimodal analgesia. Multimodal analgesia captures the effectiveness of individual agents in optimal dosages to maximize efficacy and minimize side effects from one analgesic (Yaster, 2010). This concept applies the theory that agents with different mechanisms of analgesia may have synergistic effects in preventing or treating acute pain when used in combination. Combined use of acetaminophen and NSAIDs has been proven to be more effective for "minor-to-moderate" types of surgery in children

(e.g., inguinal repair), whilst acetaminophen is also proven to be opioid sparing after major surgery in neonates and young infants.

Analgesic dosing regimens should take into account not only the severity and type of pain, and the therapeutic window of the drug, but also the age and developmental state of the child. Other analgesic techniques (e.g., locoregional and spinal) can be relevant as alternative approaches, whilst other drugs (e.g., clonidine and gabapentin) can be useful options for specific pain syndromes. Integrated PK/PD models are needed and a powerful tool to make progress. Once validated, PK/PD models can be used to derive optimal dosing regimens for children of different ages or different characteristics, which can be evaluated in a prospective study before implementation in clinical practice. The subsequent step is to develop approaches to ensure that formularies or guidelines update their drug dosing guidelines according to the most recent advances in research to enable clinicians to integrate these guidelines in daily practice (Brussee et al., 2016). In this way, the principles of clinical pharmacology applied to analgesics in children can really contribute to improved care.

Conclusions

The challenges when managing pain in pediatric patients are diverse and multiple, as pain remains a complicated, subjective experience of various etiologies, and with different mechanisms involved, whilst its assessment in preverbal patients remains difficult. As the first chapter of this section, we wanted to focus on the general principles of the clinical pharmacology of analgesics.

The physiological development or maturation of neonates, infants, and children has a significant impact on the PK and PD profile of many analgesic agents. However, the maturation of the different isoenzymes does not follow a single, uniform pattern, but displays isoenzyme-specific maturation. In addition to these maturational changes, nonmaturational covariates are also of relevance, as illustrated for drug-specific observations in preterm and critically ill children, children with obesity, and PGx.

Though significant progress has been made, ongoing investigations and research is required to achieve a thorough understanding of the impact of developmental and nondevelopmental changes in drug disposition, metabolism, and action, to further enhance safe and effective pharmacological management of pain in neonates, infants, and children.

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