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Update on the Use of Acetaminophen for Patent Ductus Arteriosus Closure

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The first report of the use of acetaminophen to close a patent ductus arteriosus (PDA) appeared in print in 2011.[1] Since that time, more than a dozen case series and clinical trials have been published.[2] Both oral and intravenous administration have been shown to be effective in closing hemodynamically significant PDAs in preterm neonates in placebo-controlled trials. In comparison studies, acetaminophen has produced rates of PDA closure similar to those of indomethacin and ibuprofen (50-80%), without having their adverse effects. Acetaminophen has not yet been approved for PDA closure by the Food and Drug Administration (FDA), but it continues to be widely studied. There are nine active trials of acetaminophen for PDA closure listed on www.ClinicalTrials.gov, including both placebo-controlled and comparison studies.

Mechanism of Action

Constriction of the ductus arteriosus after birth is prompted by a reduction in prostaglandin synthesis. The non-steroidal anti-inflammatory agents (NSAIDs) indomethacin and ibuprofen close a PDA by blocking the cyclooxygenase segment of prostaglandin synthetase, preventing it from catalyzing the beginning of the synthesis of prostaglandins from arachidonic acid. Acetaminophen is thought to produce ductal closure by blocking the peroxidase segment of prostaglandin synthetase, resulting in similar inhibition of prostaglandin production.[1,3]

It has been suggested that inhibition of peroxidase is more effective than inhibition of cyclooxygenase in the setting of hypoxia, which could make acetaminophen a more effective option than NSAIDs in more critically ill neonates with hemodynamically significant PDAs. By acting at a different site, acetaminophen does not produce the peripheral vasoconstriction that results in gastrointestinal bleeding or perforations and the reduced renal blood flow observed after NSAID use. In addition, acetaminophen has no effect on platelet aggregation and is not associated with hyperbilirubinemia.[1,3,4]

Pharmacokinetics

The pharmacokinetic profiles of acetaminophen in term infants > 32 weeks gestational age (GA), children, and adolescents are similar to that in adults.[3] Acetaminophen is rapidly absorbed after oral administration, with a C_{max} of 2 $\pm$ 1.5 mcg/mL in infants, a distribution of 1.2 $\pm$ 0.3 L/kg, an area under the concentration curve (AUC) of 38 $\pm$ 8 mcg·h/mL, and an elimination half-life of 3.0 $\pm$ 1.5 hours. Acetaminophen is metabolized through multiple pathways, including glucuronide and sulfate conjugation and oxidation via cytochrome P450 2E1 (CYP2E1) to form the toxic intermediate metabolite, N-acetyl-p-benzoquinone imine (NAPQI). This intermediate product undergoes further conjugation to form inactive metabolites which are then cleared in the urine.

Clinical Experience

The evidence supporting acetaminophen use in PDA closure includes case series, retrospective and prospective observational studies, as well as placebo-controlled and active-comparator trials.[1,5-20] Both oral and IV acetaminophen regimens have been compared to ibuprofen and indomethacin.

Retrospective and Observational Studies

The initial publication by Hammerman and colleagues at the Sahaare Zedek Medical Center in Israel described five cases of successful PDA closure with acetaminophen.[1] The infants ranged from 26 to 32 weeks GA and were treated on day of life 3 to 35. All patients had failed or had a contraindication to treatment with ibuprofen. The protocol was approved through the institutional review board and included parental consent. Acetaminophen was given enterally using a dose of 15 mg/kg every 6 hours until ductal closure was established by ultrasound at 48-72 hours.

In their 2012 letter to the editor of the *Archives of Diseases in Childhood*, Oncel and colleagues at the Zekai Tahir Burak Hospital in Turkey described their use of oral acetaminophen in eight preterm infants (median GA 28.5 weeks).[5] Five had failed treatment with ibuprofen; two patients had contraindications to ibuprofen use, with the remaining patient receiving acetaminophen after having developed an adverse effect from ibuprofen. Acetaminophen was given orally at a dose of 15 mg/kg every 6 hours for a median duration of 5 days, producing ductal closure in seven patients (87.5%). Based on their initial success, the authors began an open-label prospective study of IV acetaminophen 15 mg/kg every 6 hours for 3 days.[6] Ten preterm neonates were enrolled, with a median GA of 27 weeks (range 24-29 weeks) and a median age at the start of therapy of 6 days (2-15 days). All patients had successful PDA closure, with seven (70%) requiring only a single 3-day course.

Tekgündüz and colleagues performed a retrospective assessment of 13 preterm neonates given IV acetaminophen for PDA closure due to either a contraindication to or an adverse reaction to ibuprofen.[7] After finding elevations of both alanine transaminase (ALT) and aspartate aminotransferase (AST) in the first patient after just four doses, the authors lowered their treatment dose from 15 mg/kg every 6 hours to 10 mg/kg every 8 hours for the remaining patients. Ten patients (76.9%) patients had PDA closure demonstrated on echocardiography (ECHO). The median time to closure was 2 days (range 1-4 days). Excluding the patient in whom therapy was discontinued for increased ALT and AST levels, the success rate was 83.3%.

