Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus

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Patent ductus arteriosus (PDA) affects approximately 31% of infants whose birth weight is between 501 and 1500 g. The ductus arteriosus is a blood vessel that allows blood to bypass the pulmonary vasculature in utero. Oxygen delivery and elimination of prostaglandins are essential for the closure of the ductus after birth. For years, indomethacin has been the drug of choice for the treatment of PDA in the USA. Undesirable adverse effects prompted researchers to seek alternative agents. In April 2006, the US Food and Drug Administration approved the use of ibuprofen lysine (NeoProfen) for closure of clinically significant PDA in premature neonates. Ibuprofen's mechanism of action for closure of PDA is believed to be through the inhibition of prostaglandins. Clinical studies have shown ibuprofen to be as effective as indomethacin with fewer adverse effects.

The ductus arteriosus is a blood vessel that connects the pulmonary artery to the aorta. In utero, blood is shunted away from the lungs due to higher pulmonary resistance. Hence, blood exits the right ventricle, moves through the ductus arteriosus, and enters into the aorta. By 6 weeks' gestation, the amount of blood flowing through the ductus arteriosus is approximately 50% to 60% of total cardiac output. Prostaglandins are potent vasodilators that keep the ductus arteriosus open in utero. Normally, pulmonary resistance begins to drop when oxygenation and ventilation occur after birth. Blood enters the pulmonary circulation, which delivers prostaglandins to the lungs, where they are metabolized and cleared. Oxygenated blood also plays a major role in the closure of the ductus arteriosus. Functional closure occurs in the majority of term neonates by 9 to 12 hours after birth. Risk factors for patent ductus arteriosus (PDA) include prematurity and the presence of respiratory distress syndrome (1). The incidence of PDA is approximately 31% in neonates whose birth weight is between 501 and 1500 g (1, 2). PDA causes left-to-right shunting, which increases the risk of intraventricular hemorrhage (IVH), bronchopulmonary dysplasia, congestive heart failure, and necrotizing enterocolitis (NEC) (1, 3).

In the USA, intravenous indomethacin is the drug of choice for the treatment of PDA, and it is often prescribed by neonatologists at Baylor University Medical Center. There are safety concerns regarding the use of indomethacin because it affects renal, gastrointestinal, and cerebral perfusion; hence, it can lead to transient renal dysfunction and is associated with the occurrence of NEC. In April 2006, the US Food and Drug Administration approved the use of ibuprofen lysine (NeoProfen) for closure of clinically significant PDA in premature neonates <32 weeks' gestational age who weigh between 500 and 1500 g. Studies have shown ibuprofen to be as effective as indomethacin for the closure of PDA with fewer adverse effects (4).

PHARMACOLOGY AND PHARMACOKINETICS

The exact mechanism of action of ibuprofen for the closure of PDA in neonates is unknown. It is believed to work through the inhibition of prostaglandin synthesis (1, 4). Ibuprofen, a nonsteroidal anti-inflammatory drug, inhibits both cyclooxygenase-1 and cyclooxygenase-2, which are enzymes necessary for the conversion of arachidonic acid to various prostaglandins. Among them, prostaglandin E_2 is the most potent vasodilator of the ductus. Nonsteroidal anti-inflammatory drugs may be used for the closure of PDA in preterm infants because the immature ductus is more sensitive to prostaglandin E_2 (5, 6).

Ibuprofen is 95% protein bound and has a volume of distribution of 320 mL/kg (4). The metabolism and excretion of ibuprofen have not been studied in preterm infants. In adults, the drug is mainly metabolized by the liver, and 80% of the dose is excreted in the urine as hydroxyl and carboxyl metabolites. The average rate of clearance is 3 mL/kg/hr, which increases rapidly with postnatal age (4).

CLINICAL TRIALS

Van Overmeire et al conducted a prospective multicenter trial comparing the efficacy of ibuprofen with that of indomethacin for the closure of PDA (2). Patients included in the study were 2 to 4 hours old and <32 weeks' gestational age, with evidence of PDA and respiratory distress syndrome requiring mechanical ventilation. Patients with any of the following abnormalities were excluded from the trial: 1) major congenital

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abnormalities; 2) life-threatening infection; 3) hydrops fetalis; 4) recent intraventricular hemorrhage; 5) urine output below 1 mL/kg/hr during the preceding 8 hours; 6) serum creatinine level >1.6 mg/dL; 7) platelet count <60,000/mm^3; 8) tendency to bleed; and 9) hyperbilirubinemia requiring exchange transfusion.

Patients enrolled in the indomethacin group received three doses of 0.2 mg/kg indomethacin every 12 hours, and patients enrolled in the ibuprofen group received an initial dose of 10 mg/kg, followed by two doses of 5 mg/kg 24 and 48 hours later. If the ductus arteriosus failed to close after drug therapy, patients were given a course of indomethacin regardless of initial treatment assignment. Surgical ligation was performed for those with a contraindication for the second pharmacological treatment and those who remained on mechanical ventilation. Echocardiography was performed for all enrolled patients before and after treatment.

