Seminars in Fetal & Neonatal Medicine xxx (2017) 1–6

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Perinatal and neonatal use of paracetamol for pain relief

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Keywords:
Breastfeeding
Newborn
Pain
Paracetamol
Safety
Target effect concentration

A B S T R A C T

Paracetamol (acetaminophen) is the most widely used drug to treat pain or fever in pregnant women or neonates, but its pharmacokinetics (PK) and pharmacodynamics (PD) warrant a focused analysis. During pregnancy, there is an important increase in paracetamol clearance. Consequently, it is reasonable to anticipate that the analgesic effect of paracetamol will decrease faster, whereas higher doses may result in even higher oxidative toxic metabolites. Therefore, most peripartal PD data relate to multimodal analgesia strategies. In neonates, weight/size is the most relevant covariate of paracetamol PK. This resulted in proposed dosing regimens containing higher doses than currently prescribed in the label for term neonates. Using adequate dosing, paracetamol is a poor procedural analgesic, is effective for mild-to-moderate pain, and has morphine-sparing effects. Short-term safety has been well documented, and there is active research investigating the potential association between paracetamol exposure and atopy, fertility, and neurobehavior.

1. Introduction

Paracetamol (acetaminophen) has clear analgesic and antipyretic activities, but only very small peripheral anti-inflammatory properties [1,2]. It is the most widely prescribed drug to treat mild-to-moderate pain or fever, even in pregnant women and during the postpartum period, or in (pre)term neonates. Paracetamol may be administered by different (enteral, intravenous) routes. However, there are specific issues with both pharmacokinetics (PK, concentration–time profile) as well as pharmacodynamics (PD, desired effects, but also unwanted side-effects), warranting a focused analysis on the available data in pregnant women and their newborns.

In its therapeutic concentration range, paracetamol is primarily metabolized by the liver into paracetamol glucuronide (47–62%) and paracetamol sulfate (25–36%) as its main metabolites with subsequent elimination by the renal route in non-pregnant adults. Only 1–4% is excreted unchanged in urine, and about 8–10% of paracetamol is oxidized to 3-hydroxyparacetamol and the (hepatic) toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) [1,3]. Pregnancy changes the PK of paracetamol significantly, whereas maturational changes in paracetamol disposition occur throughout childhood, but are most prominent during early infancy. These changes throughout the different stages of life warrant the use of population-specific data describing paracetamol PK to predict exposure before we can explore potential population-specific PD (both effects as well as side-effects). In adults and children, target effect compartment concentrations of 5 and 10 mg/L have been suggested for fever and pain, respectively [3]. However, these targets may also display maturational changes in early infancy due to maturational changes and/or during pregnancy.

Intriguingly, the mechanisms of actions for paracetamol are still only partially understood. Its central analgesic effect is mediated through activation of descending serotonergic pathways. Furthermore, there is inhibition of prostaglandin synthesis (cyclo-oxygenase, COX) and the formation of an active metabolite influencing cannabinoid receptors. It seems that paracetamol also has non-selective inhibitory action on peripheral COXs, besides these central effects. However, this inhibitory action only relates to physiological, low arachidonic acid concentrations, and this explains the difference with, for example, ibuprofen, that has more robust anti-inflammatory peripheral effects in an inflammatory setting [1,2].

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http://dx.doi.org/10.1016/j.siny.2017.07.006
1744-165X/

These pharmacological targets are of importance, since they may also contribute in explaining more recent proposed positive effects of paracetamol such as closure of a patent ductus arteriosus (PDA), as well as unwanted effects of paracetamol such as issues related to atopy, fertility and/or neurobehavior following perinatal exposure.

We are aware that PDA is covered in another review in this issue on perinatal pharmacology, but would like to mention that – based on the currently used high-dosing regimens in preterm neonates for this indication – a target effect concentration of 15 mg/L is being explored. This is a much higher concentration than used to treat pain or fever. We have recently highlighted this, because these higher targets have never been evaluated in preterm neonates and should therefore be carefully evaluated in order to detect potential side-effects [4]. In this review we discuss the different aspects of PK and PD (efficacy, safety) of paracetamol during pregnancy and in neonates.

