JPPT | Single Center Retrospective Study

Evaluation of Serum Acetaminophen Concentration Utility for Closure of Patent Ductus Arteriosus

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OBJECTIVE Acetaminophen for patent ductus arteriosus (PDA) closure has gained popularity over the last decade; however, therapeutic drug monitoring for this indication remains uncertain. The exact timing and goal trough serum acetaminophen concentration ranges are not well defined. The purpose of our study is to evaluate the impact of therapeutic drug monitoring on both PDA closure rates and identify real-world risk of hepatotoxicity.

METHODS Retrospective single-center chart review of neonates admitted to the neonatal intensive care unit (NICU) between April 2016 and August 2022 with at least 1 serum acetaminophen concentration to monitor for PDA closure. Acetaminophen was initiated at 15 mg/kg administered intravenously every 6 hours and a trough serum concentration was obtained prior to the sixth or seventh dose. PDA closure was confirmed radiographically with corresponding provider documentation. Associations of efficacy to closure were analyzed using descriptive statistics.

RESULTS Thirty-eight neonates were included in the analysis, of which 18 (47%) achieved PDA closure. First serum acetaminophen trough concentration was obtained before the seventh dose [IQR, 6–8] and ranged from undetectable (< 5 mg/L) to 30.8 mg/L. Subgroup analysis of first concentrations revealed therapeutic trough, defined as 10 to 20 mg/L, did not correlate to PDA closure (no closure median concentration = 14.7 [IQR, 13–15.6] vs closure median concentration = 15.4 [IQR, 11.4–18.5], p = 0.42), or duration of treatment. No neonate experienced acetaminophen-associated toxicity.

CONCLUSIONS PDA closure did not correlate to serum acetaminophen trough concentration. The regimen of 15 mg/kg every 6 hours appears safe as no neonate experienced acetaminophen toxicity or discontinued treatment early.

ABBREVIATIONS ALT, alanine transaminase; AST, aspartate transaminase; MGfC, Massachusetts General for Children; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus

KEYWORDS acetaminophen; neonatology; patent ductus arteriosus; pediatric

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Introduction

Patent ductus arteriosus (PDA) is the abnormal persistence of the fetal ductus arteriosus following birth. The fetal ductus arteriosus is a fetal artery which connects the pulmonary artery to the aortic arch, effectively bypassing the lungs since the placenta will supply oxygen to the growing fetus in utero.[1,2] Prolonged ductal opening can cause left to right hemodynamic shunting resulting in lower systemic circulation of oxygenated blood and increased pressure to the pulmonary vascular bed. Failure of the PDA to close can lead to significant morbidity, such as necrotizing enterocolitis, bronchopulmonary dysplasia, and higher incidences of mortality.[1,2] Ductus arteriosus is kept patent by circulating prostaglandins. Non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, non-selectively inhibit cyclooxygenase (COX), and therefore prostaglandins, and are highly successful at aiding ductal closure. However, NSAIDs carry severe adverse drug effects such as gastrointestinal bleeding, renal impairment, and other cardiovascular effects.[1,2]

Acetaminophen, a peroxidase inhibitor which leads to downstream reduction of prostaglandins, has emerged as an alternative treatment modality. Acetaminophen, administered for up to 7 days, has demonstrated to be as equally efficacious as ibuprofen but with less adverse drug effects, such as reduced incidence of gastrointestinal bleeding or necrotizing enterocolitis.[2] Keeping this in mind, acetaminophen has also been associated with non-idiosyncratic, dose-dependent hepatotoxicity when surpassing the recommended daily dose limit per the manufacturer's package insert.[3] Acetaminophen is primarily metabolized through hepatic glucuronidation to a water-soluble metabolite

that is easily excreted by the kidneys. However, conjugation availability may be overwhelmed when there is too much systemic circulation of acetaminophen, and hepatic oxidation will also occur via CYP-2E1 yielding the hepatotoxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). To avoid NAPQI production, the daily dose of acetaminophen for older pediatric patients is recommended to not exceed 75 mg/kg/day.[3] In pediatric patients, cytochrome P-450 enzyme system does not achieve adult levels of activity until nearly the first year of life.[4] Additionally, neonatal CYP2E1 expression has been demonstrated to be less than that of infants 30 to 90 days old, and only increases with age, raising the question of the true risk of NAPQI production in patients who require acetaminophen in the first few weeks of life for PDA closure.[4–6] Finally, glucuronidation of morphine has been observed in the serum of preterm neonates, confirmed by metabolic detection of UGT2B7, one of the enzymes responsible for glucuronidation, further suggesting acetaminophen is a safe treatment modality for PDA closure in this patient population.[4]

