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Paracetamol for the Treatment of Patent Ductus Arteriosus in Very Low Birth Weight Infants

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Abstract

Persistent patent ductus arteriosus (PDA) is associated with significant co-morbidities and increased mortality in preterm infants, especially very low birth weight (VLBW) infants. A large number of studies on the management of PDA have been published. Despite PDA being such a common condition in preterm infants, there is no consensus on which PDAs to treat, when to treat and how best to treat. Nonspecific cyclo-oxygenase inhibitors such as indomethacin and ibuprofen have been the mainstay of medical treatment of PDA for decades. Ibuprofen has similar efficacy and higher safety profile when compared to indomethacin, as it is associated with fewer gastrointestinal and renal side effects, and is considered the drug of choice for PDA closure. Recently, there is a growing interest in paracetamol for PDA closure and it has been suggested as an alternative drug to treat PDA. Finding the optimal pharmacological treatment for PDA closure in VLBW continues to remain challenging. In this review article, we assessed the evidence of paracetamol for PDA closure VLBW infants.

Keywords: Patent ductus arteriosus; Very low birth weight infants; Paracetamol; Treatment; Cyclo-oxygenase; Non-steroidal anti-inflammatory drugs

Introduction

The ductus arteriosus remains persistent in up to 60% of preterm infants and its incidence is inversely related to birth weight and gestational age (GA) [1]. Persistent patent ductus arteriosus (PDA) is associated with a prolonged ventilation need and carries an increased risk of serious morbidities such as intraventricular haemorrhage, acute pulmonary haemorrhage, necrotizing enterocolitis, chronic lung disease, brochopulmoary dysplasia and increased mortality [2-4]. A recent observational study by Sellmer et al. [5] reported that a large PDA (>1.5 mm) on day 3 after birth was associated with threefold increase in odds of death or severe morbidity (OR of IVH 4.2 whilst OR of chronic lung disease was 3.7). Despite being such a common problem in preterm infants and its strong association with increased mortality and severe co-morbidities, there is no consensus on the treatment of PDA - which PDAs to treat, when to treat and how best to treat? The treatment options for PDA closure are: pharmacological therapy or surgical ligation.

Pharmacological closure with non-steroidal anti-inflammatory drugs (NSAIDs), mainly ibuprofen and indomethacin, is currently the standard of care for PDA closure in preterm infants [6]. However, NSAIDs are not effective in around 25-30% of patients and they can have side effects such as transient renal function impairment, diminished platelet aggregation, hyperbilirubinemia, and gastrointestinal bleeding and perforation [7,8]. NSAIDs are contraindicated in presence of renal failure, active intracerebral haemorrhage, gastrointestinal problems (necrotising enterocolitis and perforation), and thrombocytopenia. Surgical ligation is not without risk of complications from cardiothoracic surgery. Moreover, it has been reported to be associated with impaired neurological outcome in preterm infants [9].

Recently, there has been a significant interest in paracetamol for the treatment of PDA in preterm infants. In last 5 years, two randomised controlled trials (RCTs) and at least 14 observational studies have been published. The reported efficacy in PDA closure after oral and intravenous use of paracetamol in preterm infants varies significantly [10-19] (Table 1). Two RCTSs comparing oral paracetamol with oral ibuprofen reported a slightly favourable effect of paracetamol - PDA closure rate of 81.2% in paracetamol group versus 78.8% for ibuprofen [10,11]. Another study by Oncel et al. even showed a higher closure success rate in the paracetamol group (97.5% vs. 95% in the ibuprofen group) [11,14,15].

However, a recent study by Roofthooft et al. [18] reported a limited efficacy of intravenous paracetamol in PDA closure in VLBW infants. We have similar experience of limited efficacy in our centre after treatment of PDA with IV paracetamol and the unpublished data suggest that IV paracetamol was effective in PDA closure in <30% VLBW infants. A recent Cochrane meta-analysis reported that paracetamol appears to be a promising alternative to ibuprofen and indomethacin for the PDA closure [19]. However, it recommended additional studies on its efficacy, safety. Long term follow-up studies are needed before paracetamol can be recommended as standard treatment for a PDA in preterm infants. Concerns have been raised regarding the long term safety of paracetamol in preterm infants after the reported possibility of an association between exposure of paracetamol to premature brain and development of autistic spectrum disorder in childhood.

In this review article, we reviewed the literature and have attempted to evaluate the role of paracetamol in PDA closure in preterm infants.

