Persistently patent ductus arteriosus (PDA), affecting approximately one-third of all very low birth weight infants, can lead to significant morbidity and mortality. Recently, ibuprofen has been recommended over indomethacin to close PDAs because of a reduction in risk of necrotizing enterocolitis. Pulmonary hypertension is a rare but potentially fatal complication of ibuprofen administration in preterm infants. We report 2 infants who developed this complication after receiving therapeutic L-lysine ibuprofen preparation for the PDA closure. The first infant, 1 of twins weighing 640 g, was born at 24 weeks’ gestation. The second infant, born at 26 weeks’ gestation, was small for gestational age, weighing 439 g. In both cases, ibuprofen was initiated after echocardiographic confirmation of a moderate-sized to large PDA and an otherwise normal intracardiac anatomy. Both infants had echocardiographic evidence of increased pulmonary vascular resistance but shunting across the PDA was left to right. The infants deteriorated within 48 to 72 hours, and repeat echocardiograms revealed evidence of severe pulmonary hypertension. Both infants died of refractory hypotension and hypoxemia. When considering the use of ibuprofen therapy for PDA closure, clinicians should keep in mind the potential serious complication of pulmonary hypertension, even if a shunt across the PDA is left to right. Pediatrics 2012;129:e1360–e1363

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KEY WORDS
preterm infants, patent ductus arteriosis, ibuprofen, indomethacin

ABBREVIATIONS
FIO2—fraction of inspired oxygen
HFOV—high-frequency oscillatory ventilation
iNO—inhaled nitric oxide
NEC—necrotizing enterocolitis
PDA—patent ductus arteriosis, PFO, patent foramen ovale
PH—pulmonary hypertension
RVSP—right ventricular systolic pressure

*RVSP estimate in mm Hg ~ 4[(tricuspid regurgitation velocity, m/s)2, according to the modified Bernoulli equation.

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Patent ductus arterious (PDA) is common in premature neonates. The consequences of a PDA include pulmonary congestion, heart failure, pulmonary hemorrhage, and chronic lung disease due to increased pulmonary flow and renal failure and necrotizing enterocolitis (NEC) and periventricular leucomalacia due to ductal steal of blood from systemic flow. Treatment of persistent PDA varies among neonatal intensive care units. Indomethacin and ibuprofen have been used prophylactically as well as for the treatment of a PDA in preterm infants. Prophylactic indomethacin may reduce the incidence of severe intraventricular hemorrhage but does not improve survival or reduce disability in the longer term. Recently, ibuprofen preparations have been administered as an alternative to indomethacin. Ibuprofen has been found to be equally effective as indomethacin for closure of the PDA and to have less adverse effects. The use of ibuprofen for the treatment of PDA also reduces the risk of NEC. Several cases of severe pulmonary hypertension (PH) after prophylactic and therapeutic use of ibuprofen are reported in the literature. We report 2 additional fatal cases of severe PH after administration of L-lysine preparation of ibuprofen.

CASE REPORT

The first infant was a twin gestation (twin A), born at 24 4/7 weeks’ gestation via cesarean delivery for breech presentation, weighing 690 g. The mother was 33 years old and had no prenatal care. Pregnancy was complicated by gestational diabetes. Urine drug screening was positive for cocaine. She was admitted with preterm labor and received 1 dose of betamethasone before delivery. Apgar scores were 2, 6, and 7. The initial course involved mechanical ventilation and surfactant therapy on day 1 followed by moderate ventilatory support. An echocardiogram performed on day 4 revealed normal intracardiac anatomy, mild septal flattening, patent foramen ovale (PFO), no tricuspid regurgitation, moderate-sized PDA, and increased pulmonary venous return consistent with significant left-to-right ductal flow. The infant was stable at that time on conventional ventilation and fraction of inspired oxygen (FiO2) of 0.4. The infant’s PDA was treated with 3 doses of ibuprofen given 24 hours apart. After the third dose of the medication, the infant’s condition deteriorated as evidenced by frequent hypoxemic events and hypotension requiring multiple boluses, dopamine and dobutamine infusions, and high-frequency oscillatory ventilation (HFOV). He remained hypoxemic with saturations in the 60s to 70s on high ventilatory settings (FiO2 1.0, mean arterial pressure 18–20, amplitude in 40s). Inhaled nitric oxide (iNO) was started without improvement in oxygenation. A blood culture was drawn at that time and empirical antibiotics were started. The blood culture remained negative. Echocardiogram repeated on day 9 revealed evidence of severe PH and suprasystemic right ventricular systolic pressure (RVSP), with dilation of the right atrium and right ventricle, right-to-left shunting across the PFO, moderate tricuspid regurgitation predictive of RVSP greater than systemic blood pressure by umbilical arterial catheter, severe septal flattening at times concave into the left ventricular cavity, pulmonary artery flow pattern of pulmonary artery hypertension, and small right-to-left ductal shunt. The infant remained on HFOV, iNO, dopamine, dobutamine, and dexamethasone. Sildenafil was also started on day 13 without improvement in oxygenation. The infant died on day 14.

