Ductal Closure With Paracetamol: A Surprising New Approach to Patent Ductus Arteriosus Treatment

abstract

Standard pharmacologic closure of the patent ductus arteriosus currently involves the administration of 1 of 2 cyclooxygenase inhibitors: either indomethacin or ibuprofen. However, both of these drugs can be associated with potentially significant adverse effects. We present here the cases of 5 preterm infants (gestational age: 26–32 weeks; postnatal age: 3–35 days) with large, hemodynamically significant patent ductus arteriosus who had either failed or had contraindications to ibuprofen therapy. Each of these infants was treated with off-label oral paracetamol (15 mg/kg per dose every 6 hours). Ductal closure was achieved within 48 hours in all the treated infants. No toxicity was observed. *Pediatrics* 2011;128:e1618–e1621

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KEY WORDS

patent ductus arteriosus, paracetamol, ibuprofen

ABBREVIATIONS

PDA—patent ductus arteriosus
hs—hemodynamically significant
GA—gestational age
DOL—day-of-life

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Although patency of the ductus arteriosus is essential for fetal circulation, postnatal ductal closure is critical for postnatal circulatory adaptation. Persistent patent ductus arteriosus (PDA) renders the newborn vulnerable to pulmonary overcirculation with diminished systemic blood flow. Therapeutic intervention to facilitate ductal closure might be indicated.

Standard medical therapy for PDA closure has predominantly involved either indomethacin or ibuprofen, nonselective cyclooxygenase inhibitors. Both of them are successful in effecting ductal closure in ~70% of cases. However, they can cause peripheral vasoconstriction, gastrointestinal perforations, weakened platelet aggregation, and hyperbilirubinemia (ibuprofen).[1,2] An alternative treatment with fewer potential adverse effects would be welcome. We report here several cases that point toward such a potential therapeutic alternative.

CASE REPORTS

Initially, paracetamol, one of the most widely used over-the-counter medications worldwide, was given (for unrelated reason) to a 26-week-gestational-age (GA) 1-kg male infant at 2.5 weeks of age (Infant A). Two days later the staff noticed that a long-standing, persistent, hemodynamically significant PDA (hsPDA), previously resistant to 2 courses of ibuprofen, had suddenly closed. After this incidental observation, we administered off-label oral paracetamol to a small number of preterm neonates with hsPDA for whom treatment with ibuprofen was felt to be clinically contraindicated.[3] On advice of the institutional review board, parents in each case were informed that this was off-label use of a well-known medication, and parental consent was obtained. All of the infants were treated with enteral paracetamol (Acamoli [Teva Pharmaceuticals, Petah Tikva, Israel]), a paracetamol solution that contains no alcohol, at 15 mg/kg per dose every 6 hours. The index case-infant was treated for 7 days for other indications. In the ensuing cases, however, we attempted to obtain a follow-up echocardiogram within 48 to 72 hours, and if the PDA had closed, we stopped treatment at that point. Enteral nutrition was continued during treatment, and none of the infants showed evidence of increased feeding intolerance.

Infant B was a 29⅘-week-GA, 935-g, severely growth-restricted male infant who developed early Gram-negative sepsis and necrotizing enterocolitis that resulted in intestinal perforation and an hsPDA. Because of severe thrombocytopenia he was not considered a candidate for ibuprofen; thus, paracetamol was given to him off-label. A follow-up echocardiogram 2 days later revealed a closed ductus.

Infant C was a 26⅗-week-GA, 720-g female infant who was ventilated for respiratory distress syndrome. On day-of-life (DOL) 6 a large hsPDA was diagnosed and unsuccessfully treated with 2 courses of ibuprofen (on DOL 6 and 10). After the second course, a trial of off-label paracetamol was attempted. Repeat echocardiogram 1 day later revealed a closed ductus. However, on DOL 20, during a bout of methicillin-resistant *Staphylococcus aureus* sepsis, she developed a recurrent PDA; because of thrombocytopenia and previous therapeutic failures, she was not considered a candidate for ibuprofen. She was again treated with paracetamol, and a repeat echocardiogram after 3 days revealed a small, insignificant ductus that closed completely within 1 week.

Infant D was a 27⅖-week-GA, 1210-g female infant. On DOL 3 a large hsPDA was diagnosed. Because of hyperbilirubinemia, a trial of paracetamol was attempted instead of treatment with ibuprofen. After 24 hours, a repeat echocardiogram revealed a small, insignificant ductus that closed completely within 1 week.

Infant E was a 26⅐-week-GA, 868-g male infant. He was ventilated for respiratory distress syndrome and on antibiotics and inotropic support for staphylococcal coagulase-negative sepsis but nevertheless remained thrombocytopenic with a large hsPDA. On DOL 10 we decided to try off-label paracetamol. A repeat echocardiogram 2 days later revealed a small, hemodynamically insignificant ductus that subsequently closed completely.

Echocardiographic criteria are presented in Table 1. All of these PDAs would be considered moderate to severe before treatment, and there was no evidence on serial pretreatment echocardiograms that the ductus was beginning to constrict either spontaneously or in response to previous treatment attempts. In all infants, within 48 hours of beginning paracetamol, either complete ductal closure was attained or significant ductal constriction was achieved and followed by complete ductal closure within 1 week's time.