Mechanism of Paracetamol in PDA Closure

The prostaglandin-H2 synthetase (PGHS) enzyme system has two active sites: the cyclo-oxygenase (COX) and peroxidase (POX) sites. PGHS produces circulating prostaglandins (PG) that help in regulating ductal patency [20,21]. 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, PGI2 or TXA2. Non-selective COX inhibitors like NSAIDS inhibit COX site while paracetamol inhibit the POX site [22] (Figure 1). Paracetamol hereby acts as a reducing co-substrate so that less PGG2 can be converted to PGH2. On a contrary, paracetamol related POX inhibition is counteracted by PGG2 itself or lipid hydroperoxides (Figure 1).

	Author and year	Dose (mg/kg/day)	Dose Interval (hours)	Route	GA (in weeks)	Postnatal age at start (days)	Treatment duration (Max days)	Ductal closure or no ligation
Randomised controlled trials (RCTs)								
1	Dang (2013) RCT	15	6	PO	29-32	?	3	65/80
2	Oncel (2013) RCT	15	6	PO	≤ 26	2-3	3-6	12/13
		15	6	PO	<28	2-3	3-6	22/23
Uncontrolled observational studies								
1	Hammerman (2011)	15	6	PO	26-29	3-35	7	5/5
2	Yurttutan (2013)	15	6	PO	26-30	3-7	6	5/6
3	Oncel (2013)	15	6	IV	24-29	2-15	3-6	10/10
4	Alan (2013)	15	6	IV	26-35	8-19	19	0/3
5	Özmert (2013)	15	6	PO	23-32	20-47	3-6	5/7
6	Sinha (2013)	15	8	PO	27-33	4-7	2	10/10
7	Kessel (2013)	15	6	PO	26-30	?	3-11	7/7
8	Jasani (2013)	15	6	PO	28-31	?	2-4	3/9
9	Tekgunduz (2014)	15	6	IV	29	3	1	0/1
		10	8	IV	24-31	2-9	1-4	10/12
10	Nadir (2014)	15	6	PO	24-27	2-22	7	4/7
11	el-Khuffash (2014)	15	6	PO	26-33	14-56	2	0/5
		15	6	PO	26-30	8-35	7	6/7
		15	6	IV	26-32	3-41	2-5	9/9
12	Terrin (2014)	7.5-15	6-Apr	IV	24-28	2-4	3	6/8
13	Roofthooft (2014)	15	6	IV	23-26	3-33	3-7.5	6/33
14	el-Khuffash (2015)	15	6	IV	<28	16-39	6	24/30
Where: IV–Intravenous; PO–Oral/Nasogastric Administration, GA–Gestational Age in weeks								

Table 1: Showing literature review on paracetamol use in closure of persistent PDA.

The authors from previously reported studies have suggested that success rate of paracetamol in closing PDA is dose and duration dependent, which might explain why investigators have suggested and used higher than recommended dose of paracetamol in pre-term infants [16]. The paracetamol doses used to treat PDA in VLBW infants are 15 mg/kg/q6h or 60 mg/kg/day for 2-7 days. These doses are at least twofold higher than the standard recommended dose in term neonates (7.5 mg/kg/q6h; maximum of 30 mg/kg/day). There seems no scientific rationale for using the higher doses in VLBW infants as there is no published data demonstrating different clearance rate in this population.

There are no studies to suggest a paracetamol target concentration in PDA closure. A concentration-response relationship for PDA closure has been demonstrated in indomethacin and ibuprofen. Once paracetamol target concentration effective for PDA closure is established only then different doses can be studied to achieve the desired 'effective' level.

Paracetamol use in Closure of Persistent PDA

There are two published RCTs comparing oral paracetamol with oral ibuprofen and at least 14 observational studies on use of paracetamol to treat PDA in preterm infants (Table 1). Most of the studies have reported a high efficacy of paracetamol in PDA closure which is comparable to ibuprofen. However, there is significant variation in reported success rates in PDA closure between studies using a similar protocol, which is very confusing and difficult to explain [10-18]. For example, Oncel et al. [15,16] reported a 100% success rate of PDA closure with intravenous use of paracetamol whilst Roofthooft et al. [18] reported an 18% success rate after using similar protocol (same route of administration and paracetamol dose) [14].

It is no surprise to see significant heterogeneity in the designs and quality of the retrospective studies. More than half of the studies have reported use of oral paracetamol while others have used IV route for paracetamol administration. There is a significant variation in the intervention duration, study population and ductal characteristics.

Both the reported RCTs used oral route of administering paracetamol and showed a marginally favourable effect of paracetamol for PDA closure in preterm infants without any increased risk of side effects - closure rate of 81.2% in paracetamol group versus 78.8% for ibuprofen [10,11]. However, these trials had their own limitations – none of the trial was double blinded and sample size was small in both trials. These trials not only differed in their study population but also used different timing to administer paracetamol to treat the PDA. One trial studied subgroups of infants (<30 weeks, <28 weeks, and ≤ 26 weeks), while the second trial included larger infants up to 34 weeks. In our experience, PDA is not a major problem in more mature infants because of a high spontaneous closure rate. None of the trials reported long term effects like neurodevelopmental outcome.