The second infant was born to a 20-year-old mother, at 26 3/7 weeks’ gestation, small for gestational age, and weighing 439 g. The pregnancy was complicated by maternal preeclampsia, HELLP (High blood pressure, Elevated Liver enzymes, Low Platelets) syndrome, and placenta previa. The infant was delivered via cesarean section for a footling breech presentation. He was intubated in the delivery room. Apgar scores were 2, 6, and 8. He was placed on HFOV and received 3 doses of surfactant. He remained stable on moderate settings on HFOV until day 5. On day 5 an echocardiogram showed a large PDA, with a low-velocity left-to-right shunt predicting near-systemic pulmonary artery pressure, PFO with left-to-right shunt, mild tricuspid regurgitation with a gradient predictive of near-systemic RVSP compared with systemic pressure by umbilical arterial catheter, and mild septal flattening. The infant was treated with ibuprofen (L-lysine) for 3 doses. After the second dose, the infant became hypotensive and hypoxemic, requiring multiple fluid boluses, pressors, and increasing ventilatory support. The infant remained hypoxemic and hypotensive and developed persistent metabolic acidosis and anuria despite being on high ventilatory setting (FiO2 1.0, mean arterial pressure 14–15, amplitude in 50s), pressors, and hydrocortisone. iNO was started with transient improvement in oxygenation. Repeat echocardiogram on day 8 revealed evidence of severe PH and suprasystemic RVSP with right-to-left shunting across the PFO and decreased pulmonary artery flow pattern. There was trace to mild tricuspid regurgitation that could not be quantified. The right ventricle was severely dilated with flat and at times concave contour into the left ventricular cavity with moderate-to-severe hypokinesia. No ductal flow was seen. A prostaglandin infusion was started, resulting in an improvement in blood pressure, metabolic acidosis, and urine output. Over the next 2 days, the infant remained stable. However, on day 11 there was a sudden drop in blood pressure, which was not responsive to...
fluid boluses and pressors, and the infant died.

**DISCUSSION**

Ibuprofen has been used instead of indomethacin in the treatment of PDA due to its fewer side effects. Clinical trials have shown it to be equally effective as indomethacin for ductal closure. However, we observed 2 premature neonates with severe PH after ibuprofen who were unresponsive to medical therapy.

The only risk factor for PH in the first infant was in utero exposure to cocaine. Fetal exposure to cocaine is associated with PH in neonates. There was evidence of increased pulmonary vascular resistance on the initial echocardiogram. The ductal shunt, however, was entirely left to right, associated with increased pulmonary venous return to the left atrium. The second infant also had evidence of increased pulmonary vascular resistance on the echocardiogram before ibuprofen was started. This was likely due to in utero chronic hypoxemia as a result of maternal pre-eclampsia. The decision to treat the PDA despite high pulmonary vascular resistance was related to the large size of the duct, continuous left-to-right shunting, and risk of left-sided heart volume overload. In the 3 cases of PH associated with prophylactic ibuprofen reported by Gournay et al, PH was partially attributed to high pulmonary vascular resistance. Delaying the treatment might have prevented the development of severe PH in our patient. However, the success rate of pharmacologic closure of the PDA is reduced after 7 days and the surgical closure is associated with other morbidities and complications.