2. Maternal use of paracetamol

2.1. Pharmacokinetics and metabolism of paracetamol during pregnancy and the peripartal period

Urinary excretion of paracetamol glucuronide in young women is affected by pregnancy (+200%), the early (3–4 months) postpartum period (−50%), or by using oral contraceptives (+42%) as compared to healthy female volunteers not taking oral contraceptives. This results in at least a two-fold variability in total paracetamol clearance in young women (Fig. 1) [5]. Besides the differences in glucuronidation, there is also a proportional increase in clearance of unchanged paracetamol as well as the metabolites of the oxidative pathway (toxic route). The latter finding likely limits further increase of paracetamol doses in this patient group, whereas the higher clearance may explain reduced efficacy of paracetamol administration at the time of delivery [6]. Based on 34 paired maternal/cord blood analyses in term neonates, Nitsche et al. recently reported that paracetamol PK profiles in the fetus parallel that of the mother (1000 mg paracetamol, oral), suggesting

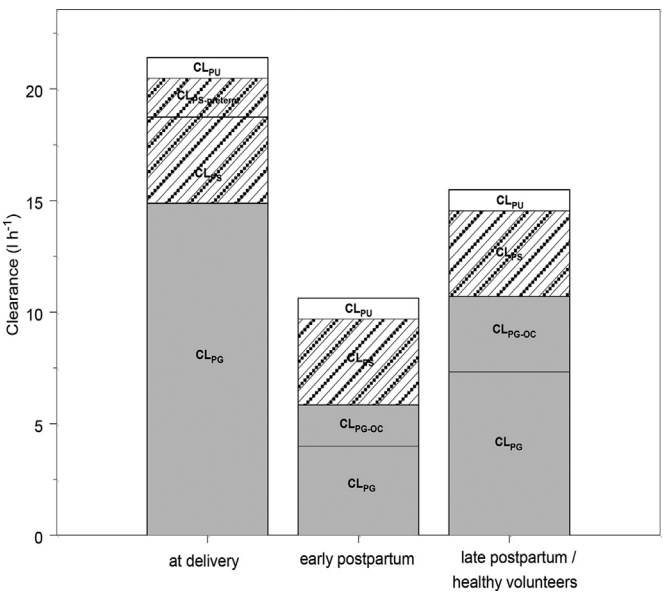

Fig. 1. Paracetamol clearance at delivery, in early postpartum (3–4 months postpartum) and in late postpartum (1 year after delivery)/healthy volunteers. The total paracetamol clearance is provided, with the contribution of the different routes of elimination. CL_{PU}, clearance by free paracetamol in urine; CL_{PS}, metabolic clearance through sulfation; CL_{PG}, metabolic clearance through glucuronidation.

that placental transfer is flow-limited. Consequently, the authors suggested that maternal plasma paracetamol levels may be used as a surrogate for fetal exposure, but the different metabolites were not considered [7]. In a cohort of 20 women, the same group described earlier the absence of any effect of paracetamol exposure (1000 mg, oral) on fetal activity in a cohort of 20 women [8].

2.2. What is known on the analgesic efficacy of paracetamol in the peripartal period?

Preoperative administration of intravenous paracetamol has a morphine-sparing effect following cesarean delivery, and similar observations have been reported following oral administration [9,10]. When compared to, or combined with, non-steroidal anti-inflammatory drugs (NSAIDS; diclofenac, ibuprofen), NSAIDS have a tendency to be more effective (morphine-sparing) compared to paracetamol in monotherapy, with relevant synergism when both compounds are combined [11–14]. A similar pattern has been described for perineal pain in early postpartum: paracetamol has some effects, NSAIDS are somewhat more potent, and the combined use is most effective [15].

