HHS Public Access

Author manuscript

Drugs. Author manuscript; available in PMC 2015 May 15.

Published in final edited form as:

Drugs. 2012 May 7; 72(7): 907–916. doi:10.2165/11632870-000000000-00000.

Patent Ductus Arteriosus in Premature Neonates

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Abstract

Persistent patency of the *ductus arteriosus* is a major cause of morbidity and mortality in premature infants. In infants born prior to 28 weeks of gestation, a hemodynamically-significant patent *ductus arteriosus* (PDA) can cause cardiovascular instability, exacerbate respiratory distress syndrome, prolong the need for assisted ventilation, and increase the risk of bronchopulmonary dysplasia, intraventricular hemorrhage, renal dysfunction, intraventricular hemorrhage, cerebral palsy, and mortality. In this article, we review the pathophysiology, clinical features, and assessment of hemodynamic significance, and provide a rigorous appraisal of the quality of evidence to support current medical and surgical management of PDA of prematurity. Cyclo-oxygenase inhibitors such as indomethacin and ibuprofen remain the mainstay of medical therapy for PDA, and can be used both for prophylaxis as well as rescue therapy to achieve PDA closure. Surgical ligation is also effective and is used in infants who do not respond to medical management. Although both medical and surgical treatment have proven efficacy in closing the *ductus*, both modalities are associated with significant adverse effects. Because the *ductus* does undergo spontaneous closure in some premature infants, improved and early identification of infants most likely to develop a symptomatic PDA could help in directing treatment to the at-risk infants and allow others to receive expectant management.

Keywords

ductus; cyclo-oxygenase; congestive cardiac failure; indomethacin; ibuprofen

Introduction

In the developing fetus, the pulmonary artery and the aortic arch are connected via the *ductus arteriosus*, a vascular shunt that diverts the right ventricular output away from the fetus's fluid-filled lungs and into the systemic circulation [1]. Whereas this ductal shunt

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closes spontaneously within a few hours of birth in full-term infants, this process is frequently delayed/ interrupted in premature infants and is associated with increased risk of clinical complications [2-5]. In this article, we review the clinical features and management of persistent patent *ductus arteriosus* (PDA) in premature infants.

Epidemiology

The incidence of persistent PDA correlates inversely with birth weight and gestational age, seen in about 30% of infants born with a birth weight less than 1500 grams, 40% of infants weighing 751-1000 grams, and more than 50% of those weighing 501-750 grams [4, 6-8]. Although spontaneous ductal closure occurs eventually in nearly a third of extremely premature neonates, more than 60% of all preterm infants born prior to 28 weeks' gestation receive medical or surgical treatment to prevent complications associated with persistent PDA such as exacerbation of respiratory distress syndrome (RDS) [9-12], pulmonary hemorrhage [13, 14], prolonged use of assisted ventilation [15], bronchopulmonary dysplasia (BPD) [10, 12, 16-20], intraventricular hemorrhage (IVH)[10, 12, 21, 22], renal dysfunction [23], necrotizing enterocolitis (NEC) [10, 12, 24, 25], periventricular leukomalacia (PVL) [26], cerebral palsy [27], and mortality [18, 22, 24, 28-30].

Pathophysiology of PDA

The *ductus arteriosus* undergoes functional closure within a few hours after birth due to constriction of the medial smooth muscle layer. A more definitive anatomical closure occurs over the next several days with intimal remodeling and loss of smooth muscle cells from the media [31-33]. With the cessation of the ductal shunt between the systemic and pulmonary circulation, the right ventricular output is now no longer diverted to the aorta and flows directly into the pulmonary circulation. The consequent increase in venous return from the lungs raises the left atrial pressures, closing the other right to left shunt of fetal life across the *foramen ovale* in the inter-atrial septum. With the closure of these two right to left shunts, the pulmonary and systemic circuits carry equal volumes of blood flow in 'series' instead of the 'parallel' configuration of fetal life. Although the physiological mechanisms involved in ductal closure are still being elucidated, postnatal changes in the systemic and pulmonary vascular resistance, sudden increase in tissue oxygenation after birth, decreased levels of prostaglandins, and increased expression of endothelin and its cognate receptors are known to play an important role [31].

