

## Neonatal clinical pharmacology : recent observations of relevance for anaesthesiologists

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**Abstract :** Neonatal drug dosing needs to be based on the physiological characteristics of the newborn, the pharmacokinetic parameters of the drug and has to take maturational aspects of drug disposition into account. We would like to provide the reader with some recently published compound-specific observations (paracetamol, ibuprofen, tramadol, propofol) in neonates of relevance for anaesthesiologists.

Age-specific dosing regimes of intravenous paracetamol have been evaluated and were well tolerated, independent of the postnatal age. Administration of ibuprofen or acetyl salicylic acid resulted in a transient reduction of 20% of the glomerular filtration rate and should be used cautiously in newborns. Both postmenstrual age and pharmacogenetics (CYP2D6) were covariates of tramadol metabolism in newborns. Tramadol seems to be a potential useful analgesic for term neonates and infants, but has limited indications in (extreme) preterm neonates. Finally, propofol clearance depends on postmenstrual and postnatal age. There is a risk for accumulation in preterms and in the first two weeks of postnatal life.

**Key words :** Newborn ; developmental pharmacology ; tramadol ; paracetamol ; propofol ; ibuprofen.

### 1. NEONATAL CLINICAL PHARMACOLOGY

Many drugs in neonates and children are prescribed off-label or are unlicensed. Although this already occurs in the out-hospital setting (30%), it is most prominent in paediatric (70%) and neonatal (90%) intensive care (20). Off-label prescription has repeatedly been associated with an increased risk of (serious) adverse drug events. It is therefore obligatory that population-specific data are collected to secure quality, safety and evidence based prescription of drugs in neonates (12, 18, 20). When a drug is prescribed, it is with the intention to attain a proportional therapeutic effect without side-effects. Clinical pharmacology aims to predict these effects based on drug, population and/or patient-specific pharmacokinetics and -dynamics. In neonates, there are important age-dependent changes in body composition, weight (size) and maturation of hepatic

and renal function, resulting in extensive interindividual variability of drug disposition (14).

Developmental differences in the physiological composition and function of barriers (e.g. skin, gut mucosa, blood-brain barrier) can alter the rate and/or extent of drug absorption. Intestinal drug metabolizing enzymes (e.g. cytochromes, CYP) and efflux transporters (e.g. efflux transporter P-glycoprotein) can change drug bio-availability. Once absorbed, distribution will occur. The body fat content is markedly lower and the body water content is markedly higher in neonatal compared to paediatric life or adulthood. These findings have impact on the distribution volume of both lipophilic (e.g. propofol) and hydrophilic (e.g. paracetamol) drugs. Following absorption, most drugs undergo (hepatic) biotransformation (e.g. tramadol) and are subsequently excreted, mainly by renal route (e.g. ibuprofen). Age-dependent maturation of hepatic and renal function results in drug-specific, age-dependent maturation of clearance and is the phenotypic result of size/weight and iso-enzyme specific ontogeny (9, 12, 14, 18, 20).

In the evaluation of age-dependent metabolic processes, co-variables should be based on general biological principles, like age or size. Gestational age (GA, weeks) is the weeks of pregnancy at birth, postnatal age (PNA, days) are the days since birth, postmenstrual age (PMA, weeks) are the weeks of pregnancy + the postnatal weeks since birth. In neonates, the most relevant variable besides age is

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size, but it is important to appreciate the limitations of the scaling for size or weight. While body weight (/kg) is used most commonly in the clinical setting, it is recognized that there is a non-linear relationship between weight and metabolism. Body surface area (/m<sup>2</sup>) was subsequently proposed, but an allometric power model (kg<sup>0.75</sup>) might be an even more appropriate scaling because of the observation of a linear relationship between the logarithm of basal metabolic rate and weight with of slope of 0.75 (8).