2.3. Paracetamol and breastfeeding

As part of analgo-sedative treatment modalities after delivery (e.g. cesarean-related pain, birth-related trauma, pre-existing pain syndromes), mothers are treated with different analgo-sedatives that may affect the nursing infant, including paracetamol. Human milk and plasma paracetamol levels were monitored in three lactating women after postpartum ingestion of 500 mg. Paracetamol concentrations remained lower in human milk (milk/plasma ratio of 0.76). Since <0.1% of the maternal dose would be present in 100 mL milk, nursing should not be discontinued following maternal paracetamol exposure [16]. Since paracetamol has opioid-sparing effects, there is obvious benefit to add paracetamol as part of a multimodal analgesia protocol, preferably combined with other 'low drug exposure' techniques like loco-regional anesthesia.

2.4. What is currently known on the safety of fetal paracetamol exposure?

2.4.1. Atopy

The proposed mechanism explaining the relationship between paracetamol exposure and atopy relates to the non-selective inhibitory action on peripheral COXs of paracetamol in a setting of physiological, low arachidonic acid concentrations; the major problem with these data is that of confounding factors. Epidemiological studies suggest a link between fetal/maternal exposure and atopy (nutrition, eczema, wheezing) in early infancy [2]. Interestingly, maternal antioxidant gene polymorphisms [e.g. nuclear erythroid 2 p45-related factor 2 (Nrf2) polymorphism, glutathione S-transferase (GST)] may modify this relation between prenatal paracetamol exposure and childhood asthma, strengthening evidence for causality. The same association and similar polymorphisms have been documented for postnatal exposure [17]. Although still debated, it seems that the association between paracetamol use during pregnancy and infant wheezing is mainly – if not completely – explained by confounders [18].

2.4.2. Genital/fertility

The proposed mechanism explaining impaired masculinization relates to reduced fetal testicular testosterone production following fetal paracetamol exposure [19]. Some epidemiological studies also provide evidence for an association between prenatal paracetamol exposure and subsequent risk for cryptorchidism or hypospadias. In

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the generation R study, the incidence of cryptorchidism was 2.1%, with 23/68 cases in the paracetamol-exposed group (4.8%; number needed to harm: 32) in the second trimester of the pregnancy [20]. Prenatal paracetamol exposure between 8 and 14 weeks gestation was associated with a shorter anogenital distance in male infants, a marker for an impaired masculinization program [19].

2.4.3. Neurobehavior

Suggested mechanisms are the potential impact on cerebral inflammation, or specific metabolites such as cannabinoids. Intriguingly, in an animal experimental model, paracetamol and Δ(9)-tetrahydrocannabinol, but not ibuprofen, resulted in developmental neurotoxicity [21]. This suggests a link with cannabinoids. As mentioned earlier, paracetamol metabolism during pregnancy does result in higher clearance into metabolites, including oxidative metabolites [5,6]. A systematic search (November 2016) in PubMed (paracetamol + fetal) resulted in 270 hits. With a focus on aspects of neurobehavioral outcome in humans, title, abstract and full paper were read (including reference check and citations search), to generate an overview of currently published observational studies on this topic (Table 1) [22–29]. Neurobehavioral outcome variables assessed related to IQ, communication, motor attainment, attention deficit hyperactivity disorder (ADHD), conduct, or emotional problems. Table 1 illustrates that exposure to paracetamol during pregnancy is widespread (37–53%), and that there are associations with several neurobehavioral outcome variables, be it with rather high numbers needed to harm (48–250).

3. Neonatal use of paracetamol

3.1. Pharmacokinetics and metabolism of paracetamol in neonates

Data on paracetamol pharmacokinetics in neonates following enteral or intravenous administration have been reported in pooled analyses [30,31]. Based on these pooled analyses, an oral dose of 25 mg/kg/day in premature neonates at 30 weeks, 45 mg/kg/day at 34 weeks and 60 mg/kg/day in term neonates has been suggested. Because of limited predictability and extensive variability, dosing recommendations for rectal administration are much less reliable [30].

For the intravenous route, the estimates of the pooled study [clearance 5 L/h/70 kg] were recently validated in a new dataset [32]. The same holds true for the maturation of the different routes (glucuronidation, sulfation, and oxidation) involved in paracetamol metabolism [33,34]. Weight or size was the most relevant covariate of paracetamol clearance, resulting in dosing suggestions that are higher compared to the on-label dosing suggestions in term neonates, and that also cover preterm neonates. On the basis of these studies, the dosing regimen of intravenous paracetamol in neonates and infants (PMA 32–44 weeks) should consist of a loading dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg every 6 h. The interval between two maintenance doses should be increased up to 12 h if PMA <31 weeks [35].

