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Clinical Pharmacology of Paracetamol in Neonates: A Review

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ABSTRACT

Paracetamol is commonly used to control mild-to-moderate pain or to reduce opioid exposure as part of multimodal analgesia, and is the only compound recommended to treat fever in neonates.

Paracetamol clearance is lower in neonates than in children and adults. After metabolic conversion, paracetamol is subsequently eliminated by the renal route. The main metabolic conversions are conjugation with glucuronic acid and with sulphate. In the urine of neonates sulphated paracetamol concentration is higher than the glucuronidated paracetamol level, suggesting that sulfation prevails over glucuronidation in neonates. A loading dose of 20 mg/kg followed by 10 mg/kg every 6 hours of intravenous paracetamol is suggested to achieve a compartment concentration of 11 mg/L in late preterm and term neonates. Aiming for the same target concentration, oral doses are similar with rectal administration of 25 to 30 mg/kg/d in preterm neonates of 30 weeks' gestation, 45 mg/kg/d in preterm infants of 34 weeks' gestation, and 60 mg/kg/d in term neonates are suggested. The above-mentioned paracetamol doses for these indications (pain, fever) are well tolerated in neonates, but do not result in a significant increase in liver enzymes, and do not affect blood pressure and have limited effects on heart rate. In contrast, the higher doses suggested in extreme preterm neonates to induce closure of the patent ductus arteriosus have not yet been sufficiently evaluated regarding efficacy or safety. Moreover, focussed pharmacovigilance to explore the potential causal association between paracetamol exposure during perinatal life and infancy and subsequent atopy is warranted.

Introduction

Paracetamol, N-acetyl-p-aminophenol (also known as acetaminophen), is a readily available, over-the-counter antipyretic and analgesic compound. It is the most often prescribed drug to treat mild-to-moderate pain or fever in infants, including neonates, and can be administered by different routes (ie, oral, rectal, or intravenous). It has analgesic and antipyretic activity, but has only very modest peripheral anti-inflammatory properties.[1–3] In its therapeutic concentration range, paracetamol is metabolized by the liver to paracetamol-glucuronide (47%–62%) and paracetamol-sulphate (25%–36%) as main metabolites, and subsequently eliminated by the renal route in adults. Only 1% to 4% is excreted unchanged in urine, and about 8% to 10% of paracetamol is oxidized to 3-hydroxy-paracetamol and the (hepatic) toxic metabolite N-acetyl-p-benzo-quinone-imine (NAPQI).[4] Maturation-related changes in paracetamol disposition, metabolic, and elimination clearance occur throughout childhood, but are most prominent in early life.[5,6] Neonates have an overall lower paracetamol metabolic and elimination clearance capacity, and the between-subject variability is explained by covariates such as size or weight, organ function, or disease characteristics.[7–9] Compared with other drugs, a relevant body of evidence on pharmacokinetic properties and disposition of paracetamol in term and preterm neonates has been reported following intravenous and enteral (oral, rectal) administration. Despite this, there is still relevant variability in dosing suggestions as retrieved in reference textbooks or websites (**Table I**).[10–13]

Although intravenous paracetamol administration remains off label for specific subpopulations (eg, limited to term neonates, or children younger than age 2 years in the United States) in many countries, these formulations are increasingly used in neonates.[8,14,15] The registered dose is 7.5 mg/kg q6h for term neonates up to infants weighing 10 kg. A dose of 15 mg/kg q6h (max daily dose 60 mg/kg) is recommended between 10 and 40 kg body weight. In clinical practice, a loading dose (20 mg/kg) and higher maintenance doses are suggested (**Table I**) and have been evaluated in regard to efficacy and safety.[14,15]

Effective and safe drug administration in neonates should consider the evolving physiologic characteristics (eg, maturation and disease) of a newborn who will receive the drug and pharmacokinetic and pharmacodynamic properties of a given

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drug. Consequently, drug disposition in neonates is as diverse as the neonates who are admitted to our neonatal intensive care units.[16,17] This is also true for paracetamol. Using a systematic bibliographic search strategy, we aim to provide an overview on the pharmacokinetic and pharmacodynamic properties of paracetamol in neonates. This will be followed by a discussion with specific emphasis on newly emerging issues related to potential effects (patent ductus arteriosus [PDA]) and side effects (atopy and emerging biomarkers).

Literature Search

Our literature search was performed using PubMed and EMBASE databases as search engines. The following key words were used: *pharmacokinetics paracetamol/acetaminophen neonate*, *metabolism paracetamol/acetaminophen neonate*, and *effects paracetamol/acetaminophen neonate*. The reference list of each article was read carefully, and the selected references were examined.