This allometric kg<sup>0.75</sup> power model may be used to scale metabolic drug clearance. This has recently been documented for propofol clearance where this approach predicted the differences in clearance between rats and humans, both children and adults, but 'simple' allometric extrapolation to human neonates overestimated propofol clearance (4, 15). This is because – in addition to the size-dependent metabolic activity – neonates display iso-enzyme specific ontogeny. Clearance is lower in neonates as compared to adults and older children, attributed to the lower metabolic capacity, in part due to maturational aspects of cytochrome P450 (CYP) or UDP-glucuronosyltransferase (UGT) iso-enzymes as well as the immaturity of renal function, i.e. lower glomerular filtration and less effective tubular reabsorption/excretion (9, 12, 14, 18, 20). For CYP iso-enzymes involved in drug metabolism (e.g. CYP3A, CYP2D6, CYP2C19), maturation occurs in the first months to first years of life. However, some iso-enzymes like esterase activity, of relevance in remifentanyl and propacetamol metabolism, already reach an adult level of activity in early life (9).

Besides age and size, it is to be anticipated that other co-variables also contribute to the phenotypic interindividual variability in pharmacokinetics. It has been repeatedly documented that genetic polymorphisms contribute to the inter-individual variability in drug metabolism in adults. Until now, similar observations of the impact of genetic polymorphisms on inter-individual variability in drug metabolism in neonates were absent but have recently been documented for CYP2D6 mediated tramadol metabolism (2, 16). Co-morbidity, co-administration of other drugs and disease severity should be taken into account as additional parameters responsible for the variability in drug clearance (11, 16, 17). Renal clearance of drugs in neonates is in general lower as compared to infants and children and increases with PNA and PMA (13, 18).

Elimination clearance is mainly through the renal route. Urine output and renal clearance in neonates strongly depends on glomerular perfusion,

mediated by the vascular tone in the afferent and efferent glomerular arterioli and strongly depend on the vaso-dilative effects of prostaglandins on the afferent glomerular arterioles (13, 18). We would like to illustrate the impact of the above mentioned maturational changes on drug disposition in neonates based on recently reported observations on the disposition of various drugs (e.g. paracetamol, ibuprofen, tramadol, propofol) in neonates frequently administered by the anaesthesiologist.

## 2. COMPOUND SPECIFIC OBSERVATIONS IN NEONATES

### 2.1. *Intravenous paracetamol in neonates : evaluation of a dosing regimen*

Adequate management of pain in neonates is a major issue (9). Effective treatment of pain in this population is still in part hampered due to the limited data on pharmacokinetics and -dynamics of analgesics. This is even true for paracetamol (7, 8). The use of an intravenous formulation likely improves prediction of concentration and effect compared to enteral formulations by the elimination of variability due to absorption kinetics and bio-availability (6). In a stepwise approach, we documented aspects of disposition, metabolism and tolerance of intravenous paracetamol in neonates (1, 6). Based on a single intravenous dose study, pharmacokinetic estimates were calculated and a repeated dose regimen was developed. This dose regimen was subsequently evaluated in a repeated dose study, and paracetamol metabolism was described during repeated dose administration. Finally, hepatic tolerance in neonates of this regimen (table 1) was documented (6).

Although all pharmacokinetic data are available, product labelling for intravenous paracetamol unfortunately does not consider the clearance maturation with age in neonates in its dosing recommendations and even differs in different regions of the world. In Australasia the same dose of 15 mg kg<sup>-1</sup> /6 h is suggested for neonates over 10 days of age and for infants and children up to 33 kg. A reduced dose of 7.5 mg kg<sup>-1</sup> /6 h is proposed in term neonates less than 10 days of age while in Europe there is no labelled use for neonates less than 10 days of age. The registered dose is 7.5 mg kg<sup>-1</sup> /6 h for neonates after 10 days of age through to infants of 10 kg. A dose of 15 mg kg<sup>-1</sup> 6 h (max daily dose 60 mg kg<sup>-1</sup>) is recommended between 10 kg and 40 kg. It is very unlikely that paracetamol clearance in neonates is