3.2. Effect compartment concentrations of paracetamol for pain relief in neonates?

Once PK have been described and validated, dosing regimens can be constructed to attain target (median) plasma concentrations with reasonable variability. In adults and children, target effect compartment concentrations of 5 mg/L for fever and 10 mg/L for pain have been suggested [3]. These regimens should subsequently be tested since target concentrations may not only depend on indications (fever, pain, or PDA), but may also display maturational differences between neonates and children. In an open-label study, 19 neonates were exposed to a loading dose of intravenous (20 mg/kg) paracetamol (resulting in a median effect concentration of 9–11 mg/L as monotherapy because of mild to moderate pain), showing a significant trend ($P = 0.02$) for lower pain scores within 30 min after administration, with a slight increase in pain scores from 5 h onwards [36]. Consequently, it was concluded that an effect compartment concentration of 10 mg/L is associated with a relevant pain score reduction, suggesting similarities in the paracetamol effect compartment concentration in neonates as compared to children [3,36].

3.3. What is known on the analgesic efficacy of paracetamol in neonates?

Adequate management of pain in neonates obviously remains a major issue in contemporary neonatal care. In an attempt to avoid opioids, there is a shift towards non-pharmacological interventions as well as paracetamol [37,38]. However (and similar to opioids or paracetamol for other subpopulations), paracetamol is not a magic bullet for all types of pain relief in neonates [37,38]. A systematic literature search (November 2016) in PubMed (paracetamol + pain + newborn) resulted in 150 hits. Following title, abstract and full paper reading when appropriate (including reference check and citations search), an overview of prospective studies on postoperative pain management was constructed (Table 2) [39–41]. The observations on paracetamol procedural (heel prick, retinopathy of prematurity screening) analgesia during procedures suggest that paracetamol is a very poor procedural analgesic. By contrast, there was a highly relevant morphine-sparing (−66%) effect of intravenous, but not rectal, paracetamol co-administration after neonatal surgery [39,40]. A similar pattern was described following traumatic pain after delivery with intravenous paracetamol being effective, while rectal administration failed [36]. This is very likely unrelated to the route, but to the doses used and plasma concentrations reached (Table 2) [39–41]. The morphine-sparing effect has also been observed in a retrospective analysis on morphine consumption in very low gestational age infants (<32 weeks) before and after introduction of intravenous paracetamol in one unit [42].

3.4. What is known on the safety of paracetamol in neonates?

Short-term safety for paracetamol has been fairly well described in (pre)term neonates, although the number of observations in the most immature subgroup (<28 weeks gestational age) is still limited. There are prospectively collected data on hemodynamics, body temperature, and hepatic tolerance [43–45]. In an open-label observational study in 72 neonates exposed to intravenous paracetamol, a very limited decrease in heart rate (−7 bpm) and mean arterial blood pressure (3 mmHg) was observed. Hypotension (defined as a mean arterial blood pressure < postmenstrual age in weeks) was documented in 9% of neonates. Interestingly, these cases already had a lower blood pressure before paracetamol administration [43]. In a study investigating body temperature trends in 99 neonates exposed to intravenous paracetamol, six cases with fever and 93 cases with normothermia were included. In neonates with fever (>37.8 °C), there was a median decrease (−0.8 °C) in the first 2 h after administration. In neonates ($n = 93$) with normothermia, hypothermia was not observed after paracetamol administration [44]. Data on hepatic tolerance (liver enzymes, glutathione) collected as part of prospective safety studies during repeated exposure have also been published [45,46]. There were no significant increases in liver enzymes when pre-exposure observations ($n = 310$) were compared with observations during

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Table 1
Cohort studies on the potential link between maternal paracetamol exposure during pregnancy, and subsequent neurocognitive or behavioral outcome in offspring in humans.