Theoretically, target serum acetaminophen concentrations can be used to guide PDA closure especially when paired with echocardiogram confirmation. However, the exact timing and goal of serum acetaminophen concentrations are not well defined and were not standardized in previous investigations.[7] While a 2020 Cochrane Review determined acetaminophen was as effective as cyclooxygenase inhibitors for treatment of PDA, the utility of therapeutic drug monitoring was not included in the scope of the analysis.[2] Retrospective studies of PDA closure and serum acetaminophen concentration monitoring revealed a range of acetaminophen concentrations, varying anywhere from 1.1 mg/L to 29 mg/L, with a median serum acetaminophen concentration of 12.3 mg/L.[8] An investigation involving oral acetaminophen dosed at 15 mg/kg every 6 hours determined 100% closure rates when serum concentrations were > 20 mg/L; however, the sample size was small (10 neonates) and is difficult to extrapolate outcomes to very low birth weight neonates.[9] The conclusions in previous investigations were clouded due to lack of standardization and inconsistent timing of blood drawing relative to dosing for the determination of serum acetaminophen concentrations.[8–10] Additionally, serum acetaminophen concentrations can be used to predict toxicity and potential need for antidote administration. Liver transaminases are used to monitor for hepatocellular injury following acetaminophen treatment, signifying NAPQI production and subsequent cellular injury. Despite this concern, hepatotoxicity remains a rare potential complication not often observed in previous investigations.[8–10]

Since the timing and goal serum acetaminophen concentration for this indication have yet to be determined, the purpose of our study is to retrospectively evaluate if routine therapeutic drug monitoring of serum acetaminophen has any impact on PDA closure or if there is any major risk of hepatotoxicity. By standardizing collection times of acetaminophen levels, we aim to assess the correlation between acetaminophen concentration and PDA closure, as well as identify real-world risk of hepatotoxicity. We expect acetaminophen to be a safe treatment modality for PDA closure treatment and routine therapeutic monitoring to add little clinical advantage to this patient population.

Materials and Methods

Design and Population. This was a retrospective, single center, cohort analysis of neonates admitted to Massachusetts General for Children (MGfC) between April 2016 and August 2022 with at least 1 serum acetaminophen concentration drawn for PDA closure monitoring obtained as a trough before the sixth or seventh dose.

Acetaminophen Therapeutic Drug Monitoring. After several years of non-standardized monitoring practices, our institution implemented a PDA management guideline in March 2019. Dosing of acetaminophen for PDA closure starts at 15 mg/kg every 6 hours for 3 days with extension up to 7 days pending echocardiogram findings. The choice of formulation, enteral or intravenous, depends on the neonate's ability to tolerate at least 60 mL of enteral feeds. First serum acetaminophen trough concentrations are obtained before the sixth or seventh dose for all patients and are repeated on day 5 for neonates prescribed a 7-day regimen. Goal concentration is defined as 10 to 20 mg/L, with institutional direction to reduce dose by 20% or extend interval to every 8 hours if supratherapeutic or increase dose by 20% if subtherapeutic. A follow-up concentration should be checked after any dose adjustments. Any serum acetaminophen concentration > 90 mg/L is defined as toxic and requires intervention. All serum acetaminophen concentrations were performed in our hospital laboratory and an undetectable concentration was defined as < 5 mg/L. All patients prescribed acetaminophen for PDA closure should have liver function tests (LFTs) checked at the end of the regimen.

Endpoints. The primary efficacy outcome is to quantify clinically meaningful PDA closure rate in relation to first serum acetaminophen trough concentration. The primary safety outcome is to determine the incidence of hepatotoxicity defined as LFTs (aspartate transaminase [AST], alanine transaminase [ALT]) at least 3 times the upper limit normal and incidence of acetaminophen toxicity per institutional definition of serum acetaminophen trough concentration > 90 mg/L.

Secondary outcome measures include identifying PDA closure rate when adhering to institutional goal trough concentration between 10 and 20 mg/L and comparing closure rates for neonates based on exposure of acetaminophen regimen in days.

Data Collection. All baseline characteristics, laboratory results, and pharmacologic regimen details were obtained from the patient's medical record. Baseline LFTs were captured if collected the same date as acetaminophen initiation. Clinically significant PDA was defined as detectable on echocardiogram with associated clinical symptoms as documented in the neonatology progress notes.

