LITERATURE REVIEW

Developmental pharmacokinetics of opioids in neonates

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ABSTRACT

Recognition and treatment of pain are now important indicators of the quality of care being delivered to neonates. However, population-specific characteristics have to be considered, necessitating an integrated, population-specific approach. Such an approach starts with a systematic evaluation of pain, using a validated pain-assessment instrument, and should be followed by effective interventions, mainly based on appropriate, i.e., safe and effective, administration of analgesics. We will illustrate the impact of age on the pharmacokinetics and metabolism of opioids using recently collected and reported observations of tramadol disposition in early neonatal life. Although distribution volume and clearance display age-dependent maturation, it is important to recognize that important, unexplained interindividual variability in drug metabolism is still observed. Research questions in the field of developmental pharmacokinetics of opioids should focus on covariables of relevance in the interindividual variability of both pharmacokinetics and pharmacodynamics of opioids in neonates and on long-term outcomes in preterm and term neonates to whom opioids were administered, with regard to behavioral consequences and effects on pain thresholds.

Key words: opioids, neonates, pharmacokinetics, interindividual variability

INTRODUCTION

Prevention and treatment of pain in preterm and term infants became major issues in neonatal care following the landmark observations of Anand et al.,[1,2] who documented that adequate analgesia decreased mortality and morbidity in preterm infants who had undergone ligation of a patent ductus arteriosus. The relevance of adequate analgesia regarding short- and long-term outcomes in neonates was confirmed in more recent studies, while more fundamental work was done to document anatomic and physiological pathways of nociception in neonates. Inadequate analgesia in neonatal life is associated with alterations in pain expression in later life; adequate analgesia, at least to a certain extent, normalizes these responses.[1,3-8] Recognition and treatment of pain are therefore important indicators nowadays of the quality of care being delivered to neonates, but population-specific characteristics have to be considered, necessitating an integrated, population-specific approach. Such an approach starts with a systematic evaluation of pain, using a validated pain assessment instrument, and should be followed by effective interventions mainly based on appropriate, i.e., safe and effective, administration of analgesics.[5,6,9] Appropriate analgesia in neonates therefore necessitates the integration of various aspects of developmental pharmacology into clinical and therapeutic decision making. Clinical pharmacology intends to predict drug-specific effects and side effects based on pharmacokinetics (dose-concentration relationships) and pharmacodynamics (dose-effect relationships) (Figure 1).[6,10,11] Developmental pharmacokinetics focuses on the maturational aspects of absorption, distribution, metabolism, and elimination of drugs during fetal, neonatal, and later stages of infancy.[10] Important alterations in renal and hepatic function occur in the perinatal period, reflected by maturational trends in drug metabolism and elimination in preterm and term infants. Renal clearance of drugs in preterm and term neonates is in general lower compared to that in infants and children, and it increases with postmenstrual (PMA) and postnatal age.[12] The specific hepatic metabolic pathways involved in drug metabolism are either nonsynthetic (known as Phase I, i.e., oxidation, reduction, hydrolysis) or synthetic (Phase II, i.e., glucuronidation, glycination, sulphation). The most important groups of hepatic enzymes involved in these metabolic processes are cytochrome P 450 (CYP) and the UDP-glucuronosyl transferase (UGT) isoenzymes, and all have an isoenzyme-specific maturational pattern.[13]

The impacts of both Phase I and Phase II processes are not always limited to pharmacokinetics alone. The

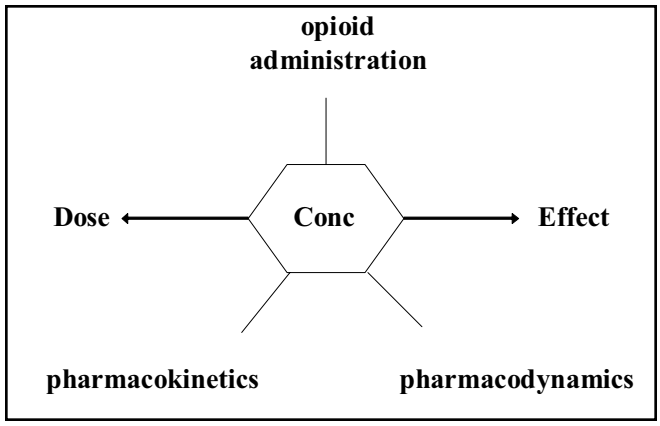

Figure 1. Schematic representation of various aspects of developmental pharmacology of opioids in neonates. Pharmacokinetics focuses on the concentration-time profile, while pharmacodynamics focuses on the concentration-effect profile.