Reference	Population	Determinant	Paracetamol use and other covariates	Impact	Comments
Liew et al. [22]	Danish cohort study N = 1491 mothers/child, any (59%) paracetamol	IQ, 5 year Wechsler, verbal (V), performance (P)	Prenatal Fever prenatal	−3.4 (0.3–6.6) (P) −4.3 (0.3–8.3) (P) −2.7 (−0.19 to 5.6)	Initial cohort 101,041 1491/3478 (43%) invited for IQ assessment Corrected for maternal IQ
Streissguth et al. [23]	1529 pregnant women Prospective cohort	421 cases evaluated IQ and ADHD behavior, 4 years	Any (46%) paracetamol Any (41%) aspirin exposure	Similar Significant	Aspirin effect, girl > boy (−10 vs −1.3 mean IQ)
Vlenterie et al. [24]	Propensity score matching (in 1630/1787 cases) 51,200 pregnancies, 40.5% any exposure	Communication, 18 months Motor attainment, 18 months	Short-term exposure <28 days (37%) Long-term exposure >28 days (3.5%)	Similar Similar 1.38 (0.98–1.95) 1.35 (1.07–1.70)	51,200/108,863 included in the analysis, questionnaires (CBCL, maternal report on motor milestone, emotionality, temperament questionnaire). NNH: 48–67
Stergiakouli et al. [25]	7796 mothers, prospective (ALSPAC study)	Conduct problems, 18 weeks Hyperactivity, 18 weeks Emotional issues, 32 weeks Total difficulties	Exposure at 18 (53%) and 32 (42%) weeks of gestation (previous 3 months)	1.42 (1.25–1.62) 1.31 (1.16–1.49) 1.29 (1.09–1.53) 1.46 (1.21–1.77)	SDQ questionnaire, total score ≥17, emotional ≥5, conduct≥4, hyperactivity ≥7, peer ≥4 or prosocial behavior ≤6 NNH total difficulties: 128
Liew et al. [26]	64,322 children, autism (1.3%), infantile autism (0.5%) (Danish National Birth Cohort)	Autism spectrum disorder, with hyperkinetic symptoms	Any (56%) paracetamol Weeks of paracetamol during pregnancy (0, 1, 2–5, 6–20, >20 weeks)	1.51 (1.19–1.92) 1.89 (1.19–3.02)	Three telephone interviews (exposure) Medical files (diagnoses) Initial cohort 101,041 pregnancies NNH any, 250
Liew et al. [27]	64,322 cases (Danish National Birth Cohort)	Hyperkinetic (2.0%) ADHD drugs (3.3%) ADHD parental SDQ (3%) Hyperkinetic (2.0%) ADHD drugs (3.3%) ADHD parental SDQ (3%)	Any paracetamol exposure Paracetamol exposure, >20 weeks	1.37 (1.19–1.59) 1.29 (1.15–1.44) 1.13 (1.01–1.27) 1.84 (1.39–2.45) 1.53 (1.21–1.94) 1.46 (1.16–1.85)	Three telephone interviews (exposure) Medical files (diagnoses) SDQ questionnaires + prescriptions Ritalin NNH any (ADHD drugs) 194
Brandlistuen et al. [28]	Norwegian Mother and Child cohort study 48,631 children, with 2919 sibling-controlled cohort study	Gross motor development Gross motor development Communication Externalizing behavior Internalizing behavior Activity level	Any paracetamol exposure (46%) Paracetamol >28 days	β: 0.10 (0.02–0.19) β: 0.24 (0.12–0.51) β: 0.20 (0.01–0.39) β: 0.28 (0.15–0.42) β: 0.14 (0.01–0.28) β: 0.24 (0.11–0.38)	Maternal paracetamol: use at 16, 30 weeks and 6 months postpartum Effects for paracetamol, not ibuprofen Questionnaires (Ages and Stages, CBCL, questionnaire, Emotionality, activity and shyness temperament)
Thompson et al. [29]	Auckland Birthweight study 871 infants, enriched for growth restricted cases	ADHD, SDQtotal ADHD, Conner's parent rating At 7 (parent) and 11 years (parent and child) of life.	Any paracetamol exposure (50%)	Parent: 0.8 (0–1.6) Child: 0.9 (0.1–1.7) Parent: 3 (1.3–4.7) (emotional lability)	Associated with paracetamol, but not antibiotics, aspirin, antacids, interview at delivery. Corrected for birthweight, socioeconomics and maternal perceived stress.