Table 1  
Dosing regimes suggestions

a. <i>intravenous paracetamol dosing regimen in neonates</i> (1, 6)	
Dosing suggestions as evaluated and used in the Leuven Neonatal Intensive Care Unit. In the implementation of the dosing regimes in clinical care, frequency of administration and relative uniformity have also been considered for reasons of safety. These dose suggestions are not similar to the labelled dosing regimen in Europe and therefore, is off-label. The current regimen has been evaluated on aspects of pharmacokinetics, metabolism and hepatic tolerance. No data on pharmacodynamics of this or any other iv paracetamol regimen are currently available in neonates. The same dosing regimen are used after oral administration, since bioavailability is > 90%.	
Loading dose :	independent of postmenstrual age 20 mg/kg iv
Maintenance dose :	dependent of postmenstrual age
	< 31 wks PMA 2 × 10 mg/kg/day
	31-36 wks PMA 3 × 10 mg/kg/day
	> 36 wks PMA 4 × 10 mg/kg/day
b. <i>Intravenous tramadol administration in neonates</i> (2)	
Dosing suggestions are based on the limited M1 production in (extreme) preterm neonates with subsequent fast maturation of M1 synthesis. Due to maturational differences in M1 synthesis, it is to be anticipated that tramadol is ineffective in preterm neonates (< 34 weeks PMA).	
Loading dose	independent of the postmenstrual age 2 mg/kg iv over 30 minutes
Maintenance dose	6-8 mg/kg/24 h in continuous perfusion
c. <i>Propofol administration in neonates</i> (3, 4)	
Impaired clearance in preterm neonates and in term neonates in the first 2 weeks of life. We therefore recommend to be very cautious with repeated doses and/or continuous drip of propofol in the first weeks of life, independent of the gestational age at birth.	
Loading (induction) dose	1 to 3 mg/kg iv slow bolus

different in different parts of the world. In addition, these dosing regimens suggest something magic about 10 days although the use of a 10 day cut off for paracetamol dosing is not justified by the currently available evidence in literature.

It seems that for intravenous paracetamol, there continues to be a gap between routine clinical care and the registered dosing. The discrepancy between registered and off-label dose for paracetamol (enteral route) has been recently stressed by BUA *et al.* (10). A similar clinical scenario exist in adults, in whom the registered dosing regimen for intravenous paracetamol is  $4 \times 1 \text{ g day}^{-1}$ .

Intravenous paracetamol is a potential useful drug that should be considered in neonates, independent of the postnatal age (7, 19). Until data on pharmacodynamics in neonates are generated and based on our observations on pharmacokinetics and tolerance, we suggest to use the dosing regimen earlier published in literature. Because of a significant higher distribution volume of paracetamol in neonates, this is based on a loading dose ( $20 \text{ mg kg}^{-1}$ ) independent of the postmenstrual age, followed by a maintenance dose of  $10 \text{ mg kg}^{-1}$ , 2 to 4 times per day to compensate for the postmenstrual age dependent differences in paracetamol clearance (table 1).

## 2.2. *Ibuprofen in neonates : quantification of renal side effects*

Non-selective cyclo-oxygenase (COX) inhibitors like ibuprofen, acetylsalicylic acid or indomethacin are administered in early neonatal life to premature neonates to induce pharmacologic constriction of the patent ductus arteriosus (PDA). It is well known that these drugs cause adverse renal effects since renal perfusion and diuresis in early life are strongly influenced by the effects of prostaglandins on the afferent glomerular arterioles (13). Urine output, glomerular filtration rate (GFR) and tubular function are all different aspects of renal function (13, 18, 20). The adverse renal effects of non-selective COX-inhibitors on diuresis and glomerular filtration rate have been described in well designed animal experiments, but it is much more laborious and difficult to investigate their effect on GFR in human neonates, since neonatal creatinaemia still in part reflects maternal renal function (18).

Observations collected in two population pharmacokinetic studies in preterm neonates on amikacin and vancomycin clearance were used to estimate the impact of ibuprofen administration on renal drug clearance. Based on these two case

studies, we concluded that prophylactic administration of ibuprofen to preterm neonates in the first day of life to enhance closure of an asymptomatic patent ductus arteriosus (PDA) reduced amikacin clearance by 21% while co-administration of ibuprofen to induce closure of a symptomatic PDA resulted in an 18% reduction in vancomycin clearance in the first month of postnatal life (5). The administration of a specific drug is always a balanced decision between potential benefits and potential risks or side effects. Although non-selective COX-inhibitors are potent analgesics, specifically after trauma or surgery, the administration of these drugs as an analgesic in neonates should be weighted against the side effects, of which renal side effects have been quantified to result in a transient 20% reduction in GFR.

