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Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants

B. Jasani, MD[a,d], D.E. Weisz, MD[b,d], and P.J. McNamara, MD[a,b,c,*]

[a]Division of Neonatology, Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada
[b]Department of Paediatrics, University of Toronto, Toronto, Canada
[c]Department of Physiology, University of Toronto, Toronto, Canada
[d]Department of Newborn and Developmental Pediatrics, Sunnybrook Health Sciences Centre, Toronto, Canada

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ABSTRACT

While cyclooxygenase inhibitors have been the most common medications used to facilitate earlier closure of patent ductus arteriosus in preterm infants, adverse effects and variable efficacy have highlighted a need for alternative options. Acetaminophen facilitates ductal closure via an alternate pathway of prostaglandin inhibition. Despite treatment with high doses, toxicity is uncommon in preterm infants, possibly due to immature hepatic metabolism. Pooled data from randomized clinical trials of early treatment demonstrate that acetaminophen has similar efficacy as cyclooxygenase inhibitors for PDA closure with a favorable side effect profile and without any apparent increase in adverse neonatal outcomes. Acetaminophen may therefore be an ideal first-line agent among moderately and extremely preterm infants, though there is a paucity of data from controlled trials regarding its use in infants at the border of viability (gestation age ≤25 weeks). Evidence from clinical studies of limited quality supports acetaminophen treatment as rescue therapy for infants with persistent PDA after unsuccessful cyclooxygenase inhibitor treatment, including those being considered for surgical ligation.

Introduction

Management of patent ductus arteriosus (PDA) in preterm neonates remains contentious with marked international variability in therapeutic approaches among neonatologists.[1] Pharmacological PDA treatment has, for the past 4 decades, largely consisted of non-selective cyclooxygenase (COX) inhibitors (e.g., ibuprofen and indomethacin). Although early treatment has high efficacy for ductal closure (60–80%),[2] failure to improve many clinical outcomes, in addition to treatment-associated complications (e.g., acute renal injury, oliguria, and gastrointestinal hemorrhage), has prompted the search for an alternative agent with higher efficacy and an improved adverse effect profile. In 2011, Hammerman et al.[3] reported the first case series of use of acetaminophen as a therapeutic agent to facilitate ductal closure in 6 preterm infants with persistent PDA. Subsequent years have witnessed a marked surge in studies evaluating acetaminophen treatment in moderately and extremely preterm infants;

*Corresponding author. Tel.:+416 813 5773; fax: +416 813 5245.
E-mail address: patrick.mcnamara@sickkids.ca (P.J. McNamara).

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specifically, characterizing ductal responsiveness in animal and *in vitro* models, defining the drug's pharmacological profile, and finally the conductance of human clinical trials and observational studies of efficacy and safety. This review will examine the potential pharmacological role of acetaminophen amidst the biology of PDA closure, the implications of its pharmacokinetic and metabolic profile on dosing and safety, and a systematic review and meta-analysis of clinical trials of PDA treatment in preterm infants.

Pharmacology

Acetaminophen (N-acetyl-p-aminophenol, APAP, or paracetamol) is commonly used worldwide in young infants as an analgesic and antipyretic with modest peripheral anti-inflammatory properties.[4–6] It is generally preferred as an analgesic over COX inhibitors because of its better gastrointestinal tolerance[7] and lack of antiplatelet activity [via thromboxane A_2 (TxA_2)], which may preserve the aggregation capacity of platelets.[8] Evidence for the biological role of acetaminophen in promoting PDA closure is emerging.

Prostaglandin in the biology of ductal closure: postulated therapeutic mechanism of action of acetaminophen in preterm patent ductus arteriosus

Circulating prostaglandins (predominantly prostaglandin E_2 [PGE_2]), released from the placenta and fetal tissues, maintain the patency of the ductus arteriosus *in utero*. Functional ductal closure after birth is initiated when increased arterial oxygen tension and a rapid reduction in prostaglandins (due to removal of the placenta and increased prostaglandin catabolism) result in ductus arteriosus smooth muscle vasoconstriction. This vasoconstriction leads to profound hypoxia in the ductal vasa vasorum, resulting in topical angiogenesis, neo-intima formation, and apoptosis. Subsequent platelet recruitment leads to luminal obstruction, fibrosis, and anatomic ductus arteriosus closure.[9–12]

