Acetaminophen for Patent Ductus Arteriosus in Extremely Low-Birth-Weight Neonates

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OBJECTIVE Although non-steroidal anti-inflammatory drugs (NSAIDs) are the current standard therapy for the treatment of patent ductus arteriosus (PDA), many neonates have contraindications to receiving or may fail NSAID therapy. To avoid surgical ligation, these patients may benefit from an alternative therapy. The objective of this research is to report the efficacy and safety of acetaminophen for the treatment of PDA in a cohort of premature neonates.

METHODS Demographics and clinical course were retrospectively evaluated for all neonates admitted during the study period who received acetaminophen for the treatment of PDA. Initial acetaminophen dosing was 15 mg/kg every 6 hours (88% intravenous). Efficacy was analyzed from ductal constriction on echocardiogram as well as need for further PDA treatment. Markers of hepatic and renal function as well as respiratory support and neonatal morbidities were evaluated to describe the safety of acetaminophen.

RESULTS Forty-one neonates were identified with a median birth weight of 760 g (IQR 614–948 g) and median gestational age of 25 weeks (IQR 24–27 weeks). Treatment was initiated at a median postnatal age of 15 days (IQR 8–19 days) for a median duration of 7 days (IQR 6–10 days). Twenty-seven neonates (66%) required no further PDA treatment, with echocardiographic PDA closure documented in 10 neonates (24%) and reduced ductal size in 15 neonates (37%). No clinically significant adverse effects attributable to acetaminophen therapy were detected.

CONCLUSIONS Most patients in this study responded to acetaminophen treatment for PDA, indicating that this therapy may be an option for extremely low-birth-weight neonates in order to avoid surgical ligation.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NSAID, non-steroidal anti-inflammatory drug; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation

KEYWORDS acetaminophen; extremely low-birth-weight infant; neonatal intensive care; patent ductus arteriosus

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Introduction

Patent ductus arteriosus (PDA) is common in pre-term neonates. Although the exact pathogenic nature of PDA remains unknown, potential complications include congestive heart failure, pulmonary edema, bronchopulmonary dysplasia (BPD), acute renal failure, spontaneous intestinal perforation (SIP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and an increased risk of infective endocarditis.¹ The current standard therapy for a hemodynamically significant PDA is non-steroidal anti-inflammatory drugs (NSAIDs), primarily ibuprofen and indomethacin. While multiple studies have demonstrated that these agents are efficacious in closing the PDA, approximately 30% of neonates fail therapy and many have relative contraindications to receiving NSAIDs, including significant renal impairment, NEC, and severe IVH.¹ Notably, extremely low-birth-weight neonates are at the highest risk for

treatment failure and contraindications to NSAIDs. In these cases, without an alternative treatment option, the patient may undergo surgical ligation to close the PDA. In addition to the potential risks of infection, pneumothorax, vocal cord palsy, and postligation cardiac syndrome, ductal ligation has been associated with significantly increased rates of BPD, retinopathy of prematurity, and neurosensory impairment.^{2,3} Therefore, it is vital to identify an alternative treatment option for patients where NSAIDs fail or are contraindicated.

In recent years, acetaminophen has emerged as a potential treatment option for PDA.⁴ Four small randomized controlled studies have found no significant difference in safety or efficacy between oral acetaminophen and NSAIDs for the treatment of PDA in premature neonates, and multiple observational studies have analyzed the efficacy of acetaminophen.^{5–9} Based on the available data, our institutional guidelines changed in late

2014 to include acetaminophen as a possible primary treatment for PDA for neonates with contraindications to NSAID treatment as well as an alternative to surgical ligation for neonates who have failed therapy with indomethacin. Acetaminophen therapy is not without risk. The primary adverse effect of acetaminophen is hepatotoxicity manifested first by clinical signs including vomiting, malaise, diaphoresis, and liver enlargement, followed by elevated bilirubin and hepatic enzymes typically 3 to 5 days into the acetaminophen course.¹⁰ The objective of this retrospective review was to examine the effectiveness and safety of acetaminophen as a treatment option for PDA closure in a single-center population of extremely low-birth-weight neonates.

Methods

Patient Population. This retrospective cohort study included assessment of outcomes in all neonates who were admitted to the neonatal intensive care unit (NICU) at St. Louis Children's Hospital between December 1, 2014, and March 15, 2016, and received acetaminophen for the treatment of PDA. The need for treatment of the PDA and the use of acetaminophen were determined by the attending neonatologist. All patients were diagnosed with a PDA on the basis of clinical signs and symptoms and verified by echocardiography read by a pediatric cardiologist.