Statistical Analysis. Descriptive statistics were used to describe population baseline characteristics. Student *t* and Wilcoxon rank sum tests were used for continuous outcome tests. χ^2 and Fisher exact test were used for categorical outcomes. Wilcoxon rank sum test was used to compare PDA closure incidence to acetaminophen level. Fisher exact test was used to compare PDA incidence outcome between 3-day and 7-day acetaminophen regimens. Microsoft Excel was used to obtain descriptive statistics, and JMP Pro 15 was used for statistical analysis.

Table 1. Population Baseline Characteristics

Characteristic*	Population (N = 38)
Gestational age	26w2d [24w4d–28w1d]
PNA at start of APAP regimen (days)	8 [5–12]
Number of female patients	18 (47%)
Duration of APAP regimen (days)	8 [4–8]
Number of APAP doses per patient	25.5 [13–28]
Number of doses per patient prior to first level	7 [6–8]
Patients exposed to NSAIDs prior to APAP	2 (5.3%)
APAP formulation by patient IV PO Both IV and PO	 29/38 (76%) 5/38 (13%) 4/38 (11%)
Dose adjustment made after first serum acetaminophen concentration by patient	4 (11%)
Total daily exposure increased by patient	2 (50%)
Total daily exposure decreased by patient	2 (50%)
First trough acetaminophen concentration (mcg/dL) < 10 10–20 > 20–< 30 30–< 40	 9 22 6 1

APAP, acetaminophen; d, days; IV, intravenous; PNA, post-natal age; w, weeks

* Median [IQR, 25–75]. Number (percent).

Results

Patient Population. Of the 50 patients who were admitted to MGfC NICU and had serum acetaminophen concentrations drawn, 12 patients were excluded, leaving 38 neonates for analysis. Seven patients were excluded as the serum acetaminophen concentration was not obtained for PDA closure and 5 were excluded as the first serum acetaminophen concentration was not drawn as a trough prior to the sixth or seventh dose. Population characteristics are shown in Table 1. At acetaminophen initiation, the median gestational age was 26 weeks 2 days with a median post-natal age of 8 days. The median duration of therapy was 8 days. The median number of doses received was 25.5, accounting for the wide spread of prescribing patterns. Of the 38 patients included, 2 patients were initially treated with ibuprofen. Twenty-nine patients were exclusively prescribed intravenous acetaminophen, while 5 were exclusively prescribed oral and 4 were exposed to both intravenous and oral acetaminophen. Of the total population, 4 patients underwent dose adjustments.

Clinical Outcomes. Of the 38 neonates included in the study, 18 achieved clinically meaningful PDA closure (Table 2). First serum acetaminophen troughs, obtained on median after 7 consecutive doses, ranged from undetectable to 30.8 mg/L (Figure 1). First serum acetaminophen troughs did not correlate to clinically meaningful PDA closure success (Figure 2). Of the 18 (47%) neonates who achieved PDA closure, 16 (89%) did not require adjustment of their acetaminophen dose. For the 2 neonates who achieved PDA closure and required dose adjustments,

Table 2. PDA Closure Outcomes

Characteristic*	Population (N = 38)
PDA closure achieved	18 (47%)
No dose adjustment made	16
Dose adjustment made	2
Dose was reduced	1
Dose was increased	1
Possible liver toxicity per LFTs (≥3 ULN ALT)	1 (2.6%)
Acetaminophen toxicity (> 90 mg/L)	0
Acetaminophen duration in doses per patient	26 [13–28]

ALT, alanine transaminase; LFTs, liver function tests; PDA, patent ductus arteriosus; ULN, upper limit of normal

* Median [IQR, 25–75]. Number (percent).

1 required a dose increase for a subtherapeutic first acetaminophen concentration defined as < 10 mg/L, and the other required an interval extension for a supratherapeutic level. There was no significant difference in serum acetaminophen concentration between neonates whose PDA closed vs those who did not; PDA closure median 14.8 mg/L [10.5–19.1], PDA did not close median 15 mg/L [7.3–21.3], p = 0.81 (Figure 2). Additionally, there was no statistical difference in PDA closure incidence when focusing on the 22 patients with therapeutic serum acetaminophen concentrations between 10 and 20 mg/L (13 patients with PDA closure achieved, 9 patients with PDA closure not achieved, p = 0.71).