In premature infants, the normal process of ductal closure is often delayed or interrupted. Very low birth weight (< 1500 grams), acute perinatal stress, moderate-severe RDS with a need for assisted ventilation within 24 hours of birth, neonatal sepsis, and higher total fluid administration during the initial few days after birth are some of the factors associated with persistent PDA [16, 34, 35]. As the pulmonary vascular resistance falls after birth, blood is increasingly shunted away from the aorta into the pulmonary artery, resulting in pulmonary overcirculation with frequent exacerbation of lung disease and increased risk of pulmonary hemorrhage and BPD[9-20, 31]. Left-to-right ductal shunting can also 'steal' blood from the systemic circulation and reduce end-organ perfusion [36], placing the preterm infant at

increased risk of complications such as renal dysfunction [23], NEC [10, 12, 24, 25], IVH and PVL [26].

Clinical Manifestations and Diagnosis of PDA

PDA can be ‘ asymptomatic’ (where no heart murmur is detected),‘symptomatic ’ (associated with a murmur),‘hemodynamically non-significant’ (no cardiovascular dysfunction), or ‘hemodynamically-significant’ (with cardiovascular dysfunction) [37]. Most infants with PDA have a characteristic systolic or systolo-diastolic murmur at the upper left sternal border [37]. A hemodynamically-significant PDA is frequently marked by additional clinical signs such as an active precordium, bounding pulses, wide pulse pressure [28], and radiological signs such as cardiomegaly, prominent pulmonary vascular markings, dilatation of the left atrium, and a horizontalized left main bronchus [6, 37]. As the shunt size increases, the electrocardiogram may also show signs of left ventricular hypertrophy and left atrial enlargement [6]. To assess the hemodynamic impact of the PDA, a clinical cardiovascular distress (CVD) scoring system can be useful (Table 1) [38]. The CVD score evaluates five variables (heart rate, peripheral arterial pulses, precordial pulsations, duration of murmur, and cardiothoracic ratio on chest X-ray); a score > 3 is strongly associated with a hemodynamically-significant PDA.

Echocardiography is the mainstay of diagnosis and assessment of PDA. It allows direct visual assessment of the ductus originating from the descending aorta distal to the left subclavian artery and connecting to the main pulmonary artery [34]. The ratio of the smallest ductal diameter to the ostium of the left PA (PDA:LPA ratio) is a useful indicator of the ductal size, where ratios of ≥1, 0.5-1, and <0.5 indicate a large, medium, and small PDA, respectively [39]. Doppler flow studies can confirm ductal patency and help assess the direction of ductal flow, cardiac anatomy, ventricular function, the ratio of estimated pulmonary to systemic blood flow [40], and pulmonary artery pressures [6]. Echocardiography can also be useful in predicting the clinical course; the ductal size on day 3-4 (PDA:LPA ratio) is a useful predictor of a hemodynamically-significant PDA, antedating the onset of clinical signs by up to 2-3 days [41].

Although no laboratory tests can reliably indicate the presence of a PDA, circulating levels of B-type natriuretic peptide (BNP), a hormone secreted by the ventricles under hemodynamic stress and congestive heart failure, can be both sensitive and specific for detecting a hemodynamically-significant PDA and for monitoring response to therapy [42, 43]. Plasma concentrations of BNP between 70 and 100 pg/mL have been used to determine a symptomatic PDA [34]. In a prospective blinded study, Sanjeev *et al.* showed that a cut-off of 72 pg/mL was useful as a screening tool for a hemodynamically-significant PDA [42]. BNP levels were higher in infants with a hemodynamically-significant PDA (n=14) compared to those without (n=15; 508.5 ± 618.2 *vs*. 59.5 ± 69.9pg/mL, $p<0.005$), and concentrations decreased after successful medical/surgical treatment of PDA (n=12; 404.9 ± 159.2 to 25.1 ± 4.1 pg/mL, $p<0.03$) [42]. Further study is needed in larger cohorts to determine whether BNP levels in early neonatal period can help differentiate between candidates for expectant *vs*. aggressive management [34].