Results

Pharmacokinetic properties and metabolism of paracetamol in neonates

Intravenous

The most recently reported pooled study on intravenous paracetamol pharmacokinetic properties was based on a population pharmacokinetic analysis of 3 published studies, resulting in 943 paracetamol observations in 158 neonates (27–45 weeks postmenstrual age [PMA]). There were only 58 preterm neonates, of whom 21 were extreme preterm, 19 had a birth weight lower than 1500 g, and 31 were small for gestational age.[8] A 2-compartment linear disposition model with first-order elimination fitted best to analyse time-concentration points. The volume of distribution was 70.4 L/70 kg and the clearance increased from 2.85 L/h per 70 kg at 27 weeks to reach 7.05 L/h per 70 kg by 42 weeks PMA.[8] Weight was the major covariate (57.5% of variance). Clearance expressed as milligrams per kilogram per hour increased only slightly with PMA (0.138 L/kg/h at 28 weeks PMA to 0.167 L/kg/h at 44 weeks PMA), and contributes to only 2.2% of variance. High unconjugated bilirubin levels only contributed an additional 1.2%. Based on this pooled analysis, it was concluded that size (predicted by weight) was the major covariate of clearance. We hereby mainly confirmed earlier clearance estimates in a further extended cohort of (pre) term neonates. Paracetamol clearance in neonates—described using allometric scaling—was one-third of the mature value reported in adults (16.2 L/h/70 kg).[6,8] Clearance maturation is slow before age 40 weeks PMA and subsequently matures rapidly to reach 90% of adult capacity at 1 year of life.[6,8] In addition, the distribution volume was higher in early infancy when compared with other pediatric populations.[6,8] The volume of distribution decreased from 27 weeks PMA (0.64 L/kg) to reach a mature value from 6 months of age (0.4–0.45 L/kg) onward. The increased volume of distribution in neonates supports the use of a larger initial dose (loading dose) of intravenous paracetamol in neonates if one aims to attain a given paracetamol threshold concentration sooner (ie, >10–11 mg/L[6,8]) because a higher distribution volume results in a proportionally lower peak concentration,[8,16] as reflected in **Table I**.

Finally, based on the pooled analysis, a mean paracetamol serum concentration of 11 mg/L was predicted in neonates aged 28 to 44 weeks PMA given a standard dose of 10 mg/kg/6 h intravenous paracetamol. In **Figure 1**, all pooled time-concentration observations collected in the Leuven cohorts are provided.[8,18,19] However, data of this drug in extreme preterm neonates were still limited. It is encouraging that since this pooled analysis, additional data have been reported or have been collected. This includes observations in a cohort of very preterm infants (<32 weeks gestational age) (N = 15). Repeated dosing (7.5 mg/kg q6h) resulted in median paracetamol levels of 10 mg/L

Table I
Dosing suggestions for paracetamol for (pre)term neonates as retrieved in reference sources.

Source	Administration route	Suggested dose
Neofax[10]		
Oral	Loading dose	20–25 mg/kg
	Maintenance	12–15 mg/kg/dose
	Interval	q6h in term neonates
		q8h in preterm neonates ≥ 32 wk PMA
		q12h in preterm neonates <32 wk PMA
Rectal	Loading dose	30 mg/kg
	Maintenance	12–18 mg/kg/dose
		q6h in term neonates
		q8h in preterm neonates ≥ 32 wk PMA
		q12h in preterm neonates <32 wk PMA
Intravenous	No suggestions provided	
BNFc[11]		
Oral	Loading dose	20 mg/kg
	Maintenance	10–15 mg/kg/dose
		q6–8 h in ≥ 32 wk
		q8–12h in <32 wk PMA
		≥ 32 wk PMA, max 60 mg/kg/d
		<32 wk PMA, max 30 mg/kg/d
Rectal	Loading dose	30 mg/kg in ≥ 32 wk
	Maintenance	20 mg/kg in <32 wk
		20 mg/kg q8h (max 60 mg/kg/d) ≥ 32 wk PMA
		15 mg/kg q12h (max 30 mg/kg/d) in <32 wk
Intravenous	Loading dose	No suggestions provided
	Maintenance	7.5 mg/kg, q4-6 h, max 30 mg/kg/d when <10 kg, and limited to term neonates
Neonatal formulary[12]		
Oral	Loading dose	24 mg/kg
	Maintenance	12 mg/kg/dose
		q4h in ≥ 32 wk PMA, q8h in <32 wk
Rectal	Loading dose	36 mg/kg
	Maintenance	24 mg/kg, q8h in term neonates
		No advice in preterm neonates
Intravenous	Loading dose	20 mg/kg, irrespective of age
	Maintenance	15 mg/kg, q6h in term cases
		12.5 mg/kg, 31–36 wk PMA
		10 mg/kg, ≤ 30 wk PMA
Dutch formulary[13]		
Oral	Loading dose	Not sufficiently supported by clinical evidence
	Maintenance	60 mg/kg/d, >32 wk PMA
		30 mg/kg/d, 28–32 wk PMA
Rectal	Loading dose	30 mg/kg, <32 wk PMA
	Maintenance	20 mg/kg, 28–32 wk PMA
		20 mg/kg, q8h in term neonates
		20 mg/kg, q12h in preterm neonates
Intravenous		Off label in preterm neonates
	Loading dose	20 mg/kg, irrespective of age
	Maintenance	10 mg/kg, max 40 mg/kg/d, in term cases
		10 mg/kg, max 30 mg/kg/d, 31–36 wk PMA
		10 mg/kg, max 20 mg/kg/d, <31 wk PMA

PMA = postmenstrual age (in weeks).