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Perinatal and neonatal use of paracetamol for pain relief

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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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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

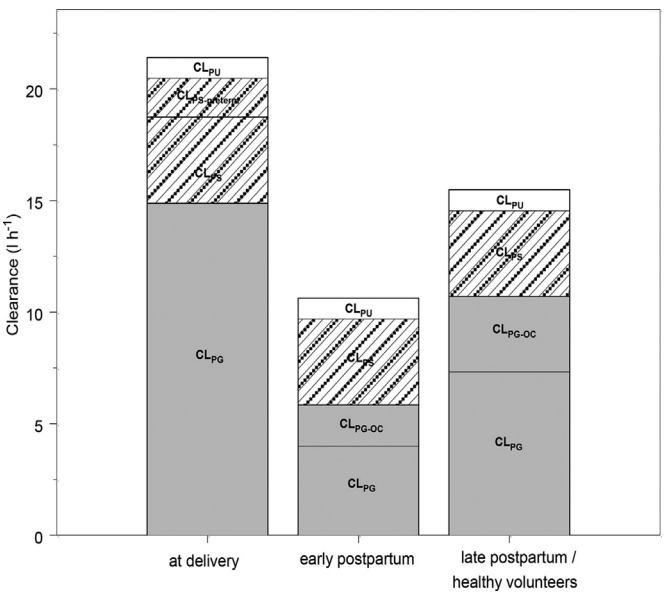

Fig. 1. Paracetamol clearance at delivery, in early postpartum (3–4 months postpartum) and in late postpartum (1 year after delivery)/healthy volunteers. The total paracetamol clearance is provided, with the contribution of the different routes of elimination. CL_{PU}, clearance by free paracetamol in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