Management of Neonatal PDA

Medical Treatment of PDA

Medical management of PDA in a premature infant is comprised of fluid restriction, cyclo-oxygenase (COX) inhibitors such as indomethacin and ibuprofen lysine, and, occasionally, cautious use of diuretics in symptomatic infants [44, 45]. COX inhibitors promote the constriction and eventual closure of the ductus [46] by inhibiting the synthesis and release of prostaglandins, which play a major role in maintaining ductal patency during fetal life [31]. While indomethacin has been the traditional 'drug of choice' for treatment of PDA, US Food and Drug Administration approved the use of ibuprofen lysine in April 2006 for closure of clinically-significant PDA in premature infants <32 weeks and weighing between 500-1500 grams. There has been considerable variability in the dosing regimens for the two drugs; Table 2 summarizes dosing regimens for indomethacin and ibuprofen lysine used for prophylactic and rescue therapy.

Surgical Treatment of PDA

Surgical ligation of a symptomatic PDA in preterm neonates is successful in closing the ductal shunt in 98-100% cases [47, 48]. The procedure is generally well-tolerated and is considered by some as a preferred first line of treatment in preterm infants who are less likely to respond to indomethacin, such as those weighing less than 800 grams with a large left atrial-aortic root ratio on echocardiography [47-52]. Surgical ligation of a hemodynamically-significant PDA can improve hemodynamics, lung compliance, and reduce the duration of mechanical ventilation [53, 54]. Offered as a prophylactic therapy, surgical ligation was effective in preventing NEC [relative risk (RR) 0.25, 95% confidence interval (CI) 0.08-0.83; p= 0.02, number needed to treat (NNT) 5] but did not reduce mortality, severe IVH, BPD, or retinopathy of prematurity (ROP)[55]. Complications of PDA ligation include pneumothorax, hypothermia, intra-operative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy and thoracic scoliosis [47, 56, 57].

Medical *vs*. Surgical Therapy for PDA

Although the efficacy of both COX inhibitors as well as surgery in ensuring ductal closure is well-established, a consensus on the choice of medical *vs*. surgical treatment remains elusive. Gersony *et al.* [58] compared clinical outcomes in 154 preterm infants who received either surgical ligation or medical treatment with COX inhibitors for a symptomatic PDA. There was no difference in mortality, BPD, bleeding, NEC, sepsis, renal insufficiency, or IVH. The surgical group had a higher incidence of pneumothorax [RR 2.68, 95% CI 1.45-4.93; risk difference (RD) 0.25, 95% CI 0.11-0.38; number needed to harm (NNH) 4, 95% CI 3-9) and severe ROP (RR 3.80, 95% CI 1.12-12.93; RD 0.11, 95% CI 0.02-0.20; NNH 9, 95% CI 5-50) compared to the indomethacin group.

Three recent observational studies have reported that infants receiving surgical ligation of PDA may be at increased risk of adverse outcomes such as chronic lung disease, ROP, and neurosensory impairment [59-61]. In some studies, surgical ligation was also associated with increased cardiorespiratory morbidity in the immediate post-operative period [59, 62]. Because of these concerns, surgical ligation is generally considered as a 'rescue' strategy in

infants who have a contraindication to treatment with COX inhibitors or have failed medical therapy [28, 63]. In a study of 3,779 infants weighing less than 1500 grams, Lee *et al*. [64] noted that 28% of infants were treated for PDA. In this group, 75% were treated with indomethacin alone, 8% with surgical ligation alone, and 17% received both indomethacin and surgical ligation.