processes might also be of relevance in the pharmacodynamics of opioids. Tramadol and codeine are partially metabolized to the more potent O-demethyl tramadol or morphine, respectively, by CYP2D6, while morphine undergoes glucuronidation by UGT2B7 to the more potent morphine-6-glucuronide.[10] The World Health Organization (WHO) analgesic ladder is a generally accepted guideline, initially developed for the treatment of cancer pain. Mild pain should be treated with nonopioid analgesics like paracetamol or nonselective cyclooxygenase inhibitors, moderate pain should be treated with opioids of moderate potency (e.g., codeine, tramadol) or combination drugs (paracetamol or nonsteroidal anti-inflammatory drugs combined with opioids of moderate potency), and severe pain should be treated with the most potent opioids (e.g., fentanyl, morphine). However, based on the above-mentioned maturational processes, the appropriate, i.e., effective and safe, administration of any analgesic remains a major challenge for caregivers. We recently summarized our observations on the pharmacokinetics of nonopioid analgesics in neonates.[9] In the present paper, we focus on various aspects of developmental pharmacokinetics of moderately potent (tramadol) and potent (morphine) opioids in neonates and young children. In our discussion, we will make some suggestions for potential directions for future research on interindividual variability in the pharmacokinetics of opioids in neonates.

DEVELOPMENTAL PHARMACOKINETICS OF OPIOIDS

Taking the above-mentioned WHO guidelines on analgesics into account, it is striking that basic pharmacokinetic estimates for moderately potent opioids like tramadol or codeine in neonates were still lacking in contrast with the available data on more potent opioids like fentanyl and morphine. Since well-known side effects of potent opioids in neonates are urinary retention, decreased gastrointestinal motility, and, most relevant, respiratory depression, opioids of moderate potency might be useful alternatives.[6,8,14,15] We therefore studied maturational aspects of tramadol pharmacokinetics and metabolism in neonates and young children. In the present paper, these observations will be used to illustrate a) the impact of age on distribution volume and clearance, b) the impact of age on Phase I–mediated metabolism, and c) the important, still-unexplained (age-independent) interindividual variability in drug metabolism.

Tramadol is an aminocyclohexanol derivative or 4-phenyl piperidine analogue of codeine. Its analgesic effect is mediated through noradrenaline reuptake inhibition, increased release and decreased reuptake of serotonin in the spinal cord, and a weak μ-opioid-receptor effect based on a 6,000-times weaker affinity for opioid receptors compared to morphine. Tramadol (M) is metabolized by either O-demethylation (CYP2D6) to O-demethyl tramadol (M1) or by N-demethylation (CYP3A4) to N-demethyl tramadol (M2).[16] The M1 metabolite has an agonistic μ opioid affinity approximately 200 times greater than tramadol. Therefore, phenotypic CYP2D6 isoenzyme activity is also of pharmacodynamic relevance.[17] Finally, tramadol and M1 also undergo Phase II processes (glucuronidation, sulfation).[18] Tramadol disposition therefore provides us with a probe to simultaneously illustrate the maturation of both CYP2D6 and UGT ontogeny.

Concentration-time profiles collected in neonates and young infants were combined with data on intravenous tramadol disposition in nine children with a median weight of 10.5 (8.5 to 24) kg and a median age of 2.4 (1.17 to 6.6) years following single intravenous bolus administration (2 mg/kg tramadol hydrochloride) as reported by Murthy et al.[16] in a population-pharmacokinetic analysis of tramadol and M1 time-concentration profiles, using nonlinear mixed-effects models (NONMEM). Tramadol pharmacokinetics were described using a two-compartment, zero-order input, first-order elimination, linear model.[17]

The central volume of distribution decreased from 25 weeks PMA (256 L/70 kg) to reach 120 percent of its mature value by 87 weeks PMA (Figure 2). This volume of distribution is of relevance when a specific concentration of a given drug should be reached for a given effect, and it is mainly of importance for calculating loading doses of the drug. In brief, relatively higher loading doses are needed in preterm and term neonates compared to older children and adults. Clearance increased from 25 weeks PMA (5.52 L/h/70 kg) to reach 84 percent of the mature value by 44 weeks PMA (standardized to a 70 kg person using allometric models). Total clearance was only 23 percent of the adult value at 25 weeks PMA, but

