Paracetamol to induce ductus arteriosus closure: is it valid?

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ABSTRACT
There remains a need for alternative medical treatments for patent ductus arteriosus (PDA) closure in extreme preterm neonates because of therapeutic failure and adverse effects associated with non-selective cyclo-oxygenase inhibitors. Reports of an association between paracetamol exposure and PDA closure have been published. However, causality cannot be taken for granted because a link between the current knowledge of the clinical pharmacology of paracetamol and (patho)physiology of ductal closure is not known. In contrast to non-selective cyclo-oxygenase inhibitors, paracetamol has limited effects at peripheral sites, is a poor antithrombotic and anti-inflammatory drug and exerts its effects primarily within the central nervous system. Although paracetamol appears an effective and safe analgesic in term and near term neonates, its effectiveness and safety for PDA closure are uncertain because the drug is administered in high doses and there remain a limited number of observations in this specific subpopulation so far. Prospective comparative trials are reasonable and are urgently needed to establish both the effectiveness and safety data of paracetamol when used for this indication.

INTRODUCTION: DO WE NEED NEW TREATMENT MODALITIES?
Closure of the patent ductus arteriosus (PDA) is a crucial part of normal circulatory adaptation to extra-uterine life. Its persistence after preterm birth is associated with an increased risk of morbidity, including necrotising enterocolitis, bronchopulmonary dysplasia and neurodevelopmental impairment.1–4 These morbidity characteristics relate to pulmonary hyperperfusion with steal phenomena from the systemic circulation. However, there is still a debate about whether a PDA is a pathology requiring treatment or if it is simply a reflection of delayed adaptation in the very preterm infant. Unsuccessful closure of the ductus might occur more frequently in the most unstable newborns predisposed for impaired outcome.1–4

Current pharmacological options to treat a haemodynamic significant PDA are limited to non-selective cyclo-oxygenase (COX) inhibitors along with fluid restriction and diuretics. Indomethacin or ibuprofen administered to preterm infants for PDA promotes ductal closure (success rate 70%–85%), but without any other short term benefits.5 Treatment with ibuprofen may even increase the risk of chronic lung disease.3 Similarly, the association between prolonged (>21 days of postnatal age) patency of the duct and chronic lung disease has recently been reconfirmed, but those neonates were also more frequently exposed to indomethacin.6 Both drugs may contribute to ‘transient’ renal impairment following exposure. There are observations that this renal impairment is reflected in reduced creatine clearance and elevated serum creatine for up to 6 weeks of postnatal life.7,8 Moreover, experimental findings in baboons describe a link between ibuprofen exposure and a reduction in renal nephrogenic zone width, which may suggest early cessation of nephrogenesis following ibuprofen exposure.9 Finally, surgical closure is also associated with poorer outcomes (eg, neurological impairment, vocal cord dysfunction).1–4

Consequently, there is certainly a place for alternative treatments that might result in better closure rates or fewer adverse effects. In addition, there are contra-indications for ibuprofen or indomethacin administration. These include thrombocytopenia or intracranial haemorrhage (impaired platelet activity), renal failure (due to decreased renal perfusion), necrotising enterocolitis, coadministration of corticosteroids (risk of intestinal perforation) or hyperbilirubinemia (competitive binding to albumin).1–4,10 Most of these contra-indications relate to the pharmacological effects of ibuprofen or indomethacin, that is, a concentration related reduction in prostaglandin synthesis through non-selective inhibition of the COX site of the prostaglandin H2 synthetase (PGHS) enzyme (figure 1).11

Several reports have been published concerning an association between paracetamol exposure and

What is already known on this topic

▸ An association between paracetamol exposure and closure of the patent ductus arteriosus has been reported in a limited number of extreme preterm neonates.

▸ There are limited data regarding the pharmacokinetics, pharmacodynamics and toxicity of paracetamol in preterm neonates.

What this study adds

▸ A median paracetamol serum concentration of 15 mg/l is likely following a 15 mg/kg 6 h dose.

▸ The target paracetamol concentration that induces closure of the ductus arteriosus is unknown.

▸ The safety of high dose paracetamol in extreme preterm neonates is uncertain.
Figure 1  The arachidonic acid metabolism, with specific emphasis on the interactions of drugs (inhibitory) or endogenous compounds (stimulating) at the consecutive enzymes involved in this pathway.

PDA closure within the past few years suggesting that this might be an alternative to non-selective COX inhibitors. In our opinion, these practices—high dose (60 mg/kg/day) of paracetamol in a specific subgroup (extreme preterm) of neonates for a specific (PDA) indication—are not supported by data concerning effectiveness and safety. In an attempt to put these observations into perspective, we will first describe the pharmacological effects of non-selective COX inhibitors and paracetamol on the PGHS enzyme complex and prostaglandin synthesis. This will be followed by a summary of the clinical observations of paracetamol exposure and PDA closure and the clinical pharmacology of paracetamol in neonates. Finally, we provide our opinion on how the hype concerning paracetamol and PDA closure should be managed in order to further improve pharmacotherapy in neonates.