In their 2015 study, El-Khuffash and colleagues at the Rotunda Hospital in Dublin evaluated the efficacy of IV acetaminophen as late treatment in 36 infants (median GA 26.1 weeks).[8] The median age at initiation of therapy was 27 days (IQR 16-39 days). The treatment regimen was the same as earlier studies, 15 mg/kg every 6 hours. The median length of therapy of 5 days (IQR 3-6 days) was slightly longer compared to other studies. Treatment resulted in PDA closure or significant constriction in 23 patients (64%). This was a significant contrast from the results of study by Roofthooft et al of late treatment in 33 infants 2 weeks of age and older. These authors reported a success rate of only 18%.[9]

Valerio and colleagues at the University of Padua have described the largest number of patients treated with IV acetaminophen in their prospective observational study published in 2016.[10] The authors treated 48 preterm neonates with hemodynamically significant PDAs. Seventy-seven percent of the patients had PDA closure, with the remaining patients requiring surgical ligation. Rates of closure were highest in neonates born at 28 weeks gestational age or later. There was no significant difference in closure rates between those with contraindications to NSAID use (initial therapy) and those with NSAID adverse effects (rescue therapy), with rates of 63.3% versus 77.8%, respectively.

Earlier this year, Pharande and colleagues evaluated the factors associated with PDA closure after oral acetaminophen in 20 infants (mean GA 25.7 $\pm$ 1.5 weeks).[11] Complete closure was reported in 10 of the patients (50%), with another four having significant reduction in hemodynamic shunting. Univariate analysis revealed significant associations between PDA closure and echocardiographic scores (a higher score, an indicator of shunting was associated with lower rates of closure), as well as concomitant furosemide use and sepsis, both of which were associated with lower closure rates. In a letter to the editor published in *Pediatric Cardiology* in response to the Pharande study, Sallmon and Koehne described their experience with oral acetaminophen following failure with NSAIDs in 19 neonates.[12] These authors reported full or partial closure in 58% of infants.

Comparison Studies

In 2014, an international group of investigators evaluated the effectiveness of variable acetaminophen regimens on PDA closure.[15] Twenty-one neonates received one of three regimens: 2 days of oral acetaminophen, 7 days of oral acetaminophen, or 2-6 days of IV acetaminophen. All patients received a dose of 15 mg/kg every 6 hours. None of the neonates in the short-course oral group had PDA closure, however six of seven neonates (86%) in the long-course oral group had ductal closure, and eight of nine neonates (89%) in the IV group. The authors concluded that the efficacy of acetaminophen may depend on the duration of therapy.

A placebo-controlled acetaminophen trial for PDA closure was published by Härkin and colleagues in the *Journal of Pediatrics* in 2016.[16] Forty-eight neonates were randomized to receive either acetaminophen (a 20 mg/kg loading dose given IV followed by 7.5 mg/kg every 6 hours) or placebo every 6 hours for 4 days, beginning within 24 hours of birth. Patients were evaluated with daily ultrasounds; pre-treatment ductal calibers were similar between groups. During the treatment period, ductal closure occurred earlier in the acetaminophen group (HR 0.49, 95% CI 0.25-0.97, $p = 0.16$). Postnatal age at ductal closure was 177 hours (95% CI 31.1, 324) in the acetaminophen group versus 338 hours (118, 557) in the controls ($p = 0.045$). The authors concluded that prophylactic use of acetaminophen resulted in PDA closure without adverse effects.

Four studies have compared oral acetaminophen and ibuprofen and found similar rates of PDA closure, including recent publications from 2016. Bagheri and colleagues randomized 120 infants to receive either acetaminophen (15 mg/kg every 6 hours for 3 days) or ibuprofen (20 mg/kg, followed by 10 mg/kg at 24 and 48 hours).[17] Echocardiography studies were performed prior to and at the completion of treatment. After the first treatment course, PDA closure was demonstrated in 55 (82.1%) of the patients given acetaminophen and 47 (75.8%) of the patients given ibuprofen ($p = 0.38$). A second treatment course resulted in closure in 6 of the 12 (50%) remaining acetaminophen patients and 11 of the 17 (73.3%) remaining ibuprofen patients ($p = 0.21$), for overall closure rates of 91% with acetaminophen and 90.3% for ibuprofen.

Yang and coworkers randomized 87 neonates to either acetaminophen (15 mg/kg every 6 hours) or ibuprofen (10 mg/kg followed by 5 mg/kg at 24 and 48 hours) for 3 days.[18] Rates of ductal closure were similar between groups, 70.5% in the acetaminophen group and 76.6% in the ibuprofen group ($p = 0.506$). Oliguria was reported in fewer patients in the acetaminophen group (2.3% versus 14% of patients in the ibuprofen group), but the difference was not statistically significant.

