Acetaminophen Serum Concentrations in Infants Treated Intravenously for Patent Ductus Arteriosus

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OBJECTIVE Although acetaminophen has emerged as a therapeutic option for treating hemodynamically significant patent ductus arteriosus (PDA) in preterm infants, limited data exist on pharmacodynamics. The objective of this research is to report serum acetaminophen concentrations at steady state in infants treated with intravenous acetaminophen for PDA and to examine associations with clinical outcomes.

METHODS This retrospective study evaluated all infants admitted during the study period who received intravenous acetaminophen for the treatment of PDA. Acetaminophen dosing was 15 mg/kg every 6 hours. A serum acetaminophen concentration was obtained 4 hours after the eighth dose. Associations between serum concentrations and efficacy, assessed by ductal constriction on echocardiogram, and safety, assessed by serum creatinine and hepatic transaminases, were explored using simple linear regression.

RESULTS A total of 36 infants were included, with a median birth weight of 720 g (IQR 585–895 g) and a median gestational age of 25 weeks (IQR 24–26 weeks). The median acetaminophen concentration in the cohort was 12.3 mg/L (IQR 6.7–16.5 mg/L; range, 1.1–29.0 mg/L). Serum acetaminophen concentrations did not correlate with infant demographics, hepatic transaminases during treatment, or duct size at treatment completion. We observed ductal closure across a wide range of serum acetaminophen concentrations.

CONCLUSIONS We did not identify an association between acetaminophen serum concentrations following intravenous therapy and ductal response or hepatic toxicity.

ABBREVIATIONS ALT, alanine aminotransferase; AST, aspartate aminotransferase; PDA, patent ductus arteriosus

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

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Introduction

Prospective studies continue to emerge suggesting the effectiveness of acetaminophen as treatment for hemodynamically significant patent ductus arteriosus (PDA).¹ Although small, these studies suggest the potential for equivalent ductal closure with lower rates of transient renal toxicity compared with standard doses of intravenous ibuprofen or indomethacin. However, numerous outstanding questions exist, ranging from optimal dosing to the long-term effects of this novel application of acetaminophen.

Recently, a retrospective study examined serum acetaminophen concentrations in 10 infants treated with enteral acetaminophen to facilitate PDA closure.² The authors noted a significant correlation between steady-state serum acetaminophen concentration and ductal response. Our institution routinely uses acetaminophen in infants with a clinically significant PDA and relative contraindications to intravenous indomethacin, including grade III/IV intraventricular

hemorrhage or spontaneous intestinal perforation, or based on attending preference, generally driven by the desire to maintain partial enteral feedings. Infants who are receiving less than 100 mL/kg/day of enteral feedings receive intravenous therapy, given the high osmolality of enteral acetaminophen.³ To extend information on the pharmacokinetic/dynamic nature of acetaminophen, we retrospectively evaluated the relationship between steady-state acetaminophen concentrations after intravenous administration and markers of efficacy/safety in infants treated for PDA at our institution.

Materials and Methods

Patient Population. This retrospective study included all infants admitted to the neonatal intensive care unit at St Louis Children's Hospital between December 1, 2014, and March 15, 2016, who received intravenous acetaminophen for treatment of PDA. The PDA was evaluated based on clinical signs and symptoms at the

Table. Baseline Characteristics*

Characteristic	Value
Gestational age, wk, median (IQR)	25 (24–26)
Birth weight, g, median (IQR)	720 (585–895)
Male gender, n (%)	16 (44)
Postnatal age at treatment initiation, days, median (IQR)	15 (7–20)
Previous NSAID therapy, n (%)	17 (47)
Serum creatinine, mg/dL, median (IQR)	0.6 (0.4–1.0)
AST/ALT, units/L, median (IQR)	23 (18–30) / 5 (0–9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAID, non-steroidal anti-inflammatory drug

* n = 36.

discretion of the attending neonatologist and verified by echocardiography read by a pediatric cardiologist prior to treatment. Each PDA was subjectively classified as “small,” “moderate,” or “large.”

Acetaminophen Therapy and Serum Measurements. All infants received a standardized intravenous acetaminophen course (Ofirmev, Mallinckrodt Pharmaceuticals, Hazelwood, MO) consisting of 15 mg/kg per dose every 6 hours for 7 days, reflecting the most common regimen used in available reports.⁴ Baseline serum creatinine and hepatic transaminases were obtained prior to initiation of therapy. A serum acetaminophen concentration along with serum creatinine and hepatic transaminases were obtained 4 hours after the eighth dose (steady state based on available pharmacokinetic data in infants).⁵ Serum acetaminophen concentrations were evaluated using the Cobas 6000 c501 analyzer (Roche Diagnostics USA, Indianapolis, IN) using a homogenous enzyme immunoassay. Assays were performed within 2 hours of the blood draw. The determination limit of this assay is 3 mcg/L. Echocardiography was repeated at the completion of the acetaminophen course.

Statistical Analysis. Statistical analysis was performed using SPSS 19 (SPSS Inc, Chicago, IL). Descriptive statistics were performed to summarize baseline characteristics for evaluable infants. The Wilcoxon signed rank test was used to compare baseline and treatment laboratory values. Linear regression was performed to examine potential associations between serum acetaminophen concentrations and patient demographics, hepatic transaminases, serum creatinine, and short-term ductal response to treatment. Study procedures were approved by the Institutional Review Board of Washington University in St Louis.