NON-SELECTIVE COX INHIBITORS, PARACETAMOL AND ARACHIDONIC ACID METABOLISM

The PGHS complex has two sites, the COX and the peroxidase (POX) sites. The COX site converts arachidonic acid to PGG2 by oxidation, subsequently converted to PGH2 by the POX site. After formation of PGH2, it is subsequently converted to PGF2α, PGE2, PGl2 or TXA2. Non-selective COX and paracetamol inhibit the COX or POX site, respectively (figure 1). Paracetamol hereby acts as reducing cosubstrate so that less PGG2 can be converted to PGH2. Paracetamol related POX inhibition is competitive since counteracted by PGG2 itself or lipid hydroperoxides (figure 1).

Prostaglandin reduction results in muscular constriction of the ductus arteriosus with profound hypoxia in the ducatal vasa vasorum. This causes topical angiogenesis, neo-intima formation and apoptosis. Together with platelet recruitment, this will result in obstruction, fibrosis and anatomic closure. Data confirming the association between prostaglandin reduction and the likelihood of PDA closure are available for both indomethacin and ibuprofen. The link between prostaglandin synthesis reduction and PDA closure was initially observed as a foetal adverse effect of maternal indomethacin administration to prevent or treat preterm labour. A similar 'serendipity' observation linked paracetamol exposure with PDA closure. As mentioned earlier, paracetamol inhibits POX mediated PGG2 to PGH2 conversion as one of its mechanisms of action.

However, it should not be taken for granted that paracetamol induces PDA closure through systemic PG reduction since paracetamol, in contrast to non-selective COX inhibitors, has limited effects at peripheral sites and is a very poor anti-thrombotic and anti-inflammatory drug. Paracetamol exerts its currently known effects (analgesia, fever reduction) through the central nervous system. It is assumed that the differences between peripheral tissues and central nervous tissues relate to the amount of PGG2 produced and the amount of lipid hydroperoxide simultaneously formed by platelet 12-lipoxygenase (figure 1). In the absence of systemic prostaglandin reduction, issues related to platelet recruitment, differences in local oxygen tension, local prostaglandin reduction or maturational differences in lipid hydroperoxide production are then needed to explain a potential pharmacological link between paracetamol and PDA closure.

REPORTS CONCERNING THE ASSOCIATION BETWEEN PARACETAMOL AND DUCTUS CLOSURE

There are currently four cohort studies with 29 individual cases reported in literature. Both oral (n=19) and intravenous (n=10) paracetamol have been used (table 1). All studies had administered 60 mg/kg/24 h for 2–7 days. Neonatal demographics are summarised in table 1. The majority (23/29) were exposed to paracetamol because of ibuprofen failure (n=8) and/or relative contra-indications (renal=2, thrombocytopenia=2, hyperbilirubinaemia=5, intestinal=11) for ibuprofen administration. At the end of the first paracetamol course, closure was observed in 20/29 cases. Closure was documented in 27/29 neonates following either a prolonged course (up to 7 days), or a second course or expectant management. These neonates represent a highly selected population with very specific clinical characteristics and high incidence of initial ibuprofen failure (8/29), making extrapolation of anticipated effects in the general population of preterm neonates problematic. Further, it remains unknown if any paracetamol effect is influenced by augmentation with NSAIDs before, during or after treatment.

WHAT IS KNOWN ABOUT PARACETAMOL IN NEONATES

Paracetamol is the most commonly prescribed drug to treat moderate pain or fever in humans. This includes (near)term
neonates and infants. Paracetamol can be administered by enteral (oral, rectal) or parenteral (intravenous) routes. A parenteral route will reduce the variability associated with enteral absorption and can be considered when enteral routes are not available. This is often the preferred route in preterm neonates. Data on the pharmacokinetics (PK) and pharmacodynamics (PD), including tolerance in preterm and term neonates, have been published.

An analysis of 943 paracetamol observations from 158 neonates (27–45 weeks postmenstrual age (PMA)) resulted in population parameter estimates (between-subject variability, %) scaled to a 70 kg person using allometry, central volume 51.9 l/70 kg (21.6%), peripheral volume of distribution 22.7 l/70 kg, clearance 16.2 l/h/70 kg, respectively. Covariate information predicted about 61% of the variance in paracetamol clearance. Weight was the major contributor (57.5%) of clearance variance. Once weight, scaled using allometry, was considered, age in this cohort (27–45 weeks PMA) was not so important. Clearance expressed as mg/kg/h increased only marginally with PMA (0.138 l/kg/h at 28 weeks to 0.167 l/kg/h at 44 weeks of PMA) and contributed only 2.2% of variance. Similar observations have been documented following rectal or oral administration. However, the number of observations in the pooled intravenous paracetamol study in extreme preterm neonates (<32 weeks) was limited to only 21 patients and observations below 27 weeks PMA were lacking.