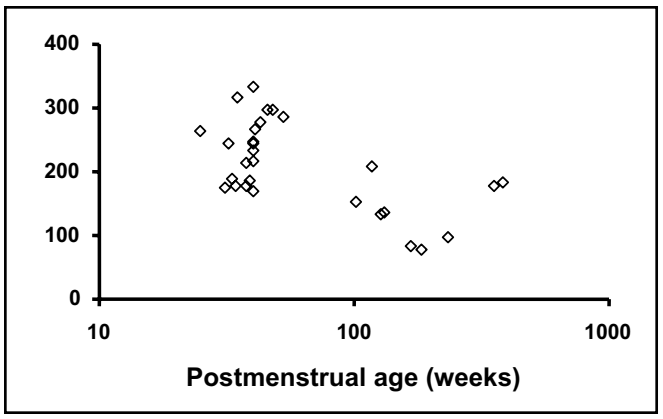

Figure 2. Age-dependent maturation of the distribution volume (L/70 kg) of tramadol in 20 neonates and nine children during intravenous administration of tramadol[17] (observations standardized to a 70 kg person using allometric models). X-axis: PMA (weeks); Y-axis: distribution volume (L/70 kg).

the maturation half-time was 10 weeks, and therefore clearance was 84 percent of the mature value by 44 weeks PMA (Figure 3).[17] The relatively lower clearance in preterm and term neonates results in lower maintenance doses compared to older children and adults. Both age-dependent trends in pharmacokinetic estimates (volume of distribution and clearance) are in line with earlier observations on morphine in preterm and term neonates.[14,15]

When tramadol metabolism is being considered, one should take into account that M1 production is also of pharmacodynamic relevance, but the CYP2D6 and UGT isoenzymes also display ontogeny. The impact of age on phenotypic CYP2D6 activity is illustrated in Figure 4. There is a fast increase in the contribution of M1 production to overall tramadol clearance in the first weeks of postnatal life, but age only partly explains the observed interindividual variability.[18]

UGT activity was assessed based on 24-hour urine collections. Compared to adult values, the contribution of glucuronidation to overall M1 elimination is at an adult level from PMA 44 to 46 weeks onwards, following age-dependent maturation with a maturation half-life of four to six weeks.[19] In line with CYP2D6 ontogeny, the impact of phenotypic glucuronidation activity is not strictly limited to either maturational pharmacokinetics or elimination, and it might also have pharmacodynamic relevance, since morphine-6-glucuronide is a more potent opioid compared to the parent compound.[6,8,11] Bouwmeester et al.[20] recently documented the relevance of UGT ontogeny to morphine disposition and thereby illustrated the fast increase in UGT phenotypic activity after the first week of life.

DISCUSSION

Neonates are able to feel pain and display cardiac, respiratory, hormonal, and metabolic changes when undergoing painful procedures. Although recognition and treatment of pain are now important indicators of the quality of care being delivered to neonates, population-specific difficulties have to be taken into account. Analgesia in preterm and term neonates differs in many ways from that in infants, children, and adults. We used tramadol disposition to illustrate various maturational aspects in early neonatal life and refer the interested reader to other, more extensive reviews on maturational pharmacokinetics of other opioids in early neonatal life.[14,15]

The relatively higher distribution volume and lower clearance in preterm compared to term neonates or infants is universal for all opioids presently available where ontogeny of drug metabolism might have a compound-specific impact. However, it is important to stress that visual inspection of Figures 2, 3, and 4 strongly suggests that age is only one of the determinants of drug metabolism in early life, since important interindividual variability that is independent of age is observed.

In general, phenotypic variation in drug disposition, pharmacokinetics, and pharmacodynamics is based on constitutional, genetic, and environmental factors.[10] In neonates and infants, it is anticipated that the phenotypic variation mainly reflects ontogeny, i.e., age-dependent (postmenstrual, postnatal) maturation. Age is, however, likely only one of the determinants of drug metabolism in early life, since important unexplained interindividual variability is observed. Consequently, there is an urgent need to search for other covariables involved in this interindividual variability. To date, based on a limited number of observations in neonates, it has to be anticipated that the birth process itself (i.e., the switch from feto-maternal to individual metabolism), disease characteristics, comorbidity, environmental factors, and/or polymorphisms contribute to the interindividual variability observed in the first months of life (Figure 5).[12,20-27]

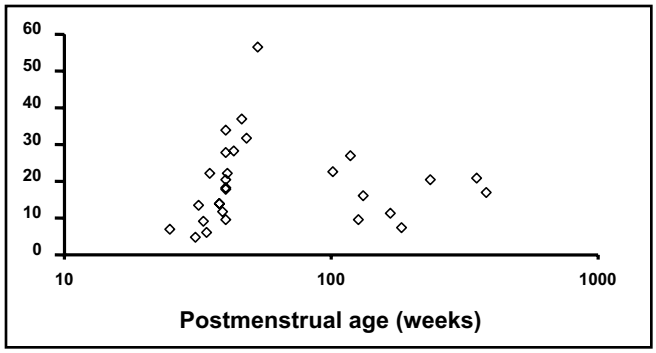

Figure 3. Age-dependent maturation of tramadol clearance (L/h/70 kg) in 20 neonates and nine children during intravenous administration[17] (observations standardized to a 70 kg person using allometric models). X-axis: PMA (weeks); Y-axis: tramadol clearance (L/h/70kg).