Acetaminophen Therapy. All acetaminophen courses followed our institutional protocol as follows. Acetaminophen was initiated at 15 mg/kg every 6 hours, reflecting the most common regimen used in previous reports. Intravenous therapy was used in neonates receiving < 100 mL/kg/day of enteral feedings; oral therapy was used in neonates receiving ≥ 100 mL/kg/day of enteral feedings. Safety parameters including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, serum creatinine, and a serum acetaminophen concentration were obtained 4 hours after a dose on day 3 of therapy. Generally, therapy was continued for 7 days in the absence of toxicity, as described in previous series and trials, although echocardiograms were obtained at the discretion of the medical care team and courses could be truncated or prolonged.

Data Collection. Data pertaining to each acetaminophen course, including regimen, route, acetaminophen concentrations, and duration of therapy, were collected from the electronic medical record. Data regarding demographics (sex, gestational age, birth weight, postnatal age at time of treatment), perinatal course (antenatal corticosteroids, surfactant administration), and neonatal course (prophylactic indomethacin; liver [alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin], renal [serum creatinine], and respiratory [mode of support required, positive end expiratory pressure, fraction of inspired oxygen] status; and the occurrence of IVH, NEC, SIP,

Table 1. Baseline Characteristics of Neonates Who Received Acetaminophen for Patent Ductus Arteriosus

Characteristic	Value (N = 41)
Gestational age, wk, median (IQR)	25 (24–27)
Birth weight, g, median (IQR)	760 (614–948)
Male sex, n (%)	18 (44)
Prophylactic indomethacin, n (%)	9 (22)
Antenatal corticosteroids, n (%)	30 (73)
Surfactant, n (%)	40 (98)

and BPD) were also collected. Bronchopulmonary dysplasia was diagnosed by using the modified Shennan definition.¹¹ Evaluation for PDA via echocardiogram was performed at the discretion of the attending neonatologist, based on clinical signs and symptoms suggestive of PDA, including murmur, palmar pulses, widened pulse pressures, and/or end-organ hypoperfusion. Upon echocardiographic evaluation by a pediatric cardiologist, each PDA was subjectively classified as “small,” “moderate,” or “large.”

Outcomes. Efficacy was defined as the need for no further PDA therapy. The incidences of complete PDA closure and ductal constriction on echocardiogram were also evaluated. Safety of acetaminophen was assessed by comparing baseline and treatment liver, renal, and respiratory status. Additionally, the occurrence of IVH, NEC, SIP, and BPD after therapy was evaluated.

Statistical Analysis. Statistical analysis was performed with SPSS 19 (SPSS Inc, Chicago, IL). Descriptive statistics were used to summarize baseline characteristics for all neonates. The Wilcoxon signed rank test and McNemar's test were used to compare baseline and treatment laboratory values and level of respiratory support and the incidences of IVH, NEC, and SIP, respectively. Adverse events were scored by using the Naranjo Adverse Drug Reaction Probability Scale.¹² To identify risk factors for treatment failure, the Mann-Whitney *U* test and Fisher's exact test were used to compare demographics and clinical characteristics of responders and non-responders. A *p* value of < 0.05 was used to define statistical significance. Study procedures were approved by the Institutional Review Board of Washington University in St Louis.

Results

During the study period, 41 patients admitted to the NICU at St. Louis Children's Hospital received acetaminophen for the treatment of PDA. The demographics and perinatal characteristics of the cohort are displayed in Table 1. Acetaminophen treatment was initiated at a median of 15 days of life (IQR 8–19 days). Echocardiographic evaluation prior to the initiation of acetaminophen revealed a large PDA in 27 neonates (66%) and

Table 2. Patient Characteristics of Responders and Non-Responders to Acetaminophen

Characteristic	Ligation Not Required (n = 27)	Ligation Required (n = 14)	p value
Gestational age, wk, median (IQR)	25 (25–28)	24 (23–26)	0.028
Birth weight, g, median (IQR)	840 (690–960)	670 (563–910)	0.108
Postnatal age at treatment, days, median (IQR)	15 (8–20)	16 (8–19)	0.968
NSAID failure, n (%)	1 (4)	6 (43)	0.002
Large PDA at treatment initiation, n (%)	16 (59)	10 (71)	0.629
Baseline positive end expiratory pressure, mm Hg, median (IQR)	6 (5–7)	6 (5–6)	0.492
Baseline fraction of inspired oxygen, median (IQR)	0.36 (0.27–0.46)	0.39 (0.28–0.51)	0.900
Intravenous acetaminophen therapy, n (%)	23 (85)	13 (93)	0.645
Acetaminophen concentration, mg/L, median (IQR)	12.4 (6.6–15.8)	12.1 (6.8–17.3)	0.776
Duration of acetaminophen therapy, days, median (IQR)	7 (6–10)	8 (6–10)	0.946