Results

The clinical characteristics and outcomes of the entire cohort have been reported previously.⁶ Of the 41 infants in the overall cohort, 36 received acetaminophen courses that were exclusively intravenous and were included in this study. Demographics of study

infants are presented in the Table.

The median acetaminophen concentration was 12.3 mg/L (IQR 6.7–16.5 mg/L; range, 1.1–29.0 mg/L). There was no association between acetaminophen concentration and baseline demographic/clinical variables, including gestational age ($r = -0.088$, $p = 0.608$), birth weight ($r = -0.125$, $p = 0.468$), postmenstrual age ($r = -0.250$, $p = 0.142$), postnatal age ($r = -0.313$, $p = 0.063$), aspartate aminotransferase (AST; $r = -0.002$, $p = 0.993$), alanine aminotransferase (ALT; $r = -0.362$, $p = 0.117$), or serum creatinine ($r = 0.322$, $p = 0.101$).

A total of 7 patients (19%) had complete ductal closure on posttreatment echocardiogram, and an additional 11 (31%) had a reduction in ductal size. A total of 23 patients (64%) required no further therapy for PDA, and 13 underwent surgical ligation (36%). There was no association between serum acetaminophen concentration and ductal size on posttreatment echocardiography ($r = 0.106$; $p = 0.539$; Figure 1). There was a significant association between acetaminophen concentration and serum creatinine during treatment ($r = 0.535$, $p = 0.002$) but no association between acetaminophen concentration and treatment hepatic transaminases (AST, $r = 0.124$, $p = 0.520$; ALT, $r = -0.110$, $p = 0.568$).

Discussion

Acetaminophen has emerged as an option to promote the closure of hemodynamically significant PDA. However, case series and clinical trials have preceded rigorous pharmacodynamic studies in infants with PDA. In this study, we explored the pharmacokinetics/dynamics of acetaminophen in a group of infants who received standardized intravenous acetaminophen dosing. We found no association between baseline infant demographics/clinical characteristics and acetaminophen serum concentrations. Furthermore, the data suggest that serum acetaminophen concentration after intravenous therapy does not correlate with short-term clinical response.

The pharmacokinetics of intravenous acetaminophen have been explored in preterm infants.^{5,7} Although a relationship exists between infant weight and pharma-

Figure 1. Relationship between acetaminophen concentration and echocardiographic findings after treatment ($r = 0.106$, $p = 0.539$).

cokinetic parameters, these studies document up to 6-fold interindividual variation in clearance and 5-fold interindividual variation in volume of distribution, resulting in a roughly 10-fold variation in steady-state serum concentrations. Single-sample steady-state serum concentrations in our cohort reflect this variability, failing to detect a reliable association between baseline demographics and acetaminophen concentrations. The significant relationship between acetaminophen concentrations and serum creatinine during treatment is not surprising, given the predominantly renal elimination of acetaminophen in infants.

The pharmacodynamics of acetaminophen to facilitate PDA closure clearly require careful examination. Our previous report of this cohort suggests the potential for a lower rate of complete ductal closure in extremely preterm infants treated at relatively late postnatal ages.⁶ A recent publication suggests these clinical findings may arise partially from an association between lower acetaminophen concentrations and higher postnatal ages.² However, we failed to detect an association between postnatal age and acetaminophen concentration (Figure 2). Additionally, we did not find any relationship between acetaminophen concentrations and ductal

Figure 2. Relationship between postnatal age and acetaminophen concentration ($r = 0.313$, $p = 0.063$).

response. In stark contrast to the recent retrospective study of serum concentrations after enteral acetaminophen, we present 7 cases of complete ductal closure with steady-state acetaminophen concentrations of <20 mg/L.

Differences in the pharmacokinetics of intravenous and enteral acetaminophen represent one plausible explanation for the contrasting findings of this study and the recent work by Bin-Nun and colleagues.² These differences have been explored extensively for non-steroidal anti-inflammatory drug therapy. Several randomized controlled trials comparing intravenous and enteral ibuprofen have documented higher efficacy rates with enteral therapy.⁸ Despite similar concentrations 4 hours after the dose, enteral ibuprofen produces a dramatically higher area under the curve.⁹ These historical examples highlight the limitations of single-point pharmacokinetic assessments and the importance of more complete pharmacokinetic/dynamic characterization of both intravenous and enteral acetaminophen for PDA.

This report has other clear limitations. The relatively small sample size highlights the single-center, clinical nature of this cohort, although this study includes substantially more infants than previously published pharmacokinetic/dynamic evaluations of acetaminophen for PDA. Given the exploratory nature of therapeutic drug monitoring in this population, we evaluated only single-sample, steady-state serum concentrations obtained in routine clinical care in this study. Therefore, both pharmacokinetic and pharmacodynamic assessments are crude, not accounting for the full concentration-time profile of acetaminophen or effects that occur when the serum concentration is outside the range described in this analysis. Additionally, this study was not designed to examine the long-term safety and efficacy of acetaminophen for PDA closure, both of which are important outstanding questions.¹⁰ Simply, the pharmacodynamic observations in this cohort highlight the need for future prospective studies carefully examining the efficacy, safety, and pharmacodynamics of acetaminophen for PDA closure.

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