When considering paracetamol PD, there are data concerning its short term safety and tolerance in (pre)term neonates. In contrast to observations in intensive care adults, there were no haemodynamic alterations during and following an intravenous loading dose administration in neonates. Similarly, afibrile neonates maintained normothermia, while temperature reduction was observed in neonates with fever. There were no signs of hepatic intolerance during and following repeated administration of intravenous paracetamol. Finally, we recently suggested that the paracetamol effect compartment concentration (10–11 mg/l) in neonates is similar to that observed in children.

We would like to stress that all these pharmacodynamic data were collected using a loading dose (20 mg/kg) and maintenance dose (20–40 mg/kg in q6–12 h intervals). These doses are higher than the on-label guideline in term neonates, but lower compared with the currently reported dosing associated with PDA closure (60 mg/kg/24 h). Furthermore, data in the very preterm neonates in early neonatal life, the usual candidates for PDA treatment, are few.

### Table 1 Characteristics of cases reported

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Postmenstrual age (week)</th>
<th>Postnatal age (days)</th>
<th>Duration (days)</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>28</td>
<td>17</td>
<td>2</td>
<td>Closed, index case, 2 courses ibuprofen earlier</td>
</tr>
<tr>
<td>935</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>Closed, growth restricted, sepsis/necrotising enterocolitis</td>
</tr>
<tr>
<td>720</td>
<td>31</td>
<td>35</td>
<td>2+2</td>
<td>Closed (delayed), previous 2 courses ibuprofen, 2 courses paracetamol</td>
</tr>
<tr>
<td>1210</td>
<td>28</td>
<td>3</td>
<td>2</td>
<td>Closed (delayed), hyperbilirubinaemia, closure within 1 week</td>
</tr>
<tr>
<td>868</td>
<td>27</td>
<td>10</td>
<td>2</td>
<td>Closed (delayed), thrombocytopenia, closure within 1 week</td>
</tr>
</tbody>
</table>

Oncel et al\(^4\) (primary treatment, no contra-indications for ibuprofen, oral)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Postmenstrual age (week)</th>
<th>Postnatal age (days)</th>
<th>Duration (days)</th>
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<tbody>
<tr>
<td>630</td>
<td>27</td>
<td>27</td>
<td>NA</td>
<td>Closed, 2 courses ibuprofen earlier</td>
</tr>
<tr>
<td>650</td>
<td>28</td>
<td>22</td>
<td>NA</td>
<td>Closed, 2 courses ibuprofen earlier</td>
</tr>
<tr>
<td>1010</td>
<td>29</td>
<td>5</td>
<td>NA</td>
<td>Closed, renal failure</td>
</tr>
<tr>
<td>2970</td>
<td>37</td>
<td>7</td>
<td>NA</td>
<td>Closed, 2 courses ibuprofen earlier</td>
</tr>
<tr>
<td>1340</td>
<td>30</td>
<td>5</td>
<td>NA</td>
<td>Not closed, hyperbilirubinaemia and thrombocytopenia</td>
</tr>
<tr>
<td>1780</td>
<td>34</td>
<td>17</td>
<td>NA</td>
<td>Closed, 1 course ibuprofen, renal failure</td>
</tr>
<tr>
<td>920</td>
<td>28</td>
<td>8</td>
<td>NA</td>
<td>Closed, 2 courses ibuprofen earlier</td>
</tr>
<tr>
<td>980</td>
<td>30</td>
<td>11</td>
<td>NA</td>
<td>Closed, 2 courses ibuprofen earlier</td>
</tr>
</tbody>
</table>

Yurttutan et al\(^4\) (contra-indications for ibuprofen, intravenous)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Postmenstrual age (week)</th>
<th>Postnatal age (days)</th>
<th>Duration (days)</th>
<th>Additional information</th>
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<tbody>
<tr>
<td>1230</td>
<td>28</td>
<td>3</td>
<td>3</td>
<td>Closed</td>
</tr>
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<td>1400</td>
<td>29</td>
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<td>Closed</td>
</tr>
<tr>
<td>1010</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>Not closed</td>
</tr>
<tr>
<td>1600</td>
<td>33</td>
<td>7</td>
<td>3</td>
<td>Closed</td>
</tr>
<tr>
<td>920</td>
<td>28</td>
<td>7</td>
<td>2+3</td>
<td>Reopening, closed with second course</td>
</tr>
<tr>
<td>1290</td>
<td>30</td>
<td>6</td>
<td>3</td>
<td>Closed</td>
</tr>
</tbody>
</table>

All patients (n=29) were exposed to 60 mg/kg/24 h administration. Data of Oncel et al\(^4\) were provided by the authors.
WHAT IS NOT YET KNOWN ABOUT PARACETAMOL AND PDA CLOSURE

Simple extrapolation from currently available data on paracetamol PK/PD in neonates is hampered because of the higher dosing currently used for PDA closure and because PK in extreme preterm neonates has not been comprehensively studied. Consequently, issues related to PK, hepatotoxicity and target or effect concentration need further examination.