NSAID, non-steroidal anti-inflammatory drug; PDA, patent ductus arteriosus

moderate PDA in 14 neonates (34%). Indications for acetaminophen included NSAID failure (n = 7), grade III/IV IVH (n = 9), SIP (n = 7), and attending physician preference (n = 18), generally based on the desire to maintain enteral feedings. At the time of initiation, 3 neonates (7%) were receiving supplemental oxygen via high-flow nasal cannula; 5 (12%), non-invasive mechanical ventilation; 25 (61%), conventional mechanical ventilator; and 8 (20%), high-frequency oscillatory ventilation.

Intravenous therapy was administered in 88% of cases. The median acetaminophen concentration was 12.4 mg/L (IQR 6.9–16.3 mg/L). Neonates were treated with acetaminophen for a median duration of 7 days (IQR 6–10 days). Twenty-seven neonates (66%) responded to acetaminophen therapy requiring no further treatment for PDA. Posttreatment echocardiograms were performed on 39 patients (95%) at the discretion of the attending neonatologist. Of these, posttreatment echocardiogram documented PDA closure in 10 neonates (24%) and a reduction in ductal size in 15 neonates (37%). Fourteen patients (34%) did not have significant improvement in PDA with acetaminophen and underwent surgical ligation for PDA closure. With the exception of gestational age and prior failure of NSAID therapy, responders and non-responders had similar baseline and treatment characteristics (Table 2).

There was a statistically significant increase in median alanine aminotransferase, but no significant increase in any other marker of hepatic injury (Table 3). Although serum creatinine differed significantly before and during treatment, the magnitude and direction of this change reflects no clinical difference or an improvement in renal function. The maximum acetaminophen concentration in the entire cohort was 29 mg/L, well below the toxic threshold defined in adult patients (>150 mg/L 4 hours after the dosing).¹³ No clinical signs of acetaminophen toxicity were observed in any pa-

tients at any point during or immediately after therapy. There was no statistically significant change in the mode of respiratory support or required settings during the acetaminophen course. There was a low incidence of NEC and SIP and no new IVH sustained after treatment with acetaminophen. All cases of NEC and SIP were deemed possibly associated with acetaminophen therapy on the Naranjo scale (+2). Twenty-five infants (61%) were diagnosed with BPD.

Discussion

This retrospective review of predominantly extremely low-birth-weight neonates with PDA demonstrated treatment success with acetaminophen in most neonates. Treatment failure was more prevalent in neonates who were more premature at birth and those who failed NSAID therapy prior to receiving acetaminophen. No adverse events were detected that were definitively attributable to acetaminophen therapy. These findings suggest that acetaminophen may be a treatment option for the closure of PDA even in extremely low-birth-weight neonates at relatively late postnatal ages.

In agreement with existing data, the response rate in this cohort suggests that acetaminophen may reduce the need for surgical ligation in neonates who have failed or have contraindications to NSAID therapy. A surprising relative contraindication to NSAID therapy in our study population was the desire to maintain enteral feedings, generally perceived as contraindicated or limited by intravenous indomethacin therapy.¹⁴ Use of acetaminophen as first-line therapy in this population is certainly experimental. Most neonates responded to acetaminophen as first-line therapy in the 4 published randomized controlled trials; however, these trials used only oral acetaminophen and had a much different patient population compared to that of our study.^{5–8} Specifically, the neonates in these studies were larger