A recent a systematic review and meta-analysis by Terrin et al. [23] concluded that efficacy and safety of paracetamol appear to be comparable with those of ibuprofen in PDA closure. In this review, meta-analysis of the uncontrolled studies demonstrated a pooled ductal closure rate of 49% and 76% after 3 and 6 days of treatment, respectively. However, the meta-analysis of two RCTs did not demonstrate such difference in the rate of ductal closure after 3 and 6 days of treatment. The meta-analysis involved small sizes, and adopted non-optimal blinding and randomisation methods. The authors of this review concluded that the results should be interpreted cautiously considering the high risk of bias and the limitations of the studies analysed.

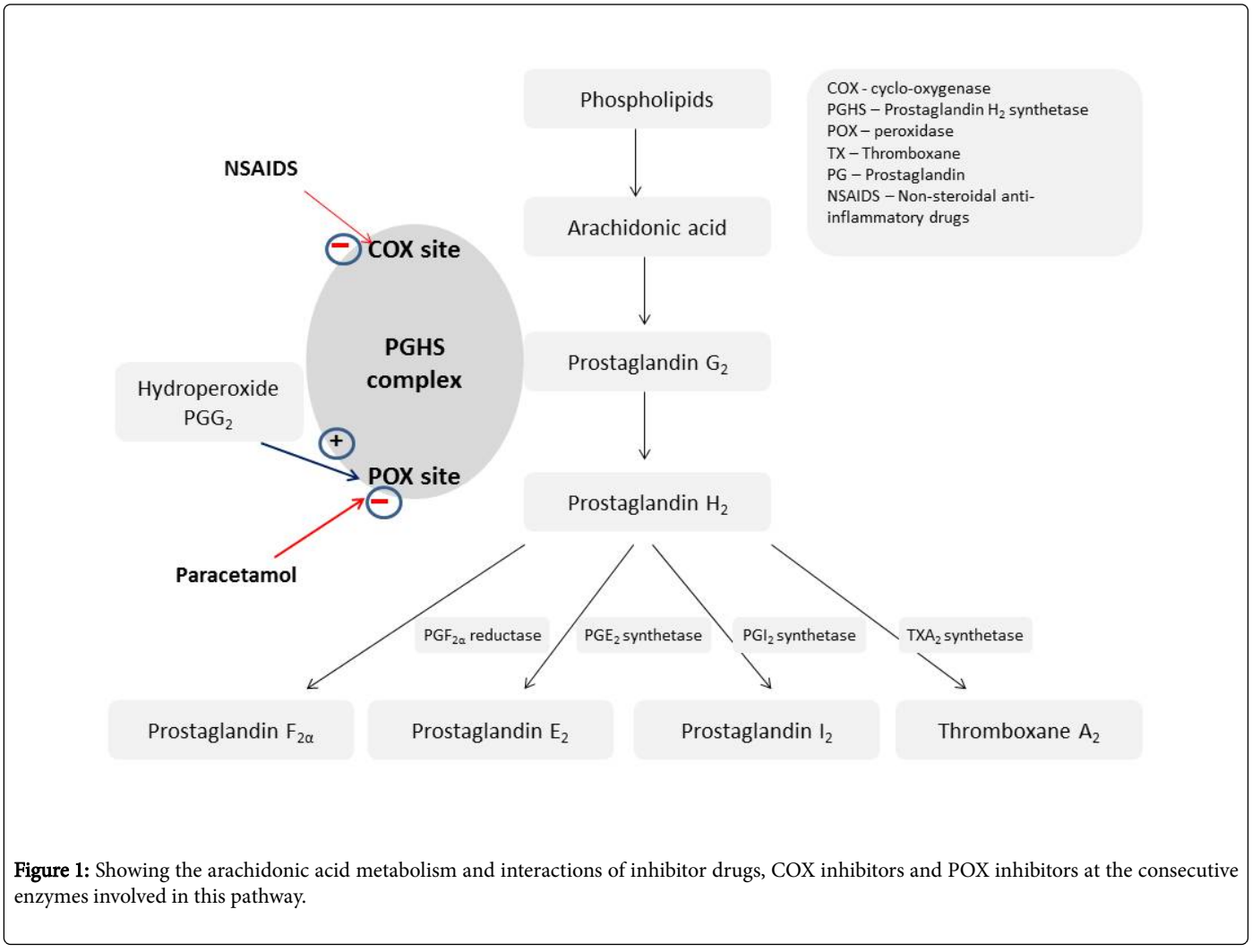

Figure 1: Showing the arachidonic acid metabolism and interactions of inhibitor drugs, COX inhibitors and POX inhibitors at the consecutive enzymes involved in this pathway.