Prophylactic *vs*. therapeutic use of indomethacin

Randomized controlled trials (RCTs) of indomethacin for prophylaxis against IVH and PDA were first published in the 1980s. Indomethacin prophylaxis, which was primarily directed against IVH, effectively closed the *ductus* in about 70% and reduced the incidence of a symptomatic PDA by 50% [65-67]. Fowlie *et al*.[12] reviewed 19 RCTs (n=2872) of prophylactic indomethacin in preterm infants <37weeks and showed a reduction in the incidence of symptomatic PDA (RR 0.44, 95% CI 0.38, 0.50) and the need for surgical ligation (RR 0.51, 95% CI 0.37, 0.71. The benefit of prophylactic indomethacin in reducing pulmonary hemorrhage, a known association of PDA [13, 14], remains unclear. Data from Bandstra [68], Couser [69], and the TIPP study [70] showed no benefit despite reducing the incidence of symptomatic PDA. In a study published in abstract form only, Domanico *et al.* [71] reported a strong trend towards prevention of pulmonary hemorrhage (5/52 in treated group *vs*. 12/48 in control; RR 0.38, 95% CI 0.15, 1.01). In a study of 1202 infants, Alfaleh *et al.* [72] noted that prophylactic indomethacin reduced the risk for serious pulmonary hemorrhage by 35% in the first week and by 23% over the course of NICU stay. Prophylactic indomethacin did not change respiratory outcomes or the incidence of pulmonary hemorrhage, gastrointestinal perforations, NEC, severe bleeding, or sepsis. Treated infants had a higher incidence of oliguria (RR 1.90; 95% CI 1.45, 2.47) but did not have major renal impairment.

In an effort to restrict the use of indomethacin and limit the possibility of adverse effects to patients with greater chance of benefit, some studies have targeted infants with an asymptomatic PDA (instead of treating all premature infants prophylactically). In a meta-analysis [73] of 3 RCTs [74-76] (n=97), indomethacin treatment of asymptomatic PDA (*vs*. placebo/no intervention)reduced the frequency of symptomatic PDA (RR 0.36, 95% CI 0.19, 0.68) and duration of supplemental oxygen (weighted mean difference −12.5, 95% CI −23.8, −1.26). There was no evidence of effect on mortality, BPD, IVH, ROP, or the total duration of ventilation.

Dosing regimens for indomethacin

Several dosing regimens of indomethacin have been used for prophylaxis and treatment of PDA (Table 2). The most commonly used prophylactic regimen includes three intravenous doses of 0.1mg/kg every 24 hours, whereas treatment usually involves an initial dose of 0.2 mg/kg followed by 2 doses of 0.1-0.2 mg/kg every 12 hours [74-76]. In cases with no success with an initial course or if the ductus reopens after initial closure, a second course may successfully close the PDA in up to 44% cases [77]. The rate of clinical reopening of ductus may be higher in infants with a birth weight less than 1000 grams and if echocardiography shows residual luminal flow [78, 79]. Although most clinicians will try

more than one course of indomethacin before opting for surgical ligation, multiple courses have not been evaluated in controlled trials.

The choice of the 12-hour dosing intervals in indomethacin therapy is largely empirical. In a retrospective study, Rosito *et al.* [80] compared indomethacin infusions over a 4-hour period every 24 hours with a new regimen where indomethacin was now infused over 30 minutes at a 12-hour dosing interval. Although there was a trend towards a higher rate of PDA closure and a lower need for surgical ligation of the *ductus* with the 12-hour dosing regimen, the differences did not reach statistical significance. The study also did not evaluate for the frequency of adverse effects in the two treatment groups.

Several studies have evaluated continuous infusions of indomethacin as a strategy to minimize adverse effects. Yoshimoto *et al*. [81] administered prophylactic indomethacin (within 6 hours of life) in 30 infants born between 23 and 24 weeks gestation at a continuous infusion of 0.01 mg/kg/hour for 12 hours. None of the treated infants developed a symptomatic PDA, compared to 11/15 controls ($p< 0.001$). There was no difference in mortality and early neonatal morbidities in the two groups. Similarly, in meta-analysis [82] of data from two trials [76, 83], there was no difference in the efficacy or safety of continuous *vs*. bolus infusion of indomethacin for treatment of PDA. The frequency of ductal reopening and of adverse effects such as oliguria, azotemia, IVH, NEC, or mortality was also similar between the two groups.