We observed severe PH in both the infants after ibuprofen therapy. However, the closure of the ductus may also have contributed to worsening of the clinical status. In the context of severe PH, right-to-left ductal shunting allows for maintenance of right ventricular cardiac output and decompression of the systemic right ventricle (fetal circulation). After ibuprofen treatment and ductal closure, both patients exhibited reversal of the normal ventricular septal contour, interpreted as indicative of suprasystemic right ventricular pressure. Septal contour was used as an indirect qualitative indicator of RVSP. In addition to the effects of hypoxemia on myocardial performance, this altered geometry further compromises cardiac output from the left ventricle, related to abnormal diastolic filling, potential for outflow obstruction, and impaired systolic wall motion. The clinical manifestations of diminished pulmonary blood flow and ventricular failure lead to intractable hypoxemia and hypotension. In the second infant, we attempted to open the ductus with a prostaglandin infusion. We did observe transient improvement in blood pressure, oxygenation, and metabolic acidosis, possibly due to improved systemic blood flow as a result of opening of the duct or as a direct vasodilatory effect of prostaglandins.

In reviewing the literature, we found several cases of PH that occurred after ibuprofen therapy. Three cases of PH were reported by Gournay et al while using ibuprofen prophylaxis for prevention of PDA in a randomized clinical trial in premature infants. The trial was stopped after 3 episodes of refractory hypoxemia with PH occurred after the first prophylactic dose of ibuprofen. After unblinding, it was found that all 3 infants had received ibuprofen. Although these researchers concluded that there was a probable relation between the adverse event and the ibuprofen administration, other possible explanations have been posed. Earlier administration of ibuprofen might have prevented the normal decrease in pulmonary vascular resistance. Mosca et al reported a case series of 227 preterm infants with PDA who were treated therapeutically with ibuprofen lysine. None of their infants developed acute hypoxemia or severe PH after L-lysine administration. However, 3 infants in the series developed moderate PH, which resolved with iNO.

Another case was reported by Bellini et al in a 32-week-gestation infant who developed PH after receiving therapeutic L-lysine preparation. Within 1 hour of administration of the second dose, severe hypoxemia was observed. Echocardiogram revealed closure of the ductus arteriosus and severe PH that responded to initiation of iNO. In their clinical trial comparing the efficacy of ibuprofen and indomethacin in the treatment of PDA, Adamska et al reported a case of PH after the therapeutic use of ibuprofen. One of the 16 infants in the ibuprofen group developed PH requiring termination of treatment. More recently, in a randomized, placebo-controlled clinical trial using ibuprofen lysine for the early treatment (within 72 hours) of PDA, Aranda et al reported 2 cases of PH in the L-lysine group and 1 case in the placebo group. Several other clinical trials compared ibuprofen and indomethacin for the treatment of PDA but did not include PH as an outcome.
a study by Katakam et al reported a trend toward increase mortality rate in the ibuprofen group that was twice the rate of the indomethacin group (17.2% vs 9.2%, \( P = .19 \)). This was a retrospective study with a limited sample size and the causes of death were not reported. Large, prospective, randomized trials are needed to investigate the relationship between ibuprofen therapy, PH, and mortality.

Although indomethacin and ibuprofen have both been found to be effective in the treatment of PDA, each drug has potentially serious side effects. PH must be considered as a rare but serious side effect in treatment with either L-lysine or tromethamine preparation of ibuprofen if an infant becomes hypoxemic or hypotensive after ibuprofen administration. Due to reduction in the risk of NEC with ibuprofen, Ohlsson et al in a recent Cochrane review recommended ibuprofen over indomethacin to close PDA. Moreover, ibuprofen may be preferred over indomethacin in preterm infants with abnormal renal function. However, the clinician should counterbalance this benefit of ibuprofen with the possible fatal side effect of PH. Practitioners should also use caution when using ibuprofen in the presence of increased pulmonary vascular resistance even if a shunt across the PDA is left to right or in presence of other risks such as maternal cocaine abuse or chronic placental insufficiency. If severe PH develops after ibuprofen therapy and the ductus is closed, use of prostaglandin infusion should be considered in an attempt to reopen the ductus in the presence of refractory hypotension and hypoxemia.

More recently, the treatment of PDA in preterm infants has become increasingly controversial. Due to the lack of benefit of treatment, significant side effects of medications, and higher rates of spontaneous closure, a more conservative approach is advocated by some experts for the treatment of PDA in preterm infants.

**REFERENCES**


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