Controversies and Concerns Regarding use of Paracetamol for PDA Closure in VLBW Infants

Pharmacokinetics and pharmacodynamics of paracetamol for the treatment of PDA in VLBW infants have not been studied. The target plasma concentration levels, effective level required to achieve successful closure of PDA remains unknown. The effectiveness of paracetamol in PDA closure has been suggested to depend on dosing, duration of treatment and route of administration [16]. The plasma level recommended for control of pain and fever is 10–20 mg/l. Kessel et al. [24] reported that plasma concentration levels of paracetamol did not exceed the recommended levels after using a dose of 15 mg/kg/q6h. Based on a predictive model Allegaert et al. [22] reported that peak level of nearly 25 mg/kg are likely to reach after four doses and it

could be assumed that plasma levels will accumulate with the 15 mg/kg/6h regimen [13]. Doses currently used for PDA closure are already higher than those recommended for analgesia (7.5 mg/kg/q6h), and the safety of the higher doses is unknown. Increasing the doses further to improve closure rates is therefore unadvisable without clear information regarding safety and pharmacokinetics in extremely preterm infants.

Paracetamol is metabolised primarily in the liver into toxic and non-toxic products. A major concern in using paracetamol in VLBW infants is the risk of paracetamol-induced hepatotoxicity. This complication is caused by the formation of a highly active metabolite, N-acetyl-p-benzoquinone-imine (NAPQ), by the hepatic cytochrome P450-dependent mixed function enzyme system involving CYP2E1, CYP1A2 and CYP3A4. NAPQ is then conjugated irreversibly with sulphydryl groups of glutathione [25,26]. Although the activity of CYP2E1 is low in neonates, NAPQ can still be formed in neonates with the concentrations of paracetamol associated with increased NAPQ1 production remaining unknown [26]. In pre-term infants, immaturity of the hepatic transporters could further increase this risk. Intravenous paracetamol has been reported to raise liver enzymes transiently 6 and this adverse effect has already been reported in three neonates by Alan et al. [27]. Even more worryingly, serious acute liver toxicity has already reported in preterm infants after intravenous use of paracetamol [28-32].

Both published RCTs used oral route for administration of paracetamol. Oral paracetamol is often contraindicated in the first few days of life in sick VLBW infants [10,11,23]. Intravenous route is the commonest and safest route for administering drugs in the sick VLBW infants who are not being enterally fed. There remains a concern regarding the safety of giving oral (enteral) medications with high osmolarity to the VLBW infants, who have not established enteral feeds fully or who have co-existing feeding difficulties. Administration of hyperosmolar medications is a risk factor for NEC in VLBW infants and even absorption is un-reliable in first few days after birth whilst they are not tolerating feeds. In our experience, haemodynamically significant PDA is less often a problem in infants of >28 weeks of gestation, who often establish feeds well and potentially could receive oral medications relatively safely. Interestingly there is no RCT on IV paracetamol or its comparison with IV indomethacin or paracetamol.

A recent Cochrane review on paracetamol for PDA in pre-term and VLBW infants concluded that further trials studying the long term safety of paracetamol should be conducting before any recommendation for its use in new-born population. Concerns have been raised regarding the development of autism or autism spectrum disorder in childhood after prenatal exposure of fetus to paracetamol [33]. In a recent animal study on mice, paracetamol was reported to have adverse effects on developing brain [19]. It would be sensible to incorporate long-term follow-up (at least up to 24 months) in the future paracetamol studies in preterm infants.

Lastly, still there remains a controversy regarding the efficacy of paracetamol in PDA closure. The published studies have reported a significant variation in success rates for PDA closure (18% to 100%) despite using similar protocols. We still lack the basic information who should we treat, when, how, and what's the best route for administering paracetamol in PDA closure.

Conclusion

Paracetamol seems to have efficacy and safety similar to ibuprofen in the treatment of PDA. Although many of the retrospective studies on paracetamol seems to be of poor quality and even the RCTs involved small number of patients with sub-optimal blinding and randomisation. Paracetamol has been reported as a relatively safe drug in VLBW infants even when higher than recommended doses were used. However, there remain concerns regarding its efficacy and safety with intravenous use. It would be reasonable to understand pharmacokinetics and pharmacodynamics of paracetamol in VLBW infants and know the target therapeutic levels effective for PDA closure in different gestational ages. We recommend well-designed RCTs to evaluate its efficacy, doses and duration of therapy and safety profile including long term effects before it can be recommended as a first line pharmacotherapy for PDA closure in preterm infants. In the meantime, paracetamol could be used treat PDA when established first line therapy (cyclo-oxygenase inhibitors) are either contra-indicated or have been ineffective.

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