At this point, we realized that these clinical observations must be validated in a prospective, randomized study. As such, we have stopped the off-label use of paracetamol for PDA pending a full prospective trial.

DISCUSSION

Traditional nonsteroidal anti-inflammatory drugs promote ductal constriction by inhibiting prostaglandin synthesis. Prostaglandin synthetase has 2 components, a cyclooxygenase and a peroxidase, that operate at distinct, active sites on the same protein with different catalytic activities. Cyclooxygenase catalyzes the beginning of prostanoid synthesis from arachidonic acid. At the active cyclooxygenase site, arachi-

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TABLE 1 PDA Characteristics Before Initiation of Treatment

	Age Paracetamol Begun, d	Internal Ductal Diameter, mm	Left Atrial–to–Aortic Root Ratio	Pressure Gradient Across PDA, mm Hg	Reverse Diastolic Flow	Ductus Diameter–to–Aorta Ratio	Previous Ibuprofen Treatment and Response	Current Contraindications to Ibuprofen
Infant A	17	2.0	1.69	15	No	0.50	2 courses of ibuprofen with no response	None
Infant B	10	2.8	2.07	10	Yes	0.97	None	Severe thrombocytopenia
Infant C	35	2.0	1.57	15	Yes	0.56	2 courses of ibuprofen with no response	Severe thrombocytopenia
Infant D	3	3.0	1.57	12	Yes	1.00	None	Hyperbilirubinemia
Infant E	10	2.0	1.48	20	Yes	0.51	None	Thrombocytopenia

donic acid undergoes oxygenation and forms PGG_2, which is then acted on by the peroxidase component of the enzyme, forming PGH_2. Indomethacin and ibuprofen compete with the arachidonic acid substrate for the active cyclooxygenase site. Thus, the potency of these drugs is influenced by endogenous arachidonic acid levels.

Paracetamol also inhibits prostaglandin synthetase activity.[4] Although its precise mechanism of action remains controversial, paracetamol seems to act at the peroxidase segment of the enzyme.[5] Peroxidase is activated at 10-fold-lower peroxide concentrations than is cyclooxygenase.[5,6] Therefore, paracetamol-mediated inhibition is facilitated at reduced local peroxide concentrations (eg, hypoxia). Theoretically, these differences would permit peroxidase inhibition to be optimally effective under conditions in which cyclooxygenase inhibition is less active[6] or, hypothetically, render it ideally suited for treatment in the PDA environment. There have been reports of paracetamol promoting ductal constriction, albeit mostly in pregnant animal models,[7,8] and there has been 1 case report of human in utero ductal closure after maternal self-medication with a combination of nimesulide and acetaminophen.[9]

Extensive clinical experience with the use of paracetamol in neonates has been accumulated over recent years, because it has been increasingly used for pain relief.[10,11] Our dosing was comparable to that recommended for intravenous administration for pain control in preterm neonates.[12] Paracetamol seems to be quite free of the adverse effects generally associated with traditional nonsteroidal anti-inflammatory drugs in preterm neonates, including peripheral vasoconstriction, gastrointestinal perforations, oliguria, impaired platelet aggregation, and/or hyperbilirubinemia.

Although hepatotoxicity in 1 term neonate has been reported, it occurred after 3 days of excessive paracetamol intake at close to 10 times the therapeutic dose.[13] Acute, single overdose in another preterm neonate proved to be relatively harmless and resulted in no hepatotoxicity.[14] Overall, it has been shown[12] that neonates tend to suffer less from the hepatotoxic effects of paracetamol than do older children.

One of our infants was not treated with ibuprofen because of hyperbilirubinemia. Although hyperbilirubinemia is not an absolute contraindication to ibuprofen treatment, the results of 2 recent studies[1,2] indicated that ibuprofen does seem to be associated with higher total bilirubin levels in premature neonates. The authors of these studies speculated that the increase in total bilirubin concentration could be caused by inhibition of hepatic glucuronidation of bilirubin by ibuprofen and unrelated to the effect on bilirubin albumin binding. Given these data, together with recent reports of low-bilirubin kernicterus in premature neonates,[15] we have elected to be cautious about giving ibuprofen to small premature neonates with hyperbilirubinemia.

CONCLUSIONS

We have presented preliminary data that support paracetamol's efficacy in closing PDAs over a wide range of postnatal ages. Although we cannot definitively prove causality, the fact that our infants had suffered from hsPDA for up to 35 days and that all of the PDAs closed/constricted within 3 days of having received paracetamol are highly suggestive. Nevertheless, we caution that these are merely preliminary observations that must be tested and validated in prospective, randomized studies. If confirmed, paracetamol could offer several important therapeutic advantages over existing therapies: (1) it has no peripheral vasoconstrictive effect; (2) it can be given to infants with clinical contraindications for nonsteroidal anti-inflammatory drugs; and (3) it seems to be effective after some ibuprofen treatment failures when the only other therapeutic option is surgery.

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