V, verbal; P, performance; IQ, intelligence quotient; NNH, number needed to harm; ALSPAC, Avon Longitudinal Study of Parents And Children; SQD: strengths and difficulties questionnaire; ADHD, attention deficit hyperactivity disorder; CBCL, Child Behavior Check List.

($n = 649$) or after ($n = 173$) paracetamol administration. This has been further confirmed by the absence of changes in liver enzymes and plasma glutathione in another cohort of 15 preterm neonates [46].

By contrast, data on long-term safety following neonatal exposure to paracetamol remain limited, and reports are based on epidemiological association-type studies. These associations suggested between fetal exposure and subsequent risks for atopy, fertility or neurobehavioral problems. Therefore, it is worth developing long-term safety studies, looking specifically at these aspects following neonatal exposure. At least for atopy-related events, there are associations with early neonatal exposure to paracetamol, although this association may reflect reverse causation [2,47]. At least, the observations that prophylactic antipyretic administration of paracetamol results in relief of the local and systemic symptoms after vaccinations, but with a reduction in antibody responses to some vaccine antigens, provide evidence on interactions between paracetamol and immune reactivity in infants [48].

4. Clinical practice improvement and future research directions

The available information on paracetamol PK and PD in pregnant women and their newborns has increased substantially in the last five years, as discussed earlier in this review. The next obvious steps are to translate this knowledge into good clinical practice and to generate new research questions to further improve our practice.

At present, there is sufficient information on maternal PK to support the concept that paracetamol clearance is increased. However, simply increasing the dose to attain time–concentration profiles similar to non-pregnant women carries the risk that this will result in further increased metabolic clearance through oxidation (toxic metabolites, e.g. NAPQI). Because of this

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Table 2
Overview of studies investigating the use of paracetamol for different types of pain in (pre)term neonates.

Reference	Study design and pain model	Paracetamol dosing	Results
Howard et al. [41]	Randomized double-blind placebo-controlled trial in 44 healthy term neonates, undergoing neonatal circumcision (Gomco), postoperative Comfort Score.	Oral paracetamol 15 mg/kg every 6 h for 24 h Start 2 h before surgery	No effects during circumcision. Postoperative score similar until 6 h when paracetamol group scored better.
Van der Marel et al. [40]	Randomized double-blind placebo-controlled trial, morphine + paracetamol or placebo, 30/54 postmenstrual age (PMA) < 45 weeks. Major thoracic (non-cardiac) or abdominal surgery.	Rectal paracetamol loading 30–40 mg/kg, 20–30 mg/kg every 6 h or every 8 h.	Postmenstrual ag <45 weeks cases had a lower need for additional morphine, but without differences between paracetamol/placebo.
Ceelie et al. [39]	Randomized, double-blind study in 71 neonates and infants (35/71 < 10 days postnatal). Major thoracic (non-cardiac) and abdominal surgery. Using validated pain scores, cumulative maintenance dose of morphine was assessed.	Morphine loading dose, followed by maintenance morphine or paracetamol intravenously (48 h). Back-up morphine.	Similar pain scores, but significant lower exposure to morphine (−66% for the maintenance dose in the paracetamol group)

phenomenon, there is obvious benefit to use paracetamol as part of a multimodal analgesia protocol. However, we should be aware that also the PK of other compounds used in such a multimodal analgesia strategy may be altered due to pregnancy, as illustrated for ketorolac (clearance +50–100% at delivery) [49]. Paracetamol PK has also been documented in neonates, resulting in dosing suggestions that are higher compared to the on-label dosing suggestions in term neonates, and that cover preterm neonates. Using adequate dosing based on these PK data, paracetamol is a poor procedural (e.g. heel prick, retinopathy of prematurity screening) analgesic, is effective for mild-to-moderate (e.g. peripartal trauma) pain, and has morphine-sparing effects after major (e.g. abdominal, non-cardiac thoracic) neonatal surgery.