The paracetamol doses used for PDA closure (15 mg/kg/q6h, 60 mg/kg/24 h for 2–7 days) in extreme preterm neonates are twice as high as the authorised recommended dose in term neonates (7.5 mg/kg/q6h, max 30 mg/kg/24 h and max 48 h). Such dosing is not based on consideration of differences in clearance within the neonatal population and results in higher plasma concentrations. To illustrate this, we have compared both dosing regimens in figure 2. These predictions were generated using parameter estimates from the pooled intravenous paracetamol PK model mentioned earlier for the first 48 h of exposure.13 Median values for weight (775 g) and age (28 weeks PMA) were taken from the cohort of 10 preterm reported neonates.13 The median predicted paracetamol concentration in preterm neonates after the first 24 h was 15 mg/l, while trough concentrations after 24, 48 and 72 h were close to the median observed paracetamol concentration (7.3 (12–28), 15.5 (10–25.2) and 14.7 (9–20.2) mg/l) reported by Oncel et al.11 These concentrations are significantly higher than the median effect site target concentration of 10 mg/l used for analgesia.19 25

A major concern in this population is the incidence of hepatotoxicity. This complication is attributed to the production of highly reactive electrophilic arylation metabolites (eg, N-acetyl-p-benzoquinone-imine (NAPQI)) by the hepatic cytochrome P-450-dependent (CYP) E1 mixed function oxidase enzyme system.26 The concentrations of paracetamol associated with increased NAPQI production are unknown in neonates. It is reasonable to anticipate population specific toxicity because the activity of CYP2E1—the major enzyme producing NAPQI—is not yet quantified, while data on the NAPQI detoxification capacity through glutathione conjugation in neonates are also lacking.27 28 Furthermore, immaturity of hepatic transporters or individual patient characteristics like malnutrition may further contribute to specific vulnerability.29 30

At present, we are unaware of any rationale to suggest a paracetamol target concentration for PDA closure. A concentration–response relationship for PDA closure has been demonstrated for indomethacin with closure in 90% of neonates at an indomethacin concentration of 3.5 mg/l.31 Ibuprofen failure has been associated with a failure to increase dose with age, a necessary step to maintain the target concentrations as clearance increases with age.32 The use of paracetamol faces a similar hurdle: it is only once the concentration–response curve is understood that paracetamol dosing can be adjusted using pharmacokinetic knowledge to achieve that target concentration. Consequently, trials should be based on dose ranging studies to establish both safety and effectiveness.

The assessment of effect also needs further considerations, including issues related to diagnostic accuracy of a significant PDA. In a recent analysis on the definitions of symptomatic PDA used in prospective studies, a variety of clinical signs (eg, murmur, hyperdynamic circulation) or echocardiographic markers (eg, diameter ductus arteriosus, left atrium to aorta ratio) emerged without much support from sensitivity or specificity analyses of the assorted markers.33 There are mechanism of action differences between non-steroidal anti-inflammatory drugs and paracetamol. Synergism, similar to that observed for analgesia, is theoretically possible. In our opinion, such research questions can only be addressed once the first question has been solved, that is, ‘does paracetamol result in PDA closure beyond the natural history of this phenomenon?’

It seems reasonable to explore the PK/PD of paracetamol for PDA closure. However, properly designed prospective, randomised controlled trials are needed to evaluate the effectiveness of paracetamol compared with ibuprofen or indomethacin for closure of the PDA before this can ever become clinical practice. We remain in an unexplored area for issues related to paracetamol safety (eg, liver, haemodynamics, thermodynamics, atopy).22–26 34 Investigation of paracetamol adducts may be a useful marker to investigate hepatotoxicity.35 Safety data must be a crucial part of any prospective, randomised controlled trial. Long term outcome also needs to consider potential differences in respiratory (bronchopulmonary dysplasia, atopy) or renal outcomes when compared with current standard treatments.

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Competing interests None.

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REFERENCES


Figure 2 Prediction of the paracetamol concentration–time profile for a 775 g weight, postmenstrual age (PMA) 28 weeks baby (15 mg/kg/q6h) based on the published intravenous paracetamol pharmacokinetic model (black line).13 19 This prediction is compared with the on-label dosing (7.5 mg/kg/q6h) in a term neonate (3.5 kg, 40 weeks PMA) for 48 h (grey line).
Review


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