Ibuprofen therapy for PDA

In a study of 160 infants weighing less than 1000 grams with a clinically-symptomatic PDA, Richards *et al.* [5] showed that 70 (44%) infants had PDA closure after a single course of ibuprofen, and 32/80 (40%) following a second course. Infants born prior to 26 weeks of gestation (n=83) were less likely to respond after both the first (27.7% *vs*. 63.6%; $p<0.001$) or second (30.9% vs. 60.0%; $p =0.026$) courses. In other studies, oral and intravenously-administered ibuprofen may achieve a similar efficacy in ductal closure. Gokmen *et al*. [84] randomized 102 infants born with a birth weight less than 1500 grams to receive either oral or intravenous ibuprofen for closure of PDA. All infants received an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours. The investigators detected a higher rate of PDA closure in the oral ibuprofen group compared to intravenous ibuprofen group (84.6% versus 62%) after the first course of the treatment ($p = 0.01$). Although clinical renal injury was not detected, infants receiving oral ibuprofen showed a rise in cystatin-C levels (a marker of renal function that reflects glomerular filtration rate better than serum creatinine) after treatment ($p = 0.001$), indicating that infants with borderline renal function may need careful monitoring. Infants receiving intravenous ibuprofen did not show these changes.

Ibuprofen has also been used for prophylaxis against PDA. Ohlsson *et al.* [46] performed meta-analysis on seven studies (n = 931) comparing prophylactic ibuprofen with placebo/no intervention. Ibuprofen decreased the incidence of PDA [RR 0.36, 95% CI 0.29, 00.46); RD −0.27, 95% CI −0.32, −0.21; NNT 4, 95% CI 3, 5) and reduced the need for surgical ligation. Results from two studies administering oral ibuprofen had similar results, but showed an increased risk of gastrointestinal bleeding (NNH 4, 95% CI 2, 17) [85,

86].Ibuprofen also negatively affected renal function. There was no difference in mortality, IVH, and BPD.

Indomethacin *vs*. ibuprofen for treatment of PDA

Jones *et al*. [87] reviewed evidence from 10 randomized trials to evaluate the effects of indomethacin or ibuprofen compared with placebo on PDA closure, morbidity, and mortality in preterm infants with an echocardiographically- or clinically-significant PDA beyond 24 hours after birth. Included studies [44, 58, 74-76, 88-97] compared intravenous indomethacin vs. intravenous ibuprofen (10 trials), intravenous indomethacin vs. placebo (9 trials), and intravenous ibuprofen vs. placebo (1 trial). Both intravenous indomethacin (RR 2.39, 95% CI 2.05 to 2.78) and intravenous ibuprofen (RR 2.40, 95% CI 2.03 to 2.84) closed a PDA more effectively than placebo. Other studies [98, 99] have shown a similar efficacy of the two drugs. The two drugs also have a similar failure rate for PDA closure, ranging between 0-50%; Ohlsson *et al.* [100] performed a meta-analysis on data from 19 trials (n=956 infants) for failure rates after 1-3 doses of ibuprofen compared to indomethacin. They did not find a significant difference between the two groups (RR 0.94, 95% CI 0.76-1.17; RD −0.02, 95% CI −0.07 to 0.04).

Adverse effects of indomethacin *vs*. ibuprofen during treatment of PDA

Little *et al*. [79] reviewed the clinical course of 167 infants treated with indomethacin for a symptomatic PDA, and noted adverse effects in 73% patients. Indomethacin therapy was associated with thrombocytopenia (36%), azotemia (31%), sepsis (30%), oliguria (25%), hyponatremia (25%), IVH (16%), pulmonary interstitial emphysema (11%), NEC (8%), intestinal perforation (4%), and bleeding (3%).

In a systematic review of 19 studies (n=956) comparing ibuprofen and indomethacin to placebo in preterm <37weeks and <2500g, Ohlsson *et al.* [100] detected reduced risk of developing NEC with ibuprofen (RR 0.68, 95% CI 0.47-0.99; RD −0.04, 95% CI −0.08 to −0.00; $p = 0.04$). The proportion of infants with oliguria was also significantly lower in the ibuprofen group (RR 0.28, 95% CI 0.14, 0.54; RD −0.09, 95% CI −0.14, −0.05) than in those treated with indomethacin. Infants in the ibuprofen group also had lower serum/plasma creatinine levels 72 hours after initiation of treatment (weighted mean difference −4.70 mmol/L, 95% CI −8.88, −0.53). These differences in renal toxicity are consistent with physiological studies that show greater impairment of renal perfusion when exposed to indomethacin as compared to ibuprofen [91, 92, 101, 102]. There were no differences in infants treated with indomethacin or ibuprofen in bilirubin levels, IVH, NEC, ROP, sepsis, rate of surgical ligation, length of hospital stay, or mortality.