By contrast, there is still very limited information on the maternal–fetal interaction, including placental transfer and metabolism of paracetamol. These kinds of studies may also provide additional mechanistic information to explore the association between fetal paracetamol exposure and long-term safety (e.g. atopy, fertility and neurobehavioral). The same holds true for neonatal paracetamol exposure, since only short-term safety has been well documented. However, this kind of research should be further conducted using the best available research models (prospective, multivariable, valid measurements) and should be supported by data on human perinatal physiology and pharmacology (e.g. placental transfer and metabolism) and animal experimental studies (dose, models) relevant to the human setting.

At present (Table 1), exposure to paracetamol and outcome variables are regularly based on maternal recall and interviews or questionnaires and there is a limited set of potential covariates available to build the predictive models. Animal experimental studies investigating the link between, for example, fetal paracetamol exposure and neurobehavioral outcome, have been reported [50]. Interspecies scaling should be applied to predict pharmacokinetic parameters between the animal and human setting, and these predictions should be confirmed as part of the investigation. In addition, these animal experimental studies should reflect the human setting. Although continuous exposure to paracetamol throughout fetal rat life and infancy may result in more recognizable effects, it also makes it difficult to translate this to the human setting [50]. In clinical practice, paracetamol is mostly used on indication (e.g. fever or pain relief), but almost never throughout pregnancy (Table 1). Finally, as illustrated for morphine in juvenile rats, both the indication (e.g. inflammatory pain) and morphine exposure modulated the outcome.

In conclusion, paracetamol is not the magic bullet for any type of pain relief in pregnant women and their newborns. However, when using the dosing recommendations based on the available PK and as part of multimodal analgesia in pregnant women, or for the right indications (monotherapy for mild-to-moderate pain, opioid-sparing for moderate-to-severe pain, but not procedural pain) in neonates, it is a very valuable tool to improve comfort and outcome.

4.1. Practice points

- Paracetamol clearance in pregnant women and in early postpartum is significantly higher, mainly driven by increased glucuronidation. However, higher doses to attain similar concentration–time profiles may be unsafe because there is also a proportional increase in the formation of toxic metabolites through the oxidative pathway.
- Because of the increased clearance at delivery, the analgesic effect of paracetamol will be reduced in extent and duration in these women. Consequently, multimodal analgesia seems to be a reasonable strategy in this population.
- Paracetamol PK has been documented in neonates. Weight or size is the most relevant covariate of paracetamol clearance, resulting in dosing suggestions that are higher compared to the on-label dosing suggestions in term neonates, and that cover preterm neonates.
- Using adequate dosing based on these PK data, paracetamol is a poor procedural (e.g. heel prick, retinopathy of prematurity screening) analgesic, is effective for mild to moderate (e.g. peripartal trauma) pain, and has morphine sparing effects after major (e.g. abdominal, non-cardiac thoracic) neonatal surgery.

4.2. Research directions

- There is a need for additional research on the association between fetal paracetamol exposure and long-term safety (e.g. atopy, fertility and neurobehavior). The same holds true for neonatal paracetamol exposure, since only short-term safety has been well documented.
- However, this kind of research should be conducted using the best available research models (prospective, multivariable, valid measurements) and should be supported by data on human perinatal physiology and pharmacology (e.g. placental transfer and metabolism) and animal experimental studies (dose, models) relevant to the human setting.

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Conflict of interest statement

None declared.

Funding sources

Karel Allegaert has been supported by the Fund for Scientific Research, Flanders (fundamental clinical investigatorship 1800214N), and his research activities are further facilitated by the agency for innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO 130033).

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Please cite this article in press as: Allegaert K, van den Anker JN, Perinatal and neonatal use of paracetamol for pain relief, Seminars in Fetal & Neonatal Medicine (2017), http://dx.doi.org/10.1016/j.siny.2017.07.006