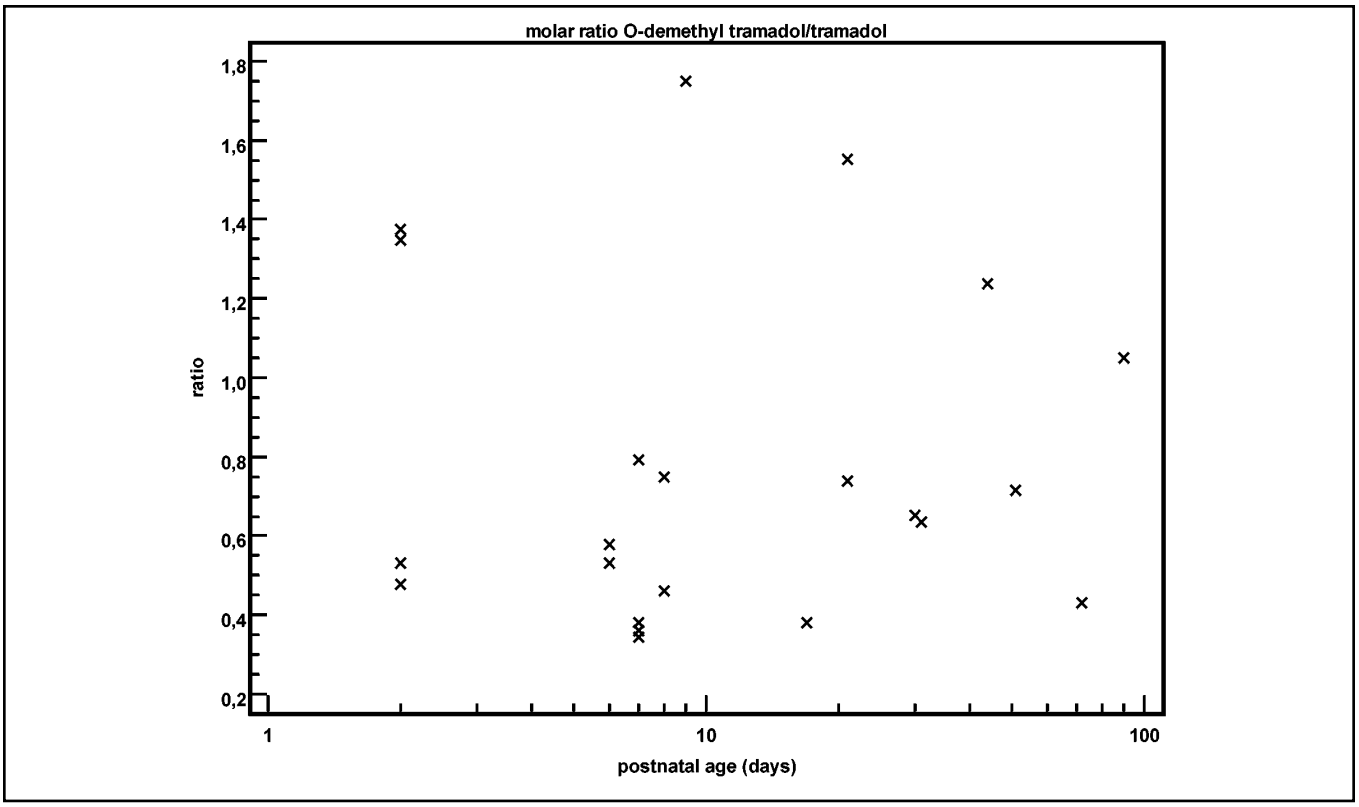

Figure 4. Observations on the molar O-demethyl tramadol:tramadol ratio eight hours after initiation of continuous intravenous tramadol administration could be made for 12 out of 20 included infants (range 1 to 90 days postnatal age). The significant increase in this ratio reflects increased phenotypic CYP2D6 activity in the first three months of postnatal life.[18]

Birth itself, either preterm or at term age, seems to be of relevance when drug metabolism and disposition are considered. Using a ^{15}N methacetin urine test, Krumbiegel et al.[21] documented the postnatal maturation of both CYP and glucuronidation capacity in term and preterm infants, thereby illustrating the relevance of both PMA and postnatal age. This is well known for the endogenous bilirubin metabolism (UGT1A1) but has also been documented by Bouwmeester et al.[20] for morphine glucuronidation (UGT2B7).