There were no incidences of acetaminophen concentration exceeding toxic values > 90 mg/L. One patient out of 17 who had post therapy LFTs collected, had an elevated ALT ≥ 3 times upper limit of normal. The patient's corresponding serum acetaminophen concentration was 19 mg/L and treatment was not discontinued early.

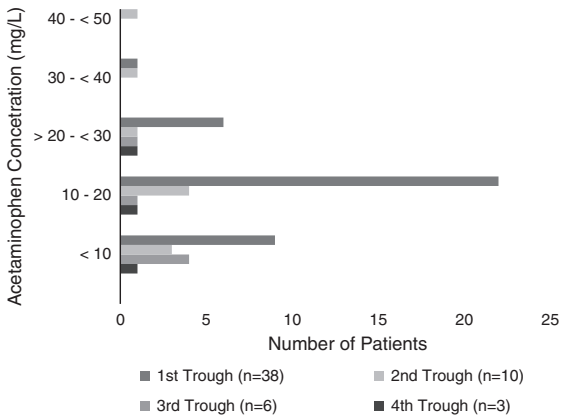
The duration of acetaminophen therapy also did not correlate to PDA closure, though it is worth noting numerically more patients achieved PDA closure when prescribed longer durations of therapy (Figure 3). In patients prescribed 3-day regimens, approximately 22% achieved PDA closure (2 out of 9 patients), whereas 44% (7 out of 16 patients) achieved PDA closure with 7 total days of therapy. Notably, 13 patients were prescribed regimens outside of 3 days or 7 total days (plus or minus 1 day) of acetaminophen therapy. Incidence of PDA closure in this subgroup of 13 patients was 69% (9 out of 13 patients). Figure 3 specifically shows that when comparing the proportion of closures within each regimen received, there is no statistical difference in PDA closure outcomes.

The formulation of acetaminophen was captured for each patient included in this study (Table 1). Unfortunately, subgroup analysis of formulation impact on serum acetaminophen concentration was not performed due to the small sample size of patients who exclusively received enteral acetaminophen (n = 5).

Discussion

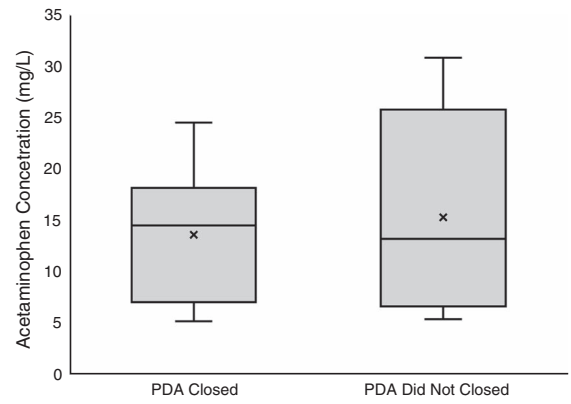
While previous investigations have reported observational findings of varying serum acetaminophen concentrations for PDA closure, our investigation provides an analysis of therapeutic drug monitoring for this indication over a period of 7 years. For the duration of the

Figure 1. Population serum acetaminophen concentrations.



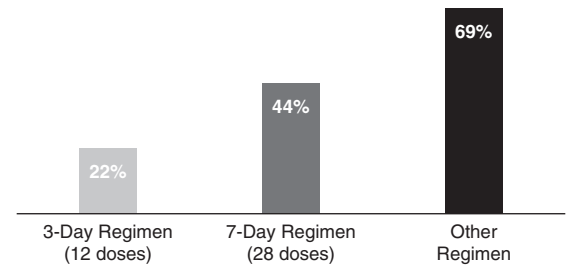
First trough defined as a trough concentration obtained before the sixth or seventh acetaminophen dose for patent ductus arteriosus closure for all patients. Additional trough concentrations were obtained based on provider discretion at any point during the acetaminophen course treatment.

Figure 2. PDA outcome by serum acetaminophen concentration.



Patent ductus arteriosus (PDA) closure median 14.8 mg/L [10.5–19.1]. PDA did not close median 15 mg/L [7.3–21.3], p = 0.81. PDA closure included 18 first serum concentrations and unsuccessful PDA closure included 20 first serum concentrations.

Figure 3. Incidence of PDA closure per acetaminophen regimen.



p > 0.05 for group comparisons for patent ductus arteriosus (PDA) closure in patients prescribed 12 doses (n = 9) or 28 doses (n = 16), +/− 1 dose, total acetaminophen exposure. Other regimen includes any regimen outside of 12 or 28 doses (n = 13). Range includes 9–32 doses administered.

study, we report no instances of acetaminophen toxicity or premature treatment termination for transaminitis. Despite a standardized approach to therapeutic drug monitoring, PDA closure rate did not differ significantly between those who achieved therapeutic acetaminophen levels and those who did not.