Dash and colleagues compared enteral acetaminophen and IV indomethacin in 77 preterm neonates with hemodynamically significant PDA. Patients were randomized to either acetaminophen (15 mg/kg every 6 hours for 7 days) or ibuprofen (0.2 mg/kg once daily for 3 days). PDA closure rates were 100% in the acetaminophen group and 94.6% in the indomethacin group ($p = 0.13$). Adverse reactions were similar between the groups. The authors concluded that acetaminophen was as effective as IV indomethacin, but not superior.

Another recent study compared IV acetaminophen, ibuprofen, and indomethacin. This study, conducted at Egypt's Tanta University Hospital, enrolled 300 preterm neonates with a hemodynamically significant PDA. Patients were randomized to acetaminophen 15 mg/kg every 6 hours for 3 days, ibuprofen 10 mg/kg followed by 5 mg/kg daily for 2 days, or indomethacin 0.2 mg/kg every 12 hours for 3 doses. Echocardiographic studies were done prior to and 3 days after treatment. There were no significant differences in PDA closure rates between all the treatments ($p = 0.868$). There was a significant increase in serum creatinine and blood urea nitrogen (BUN) levels compared to baseline in the ibuprofen and indomethacin groups (both $p < 0.001$), as well as significant reductions in platelet count and urine output (both $p < 0.001$). The ibuprofen group also had a significant increase in bilirubin levels ($p = 0.003$). There were no differences in hemoglobin or hepatic enzymes. These results, as well as those of the earlier studies, suggest that acetaminophen is as effective as NSAIDs for PDA closure, with a lower incidence of clinically significant adverse reactions.

Contraindications and Warnings

Acetaminophen is contraindicated in patients with a known hypersensitivity to the active drug or drug product excipients and in patients with severe liver disease. All products carry a black box warning for acute liver failure and call attention to the need to ensure that the total daily dose remains below the recommended maximum. The prescribing information for IV acetaminophen also contains a black box warning for the risk of medication errors. The warning highlights the risk for dosing and administration, particularly when using weight-based dosing in patients under 50 kg. An additional warning describes the risk of rare, but serious, skin infections, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis.[3]

Adverse Reactions

The studies of acetaminophen in PDA closure published to date have not identified any significant adverse reactions. In pediatric trials of acetaminophen for analgesia, the most common adverse reactions were nausea, vomiting, constipation, and pruritus, occurring in similar rates in the placebo group.[3]

Hepatotoxicity is a known risk of high-dose acetaminophen exposure or use in patients with severe underlying hepatic or renal impairment. An early retrospective study of the use of IV acetaminophen for analgesia in 189 neonates found no adverse effects on hepatic transaminases.[21] Several studies of acetaminophen for PDA closure have also found no effect on hepatic transaminases. Others, however, have reported patients with clinically significant elevations. In addition to the patient described in the Tekgündüz study,[7] Weiz and colleagues identified one out of their 26 patients with elevated ALT and AST values at the conclusion of treatment, but the elevation also coincided with the development of sepsis.[11] Luecke et al found a statistically significant difference in the median ALT after treatment in their study of 41 neonates (6 versus 8 units/L, $p = 0.019$), but no difference in AST or alkaline phosphatase.[12]

Drug Interactions

Medications that induce or inhibit CYP2E1 may alter the metabolism of acetaminophen. Chronic oral acetaminophen use may increase INR values in patients taking warfarin.[3]

Availability and Cost

Oral acetaminophen is available in a 32 mg/mL suspension for infants, in cherry and grape flavors, as well as a dye-free cherry-flavored preparation. Intravenous acetaminophen is available as a 10 mg/mL solution in a 100 mL single-dose vial or IV bag.[3] Both oral and IV dosage formulations may be stored at room temperature. Oral suspensions of acetaminophen and ibuprofen typically have a retail cost of approximately $2 to $5 per 120 mL bottle. Acetaminophen injection has an average wholesale price (AWP) of $48 per vial. In comparison, the AWPs for indomethacin and ibuprofen lysine injection are $552 to $634 and $487 to $547 per vial, respectively.

Dosing Recommendations

Most case series and clinical trials published to date have used an acetaminophen dose of 15 mg/kg given every 6 hours. Alternative regimens have included a 20 mg/kg IV loading dose followed by 7.5 mg/kg every 6 hours. The length of treatment is typically guided by echocardiographic studies to ensure ductal closure. Treatment duration has varied among the published studies, with a range from 1 to 7 days in most. It is recommended that enteral acetaminophen be given only when the patient is able to tolerate enteral feeds. Intravenous acetaminophen should be administered on a syringe pump over 15 minutes.

Summary

The efficacy of acetaminophen for PDA closure in preterm infants has been established in multiple case series and clinical trials. Rates of PDA closure after acetaminophen use are similar to that produced by indomethacin and ibuprofen, but acetaminophen offers the advantage of fewer serious adverse effects. In patients requiring parenteral treatment, acetaminophen is also significantly less expensive.

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