### 2.3. Intravenous tramadol in neonates: covariates of drug metabolism

Well known side effects of potent opioids in neonates are urinary retention, decreased gastrointestinal motility and most relevant, respiratory depression (7, 19). We therefore studied maturational aspects of tramadol disposition in neonates and young infants. Tramadol is an aminocyclohexanol derivative or 4-phenyl piperidine analogue of codeine. Its analgesic effect is mediated through noradrenaline re-uptake inhibition, increased release and decreased re-uptake of serotonin in the spinal cord and a weak mu-opioid receptor effect based on a 6000 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). The M1 metabolite has a mu-opioid agonistic affinity approximately 200 times greater than tramadol. Therefore, phenotypic CYP2D6 iso-enzyme activity is also of pharmacodynamic relevance (2).

Since data on contributors to the variability of overall tramadol clearance and *O*-demethyl tramadol (M1) formation in preterm neonates and young infants were limited, a population pharmacokinetic analysis of tramadol and M1 was undertaken using non-linear mixed effects models based on 593 observations collected in 57 neonates and young infants. Covariate analysis included weight, postmenstrual age (PMA), postnatal age (PNA), creatinaemia, (cardiac) surgery, cardiopathy and cytochrome (CYP)2D6 polymorphisms, classified by CYP2D6 activity score. Tramadol clearance at term age was 17.1 litre h<sup>-1</sup> (70 kg)<sup>-1</sup> (CV 37.2%).

Size (37.8%) and PMA (27.3%) contribute to this variability. M1 formation clearance, i.e. the contribution of M1 synthesis to clearance, was 4.11 litre h<sup>-1</sup>(70kg)<sup>-1</sup> (CV 110.9%) at term age. Size and PMA were the major contributors (52.7%) while the CYP2D6 activity score contributes 6.4% to this variability. M1 formation clearance is very low in preterm neonates, irrespective of the CYP2D6 activity score with subsequent CYP2D6 activity score dependent maturation (2).

The current pharmacokinetic observations suggest a limited mu-opioid receptor-mediated analgesic effect of M1 in preterm neonates and a potential CYP2D6 polymorphisms dependent effect beyond term age. Prospective studies on pharmacodynamics and the relation between pharmacokinetics and -dynamics in this specific population are needed but it can at least be anticipated that both age and pharmacogenetics will contribute to the interindividual variability. In the meanwhile, we suggest to use a loading dose of 2 mg kg<sup>-1</sup> over 30 minutes, followed by a maintenance dose of 6 to 8 mg kg<sup>-1</sup> 24 h<sup>-1</sup> in (near) term neonates and infants (table 1). In line with the use of tramadol in other populations, we co-administer paracetamol in the postoperative setting.

### 2.4. Propofol clearance in neonates: both postmenstrual and postnatal age are of relevance

Although disposition of propofol has been extensively studied in different populations of adult and paediatric age, data in neonates were still very limited. Propofol is a highly lipophilic compound and exhibits rapid distribution from blood into the central nervous system with subsequent redistribution. Elimination kinetics are triphasic and characterized by fast metabolic clearance. Although the use of propofol became standard of care for intravenous induction of anaesthesia and has been repeatedly reported in literature, the administration propofol still is off label in neonates (1-10).

In adults, urinary excretion of unchanged propofol only marginally (<1%) contributes to overall propofol clearance. Propofol clearance mainly depends on the hepatic blood flow (high extraction drug) with subsequent metabolism. Although multiple hepatic and extrahepatic human cytochrome (CYP) P450 isoforms (hydroxylation) are involved in propofol metabolism, glucuronidation is the major metabolic pathway (3, 4, 15). During paediatric life, phase I and phase II hepatic metabolism displays iso-enzyme dependent ontogeny while there are progressive changes in body

composition with subsequent effects on the relative distribution volume of lipophilic compounds. These maturational processes are most prominent in early neonatal life (13, 14). It is therefore to be anticipated that propofol disposition displays maturation.