Limitations. Given the nature of this single center, retrospective cohort analysis, the results of this study may have been impacted by institutional prescribing bias. The small sample size of this study was maximized by expanding the timeframe of the study from when our current electronic medical record system went live to present, however larger, prospective studies need be performed to confirm our findings. In terms of the duration of regimen findings, we acknowledge there was a wide range of doses prescribed in our retrospective study including oral and IV acetaminophen administration. Institutional practice recommends 3-day treatment with extension up to 7 days if PDA is not closed, which could explain the diversity in regimen observed. However, we reported our findings in both total doses of acetaminophen received and total days to strengthen our analysis. When evaluating the spread of the serum acetaminophen concentrations observed in this investigation, we do not currently have a good explanation as to why some patient's concentrations were undetectable despite receiving acetaminophen doses as documented by the medical record. This finding may add to current literature that despite a homogenous population, demonstrated by the narrow IQR of gestational and post-natal age, there may be some developmental pharmacokinetic variation that we have yet to discover in the premature neonatal population. It is worthwhile to note for the 9 neonates who had subtherapeutic first trough levels, a corresponding dose increase was only performed for 2 patients. We also acknowledge that while all patients included had an appropriately timed first level, not all patients with extension of therapy had repeat levels, despite institutional guidance. Twenty-five neonates had extension of therapy ranging from 6 to 9 days. Of the 25, eleven patients did not have a repeat level and only 4 patients did not have an initial therapeutic level (10–20 mg/L). PDA closure was still observed for 2 of those 4 patients despite no dose adjustments being made. Therefore, while all patients should have had a second level obtained if therapy extended past 5 days, we feel confident that this did not impact the validity of our conclusion as PDA closure was still observed in patients without initial therapeutic levels. Finally, baseline LFTs were not required per institutional guidance, and therefore paired comparisons of transaminases pre-, during, or post-acetaminophen therapy could not be conducted. Although only 17 patients had post therapy LFTs drawn, only 1 neonate experienced elevated transaminases but did not display signs or symptoms of acute liver injury nor a toxic acetaminophen concentration at steady state. We are reassured that no acetaminophen concentration was considered toxic per institutional guidance.

Conclusion

Given there was no difference in proportion of patients who achieved PDA closure with a therapeutic serum acetaminophen trough concentration, we recommend against routine acetaminophen therapeutic drug monitoring for PDA closure. No infant experienced acetaminophen toxicity defined as > 90 mg/L or clinically significant transaminitis. Our results confirm that even with a standardized approach, there seems to be little utility in obtaining additional lab draws in a patient population where we should minimize blood samples as much as possible.

Article Information

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Ethics Approval and Informed Consent. This retrospective data analysis did not require institutional review board review and informed consent was not required.

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References

1. Gillam-Krakauer M, Reese J. Diagnosis and management of patent ductus arteriosus. *Neoreviews*. 2018;19(7):e394–e402.
2. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. *Cochrane Database Sys Rev*. 2020;1:CD010061.
3. Acetaminophen [package insert]. Bethlehem, PA: B. Braun Medical Incorporated; Revised February 2021.
4. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology–drug disposition, action,

and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167.
5. Johnsrud EK, Koukouritaki SB, Divakaran K, et al. Human hepatic CYP2E1 expression during development *J Pharmacol Exp Ther*. 2003;307(1):402–407.
6. Vieira I, Sonnier M, Cresteil T. Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem.* 1996;238(2):476–483.
7. Singh Y, Gooding N. Paracetamol for the treatment of patent ductus arteriosus in very low birth weight infants. *J Neonatal Biol*. 2016;7(5):100–116.
8. McPherson C, Luecke CM, Liviskie CJ, et al. Acetaminophen serum concentrations in infants treated intravenously for patent ductus arteriosus. *J Pediatr Pharmacol Ther*. 2019;24(2):134–137.
9. Bin-Nun A, Fink D, Mimouni FB, et al. Paracetamol serum concentrations in neonates treated enterally for ductal closure: a pilot study. *J Pediatr*. 2018;198:304–307.
10. Yurttutan S, Oncel MY, Arayıcı S, et al. A different first-choice drug in the medical management of patent ductus arteriosus: oral paracetamol. *J Matern Fetal Neonatal Med*. 2013;26(8):825–827.