Disease severity might also have an effect on drug disposition, as has been shown in adults.[22] However, it might be more difficult to document a modest additional decrease in an isoenzyme-specific phenotypic activity when the a priori "healthy" phenotypic activity is itself low. In young children, though, this additional limited decrease in phenotypic activity might be of even more clinical relevance. Lynn et al.[23] documented that morphine clearance in children following cardiac surgery (postnatal age 1 to 380 days) is slower compared to cases of noncardiac surgery, whereas Carcillo et al.[24] reported on the negative effect of sepsis-mediated multiple organ failure on overall phenotypic CYP activity in children.

At present, there is still limited information on the impact of various environmental factors on drug metabolism in early neonatal life. Maternal tobacco consumption during pregnancy is associated with enhanced UGT activity.[10,13] More recently, Blake et al.[25] documented the effect of either breastfeeding or artificial feeding on drug metabolism in the first six months of postnatal life; caffeine disposition (3-demethylated metabolites) was enhanced, while no differences in dextromethorphan metabolism (3-hydroxy morphinan) were observed in formula-fed infants in the first year of life. It is to be anticipated that the history of the individual neonate or infant (previous surgery, previous drugs administered) will also contribute to interindividual variability in developmental pharmacokinetics.

Finally, polymorphisms likely contribute to the phenotypic pharmacokinetic activity observed in early neonatal life. Extreme preterm neonates all are phenotypic CYP2D6 slow metabolizers, but it is very likely that with increasing age the individual CYP2D6 activity will progressively reflect more of the various polymorphisms (wild type, slow metabolizer, or ultrarapid metabolizer) of this isoenzyme, in line with observations in children and adults.[26,27]

Future clinical research projects should try to shift from the presently available population-pharmacokinetic estimates toward more individualized titration of opioids,

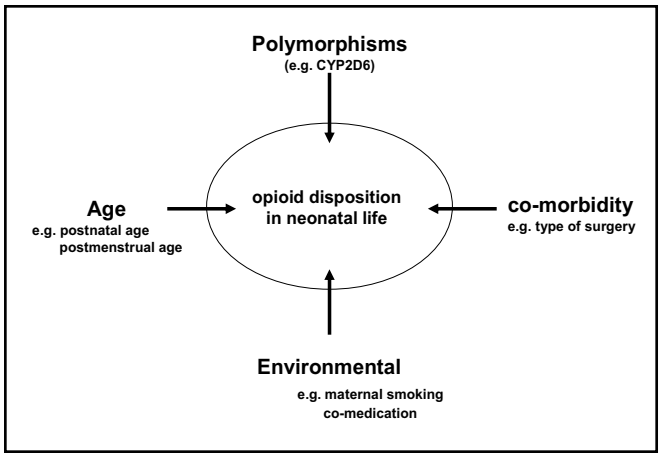

Figure 5. Contributors to interindividual variability in opioid disposition; covariables mentioned are discussed in the paper.[12,20-27]

taking the above-mentioned covariables into account. The implementation of multivariable models, like NONMEM, provide us with the tools to disentangle the impact of various covariables in this specific population, ultimately leading to more effective use of drugs. In neonates, besides allometric scaling, ontogeny is of relevance.[28-30]

Until additional data become available, we should try to implement the above-mentioned observations and data presently available into our clinical decision making. From a clinical point of view, it is important to stress that assessment in nonverbal patients should be based on systematic evaluation of pain expression, using validated pain scales, and should be followed by the titrated administration of analgesics as part of a "balanced analgesic approach." Also, physicians should anticipate that the need for opioids will display important interindividual variability, based in part on age and in part on other involved covariables.[31]

In searching for a balanced analgesic approach, the type of analgesic and the indications to initiate and/or continue administration should be (re)considered. Research questions in the field of neonatal opioid administration should focus on covariables of relevance in the interindividual variability of both pharmacokinetics and pharmacodynamics of opioids in neonates and on long-term outcomes of preterm and term neonates to whom opioids were administered, with regard to behavioral consequences and effects on pain thresholds.

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