Postnatal ductal patency is promoted by the ongoing production of circulating prostaglandins catalyzed by the enzyme prostaglandin H_2 synthetase (PGH_2) complex. PGH_2 has both COX and peroxidase (POX) sites that work in series to produce PGH_2, the precursor to PGE_2.[13] The COX site converts free arachidonic acid to PGG_2 by oxidation, which is then converted to PGH_2 by the POX site. PGH_2 serves as a substrate for several cell-specific isomerases and synthases to produce biologically active prostaglandins, PGI_2 and thromboxane (TxA_2).[14,15] Non-selective COX inhibitors inhibit the COX site, while acetaminophen is believed to inhibit the POX site of the bi-functional COX enzymes (Fig. 1). Acetaminophen may facilitate PDA closure via inhibition of the POX moiety, acting as a reducing co-substrate so that less PGG_2 is converted to PGH_2. Acetaminophen-related POX inhibition is competitive and counteracted by PGG_2 itself or lipid hydroperoxides (Fig. 1). POX inhibition results in phenoxy radical formation from a critical tyrosine residue that is essential for COX resynthesis and activity. COX depends on POX activity.[7,16,17] POX inhibition is however, independent of COX activity.[18]

Pharmacokinetics, metabolism, and dosing of acetaminophen in preterm infants

Acetaminophen is metabolized by the liver and, in adults, undergoes conjugation with glucuronide (acetaminophen-glucuronide, 52–57% of urinary metabolites) by glucuronyl transferase and sulfation (acetaminophen-sulfate, 30–44%) by sulfotransferases.[19] Neonates have an acetaminophen clearance per kg bodyweight similar to adults but with proportionally lower glucuronidation and higher sulfation. Glucuronidation metabolism of acetaminophen increases with advancing gestational age.[20] A minor fraction (5–10%) of acetaminophen is oxidized, via CYP2E1, to a highly reactive toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI), that is highly reactive and primarily responsible for acetaminophen-induced hepatotoxicity. At therapeutic doses, NAPQI is immediately inactivated by conjugation with glutathione, avoiding the toxic effects of mitochondrial dysfunction, oxidant stress, and hepatic cellular necrosis that may occur when NAPQI covalently binds to cellular proteins and forms toxic adducts. Despite increasing use of acetaminophen in preterm infants, very few cases of clinically detectable toxicity have been reported,[21,22] which may be attributed to low activity of cytochromes P450 (including CYP2E1) in the immediate postnatal period, minimizing formation of the toxic metabolite NAPQI. A single high dose of acetaminophen (10–20 mg/kg) in preterm infants (GA 24–32 weeks) does, however, result in detectable acetaminophen-glutathione and downstream metabolites (a measure of exposure to the toxic CYP2E- metabolites), indicating the need for careful monitoring for toxicity.[23]

Data on acetaminophen pharmacokinetic/pharmacodynamic properties in neonates suggest that a compartment concentration of 10–20 mg/L results in a therapeutic analgesic effect.[24,25] To achieve this, loading doses (intravenous or oral 20 mg/kg, rectal 30–40 mg/kg), followed by maintenance (intravenous or oral 10 mg/kg, rectal 1–18 mg/kg) doses (every 6 hours in term neonates, every 8 hours in preterm <32 weeks infants), respectively may be administered.[26,27] These doses are well tolerated with less hepatotoxic effects in neonates compared to older children when administered for a limited time (48–72 hours).[28,29] The applicability of these doses for premature infants with high-volume PDA shunts, which may potentially compromise liver or renal perfusion, has not been studied so caution is advised regarding the extrapolation of these findings.

Pharmacokinetic profile of acetaminophen in preterm neonates with PDA

A limited number of studies have investigated serum acetaminophen concentrations among preterm infants treated for PDA, where most infants received a dose of 15 mg/kg every 6 hours for 12 doses (72 hours). It is noteworthy that although this was the most commonly used dosing scheme in clinical trials to date, it is twice as high as the previously recommended maximum dose in preterm infants and was adopted without dose ranging studies to establish safety and efficacy.