To document co-variables who contribute to interindividual variability in propofol pharmacokinetics in preterm and term neonates, population pharmacokinetics were estimated based on 235 arterial blood samples collected in 25 (pre)term neonates after intravenous bolus administration of propofol (3 mg/kg, 10 seconds). Covariate analysis included PMA, PNA, GA, weight and creatinaemia. In a three compartment model, PMA was the most predictive covariate for clearance ( $p < 0.001$ ) when parameterized as  $[CL_{std} \cdot (PMA/38)^{11.5}]$ . Standardized propofol clearance ( $CL_{std}$ ) at 38 weeks PMA was 0.029 L/min. The addition of a fixed value in neonates with a postnatal age of  $\geq 10$  days further improved the model ( $p < 0.001$ ) and resulted in the equation  $[CL_{std} \cdot (PMA/38)^{11.5} + 0.03]$  for neonates  $\geq 10$  days. It was therefore concluded that both PMA and PNA contribute to the interindividual variability of propofol clearance with very fast maturation of clearance in neonatal life.

The PNA-dependent fixed value is 0.03, similar to the standardized propofol clearance (0.029 L/min) at 38 weeks PMA. This means that propofol clearance in a 38 weeks GA and  $< 10$  days PNA is similar to a preterm neonate of PMA 27 weeks, but  $> 10$  days PNA. This is of relevance in neonates since both preterm neonates and neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol. Single induction doses of 1 to 3 mg kg<sup>-1</sup> of propofol are mainly cleared through diffusion, while during repeated doses or during continuous maintenance dose, metabolic clearance rate is insufficient, resulting in higher plasma concentrations and delayed recovery (table 1).

### 3. SUMMARY AND PERSPECTIVES

Prevention and treatment of pain in neonates became a major issue in neonatal care since ANAND *et al.* documented that adequate analgesia decreased mortality and morbidity in preterm infants who underwent ligation of a patent ductus arteriosus (7). Recognition and treatment of pain are therefore nowadays important indicators of

quality of care delivered to neonates but population specific characteristics have to be considered. Such an approach starts with systematic evaluation of pain using a validated pain assessment instrument and should be followed by effective interventions, mainly based on appropriated, i.e. safe and effective administration of analgesics (7, 19). In the current review, we focussed on observations reported by the Leuven group in the last 5 years on aspects of drugs in neonates frequently administered by anaesthesiologists. We are aware that this paper therefore does not completely reflect the various modalities (e.g. non-pharmacological treatment, loco-regional techniques) currently available to treat pain in neonates. Taking this focus into account, observations on paracetamol, ibuprofen, tramadol and propofol disposition in neonates were discussed.

Age-specific dosing regimes of intravenous paracetamol in neonates have been evaluated and are safe, independent of the postnatal age. This drug has only been licensed from 10 days PNA onwards in Europe, although we are unaware of any argument against its use in the first week of life. A off-label dosing regimen has been suggested, based on unit-specific pharmacokinetic studies and evaluation (table 1) (1, 6). Administration of ibuprofen or acetyl salicylic acid results in a transient reduction of about 20% of the GFR and therefore should be used cautiously as an analgesic in newborns (5). Both PMA and pharmacogenetics (CYP2D6) were covariates of tramadol metabolism in newborns. Based on these observations, tramadol seems to be a potential useful drug for term neonates and infants, but likely has limited indications in (extreme) preterm neonates. A dosing regimen, based on a loading dose and maintenance dose has been formulated (2). Finally, propofol clearance depends on both postmenstrual and postnatal age. Preterm neonates and neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol. We therefore strongly suggest to limit its use in this specific population to single bolus administration for induction of anaesthesia (3, 4).

We are very much aware that the above mentioned studies have their limitations. Most of the studies have focussed on aspects of pharmacokinetics and not on pharmacodynamics yet and all drugs evaluated are at least for some subpopulations still off-label or unlicensed. Even taking these limitations into account, we hope that we provide anaesthesiologists with information on the use of various analgesics or anaesthetics in neonates.

### Acknowledgements

The clinical research of K Allegaert is supported by the Clinical Research Fund (Klinisch Onderzoeksfonds) of the University Hospitals Leuven, Belgium.

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