Limitations of Pharmacotherapy for PDA

Pharmacotherapy for PDA has been shown to be efficacious in achieving ductal closure but is associated with notable side effects. Studies evaluating COX inhibitors for treatment of neonatal PDA are frequently limited by small sample size and lack of precision, making it difficult to draw strong conclusions regarding dosing regimens, comparative efficacy, and safety profiles of the drugs. Although both COX inhibitors and surgery are highly effective

in closing the *ductus*, the routine use of COX inhibitors in preterm infants is now being increasingly questioned: RCTs show little evidence of benefit when used for the treatment of PDA; prophylactic COX inhibitor therapy has not improved neurodevelopmental outcome; COX inhibitors are associated with significant side effects; and there is a high potential for spontaneous ductal closure [103-105]. The *ductus* may close spontaneously by postnatal day 8 in up to 40% of infants born with a birth weight less than 1000 grams [34].

Conclusions

Persistent patency of the *ductus arteriosus* is a major cause of morbidity and mortality in premature infants. Medical management of PDA in premature infants is comprised of fluid restriction and cyclo-oxygenase (COX) inhibitors such as indomethacin and ibuprofen lysine. In selected cases, surgical ligation of the ductus is also an option. There is a need for novel clinical/laboratory markers for early identification of infants at risk of developing a persistent and symptomatic PDA. Such an approach could potentially allow most premature infants to receive expectant management and limit active treatment to a few selected patients [103].

Abbreviations

WMD	Weighted mean difference
RR	Relative Risk
OR	Odds Ratio
RD	Risk Difference
CI	Confidence Interval
NNT	Number needed to treat
LPA	Left Pulmonary Artery
CVD	Cardiovascular Distress
RCT	Randomized Controlled Trial
RDS	Respiratory Distress Syndrome
NEC	Necrotizing Enterocolitis
BPD	Bronchopulmonary Dysplasia
IVH	Intra-ventricular Hemorrhage
PVL	Periventricular Leukomalacia

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Table 1

Cardiovascular Distress Score (CVD) in Premature Infants with PDA [38]

Parameter		**SCORE**	
	0	**1**	**2**
Heart rate (bpm)	<160	160-180	>180
Heart murmur	None	Systolic murmur	Murmur continues to diastole
Peripheral pulse	Normal	Bounding brachial	Bounding brachial and dorsal pedis
Precordial pulsation	None	Palpable	Visible
Cardiothoracic ratio	<0.60	0.60-0.65	>0.65

Table 2

Pharmacotherapeutic Options for Neonatal PDA

Drug	Dosing Regimen
Indomethacin Prophylaxis [12, 54, 74-76]	**I.** Short 3-dose course of prophylactic indomethacin (0.2, 0.1, 0.1 mg/kg, administered at 24-hour intervals) **OR** **II.** Extended 6-dose course (0.2, 0.1, 0.1, 0.1, 0.1, 0.1 mg/kg, at 24-hour intervals) starting within 15 hours of birth **OR** **III.** 3 dose course of 0.1mg/kg IV at 24-hour intervals
Indomethacin Treatment [100]	**I.** 1st dose: 0.2 - 0.3 mg/kg IV 2nd dose: 0.2 mg/kg IV Q 12-24 hours after 1st dose if PDA persists 3rd dose: 0.2 mg/kg IV 12-24 hours after 2nd dose if PDA persists **OR** **II.** 0.2 mg/kg/dose PO/IV for three doses given at 12 hourly intervals
Ibuprofen Prophylaxis [46]	**I.** Oral suspension 10mg/kg; 5mg/k, 5mg/kg PO q 24hrs for symptomatic PDA
Ibuprofen Treatment [5, 84]	**I.** Loading dose of 10mg/kg IV/PO on day 1, followed by 5mg/kg/dose at 24 hrs and 48 hrs subsequently **OR** **II.** Oral ibuprofen 10 mg/kg/dose for three doses given at 24 hourly intervals