Table 3. Safety Parameters

Parameter	Baseline	Treatment	p value
Alanine transaminase, units/L, median (IQR)	6 (0–8)	8 (5–13)	0.019
Aspartate transaminase, units/L, median (IQR)	24 (19–30)	25 (19–35)	0.362
Alkaline phosphatase, units/L, median (IQR)	405 (263–604)	381 (328–636)	0.286
Bilirubin, mg/dL, median (IQR)	3.0 (1.6–4.4)	2.8 (1.8–3.8)	0.314
Serum creatinine, mg/dL, median (IQR)	0.6 (0.4–1.0)	0.5 (0.4–0.8)	0.040
Positive end expiratory pressure, mm Hg, median (IQR)	6 (5–7)	6 (5–7)	1
Fraction of inspired oxygen, median (IQR)	0.37 (0.27–0.49)	0.35 (0.26–0.42)	0.131
Any intraventricular hemorrhage, n (%)	19 (46)	19 (46)	1
Grade III/IV intraventricular hemorrhage, n (%)	9 (22)	9 (22)	1
Necrotizing enterocolitis, n (%)	0 (0)	4 (10)	0.13
Spontaneous intestinal perforation, n (%)	7 (17)	8 (20)	1

(mean birth weight of 900–1700 g), more mature (mean gestational age of 27–32 weeks), and younger at initiation of acetaminophen treatment (≤ 14 days). Notably, treatment response to acetaminophen in these studies was higher with increasing gestational age and inversely related to postnatal age. Our relatively low complete closure rate in an older, more premature population further supports this relationship. Additionally, our results demonstrate decreased response to acetaminophen therapy after previous failure of NSAID therapy. This finding may be due to the overlapping mechanisms of these agents, but also likely relates to the common demographic risks for treatment failure mentioned above in both classes of medication.^{15,16}

To our knowledge, no randomized controlled trial to date addresses a patient population similar to that of the current report. The use of acetaminophen to facilitate ductal closure in this population is supported by numerous observational studies.^{9,17–22} Similarly to the randomized controlled trials, most neonates in these reports were more mature than our study population and most acetaminophen courses were initiated within the first week of life. Notable exceptions include recent reports of acetaminophen use in extremely premature neonates treated at a late postnatal age.^{17,18,21,23} Findings in these reports correlate well with our study, demonstrating a low rate of complete ductal closure, but a high rate of clinical constriction requiring no further intervention. These findings highlight the utility of a composite endpoint representing clinical efficacy (absence of the need for further PDA therapy) as opposed to the disease-oriented outcome of PDA closure on echocardiogram. The former may be the most appropriate endpoint for observational trials at this time, given the uncertain importance of complete ductal closure.²⁴ In this context, clinicians are increasingly prioritizing adverse effect profile over absolute efficacy in pharmacologic PDA therapy, as evidenced in this cohort.

No significant adverse effects have been noted

with the use of acetaminophen in prior studies. Although there was a statistically significant increase in alanine aminotransferase in our study, the finding was not deemed clinically significant as no other signs or symptoms of hepatotoxicity were observed. It was challenging to evaluate the relationship between acetaminophen therapy and NEC, SIP, and BPD in this high-risk population. However, Naranjo scores evaluating these potential adverse effects were low and we do not feel these morbidities were disproportionately represented in patients receiving acetaminophen, compared to our overall population. Additionally, in this population specifically selected for PDA treatment owing to a preponderance of clinical risk factors for morbidities, rates of posttreatment NEC and SIP were similar to those reported in randomized controlled trials comparing ibuprofen and indomethacin.²⁵ Notably, BPD rates in our cohort were dramatically higher, likely attributable to patient selection, but requiring attention in ongoing controlled trials of acetaminophen therapy.

This study has several limitations. Without a control group, this study cannot differentiate between potential spontaneous closure/constriction during the treatment period and the effect of acetaminophen on the PDA. Although the reported rate of spontaneous PDA closure in extremely low-birth-weight neonates is approximately 34%, the rate of spontaneous closure at 2 weeks of life and beyond, as the neonates were in this study, is not reported.²⁶ The study was retrospective and observational; therefore, acetaminophen initiation was at the discretion of the attending neonatologist and thus not uniform. Additionally, there is possible variability in the subjective measure of each PDA on echocardiogram, as no quantitative measures were obtained and each echocardiogram was not read by the same pediatric cardiologist. Despite these limitations, our data suggest potential benefit of acetaminophen for the treatment of PDA, especially in the setting of relative contraindications to NSAID therapy.

Conclusions

This study demonstrates a significant clinical response to acetaminophen for PDA in a predominantly extremely low-birth-weight population, with over half of the patients requiring no further treatment for PDA. These findings suggest acetaminophen is a potential alternative therapy for the closure of PDA in order to avoid the adverse effects of NSAID therapy and/or the morbidity and mortality associated with surgical ligation. However, randomized studies are needed to verify the effect of acetaminophen on PDA and evaluate long-term outcomes.

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