A total of 148 patients were enrolled from five tertiary neonatal intensive care units (NICUs) in Belgium. Baseline characteristics were similar between the two groups. PDA was closed in 49% of the patients assigned to the indomethacin group compared with 52% of those enrolled in the ibuprofen group (P = 0.88). A second course of drug therapy was needed in 9% of the patients in the indomethacin group compared with 12% in the ibuprofen group (P = 0.48). The ductus was surgically ligated in four patients in the indomethacin group and three patients in the ibuprofen group. Among those for whom the initial drug therapy failed, four predictors were identified: 1) gestational age <26 weeks; 2) antenatal indomethacin <48 hours before birth; 3) high-frequency oscillatory ventilation; and 4) ductal shunt velocity. Oliguria developed in 14 patients in the indomethacin group vs 5 patients in the ibuprofen group during the 3 days after the start of therapy (P = 0.03). Urine output was significantly lower among patients in the indomethacin group from day 3 to day 7 of therapy (P < 0.001). The increase in serum creatinine was significantly greater from day 4 to day 8 in the indomethacin group than in the ibuprofen group (P = 0.04). The incidence of other adverse effects such as NEC and worsening IVH was not statistically different between the two groups, and the survival rate at 1 month was not statistically different (P = 0.76).

Lago et al conducted a prospective randomized controlled study to compare the safety and efficacy of indomethacin vs ibuprofen for the treatment of PDA in two NICUs in Italy between January 1998 and December 2000 (7). Eligible patients had to meet the following criteria: 1) gestational age ≤34 weeks; 2) postnatal age of 48 to 72 hours; 3) respiratory distress syndrome treated with mechanical ventilation; and 4) echocardiographic evidence of PDA. Patients were excluded if they were found to have any of the following: 1) major congenital abnormalities; 2) persistent pulmonary hypertension; 3) recent bleeding; 4) a platelet count <50,000/mm^3; 5) urine output <1 mg/kg/hr during the previous 12 hours; 6) a serum creatinine level >140 mmol/L; and 6) a serum urea nitrogen level >14 mmol/L.

A total of 175 patients were enrolled in the study. Eighty-one patients who were assigned to the indomethacin group received three doses of 0.2 mg/kg every 12 hours. Ninety-four patients who were assigned to the ibuprofen group received an initial dose of 10 mg/kg and two doses of 5 mg/kg 24 and 48 hours later. The closure rate was 69% in the indomethacin group vs 73% in the ibuprofen group. For adverse events, 15% of the patients in the indomethacin group experienced oliguria vs 1% in the ibuprofen group (P = 0.017). Posttreatment serum creatinine levels were significantly higher in the indomethacin group than in the ibuprofen group (P = 0.03). These effects were transient and resolved 24 hours after the end of treatment. The incidence of respiratory complications, NEC, and worsening IVH was not significantly different between the groups.

Thomas and colleagues conducted a meta-analysis to compare the efficacy and safety of indomethacin and ibuprofen for the closure of PDA (8). Nine studies published from 1995 to 2003 were identified in an extensive literature search. Of note, the aforementioned studies by Van Overmeire et al and Lago et al were included in this meta-analysis. There was no significant difference between indomethacin and ibuprofen for the closure of PDA (P = 0.7). Five of the nine studies reported serum creatinine levels and urine output. The trials found a significantly smaller increase in serum creatinine (P < 0.001) and a significantly smaller decrease in urine output favoring ibuprofen (P < 0.001). Three studies found the incidence of IVH to be similar between the indomethacin (27%) and ibuprofen (20%) treatment groups (P = 0.22). The incidence of NEC, sepsis, and gastrointestinal bleed was similar.

Besides causing renal impairment, indomethacin can decrease cerebral blood flow. Patel et al conducted a prospective randomized controlled trial comparing the effects of ibuprofen and indomethacin on cerebral hemodynamics (9). Thirty-three patients from four NICUs in London were enrolled in the study, 15 patients in the indomethacin group and 18 patients in the ibuprofen group. Patients in the indomethacin group received an initial dose of 0.2 mg/kg followed by two doses of 0.2 or 0.25 mg/kg (depending on postnatal age) 12 and 24 hours later. Patients in the ibuprofen group received an initial dose of 10 mg/kg followed by two doses of 5 mg/kg 24 and 48 hours later. Near-infrared spectroscopy was used to determine cerebral blood flow and volume changes. Cerebral oxygen delivery was also calculated.

For patients in the indomethacin group, the mean value for cerebral blood flow decreased from 13.6 to 8.3 mL/100 g/min after the first dose, while it changed from 13.3 to 14.9 mL/100 g/min in patients who received ibuprofen (P < 0.001). The mean cerebral blood flow again decreased from 16.7 to 11.8 mL/100 g/min after the 24-hour dose of indomethacin, while it increased slightly from 15 to 15.5 mL/100 g/min after the 24-hour dose of ibuprofen (P < 0.001). There were no significant changes in mean cerebral blood flow after the 48-hour doses of normal saline and ibuprofen. The mean cerebral oxygen delivery also decreased significantly after indomethacin treatment. It decreased from 2.6 to 1.5 mL/100 g/min after the first dose of indomethacin, while it increased slightly from 2.2 to 2.5 mL/100 g/min after the first dose of ibuprofen (P < 0.001). The mean cerebral oxygen delivery again decreased

from 2.8 to 1.9 mL/100 g/min after the 24-hour dose of indomethacin, while it increased from 2.3 to 2.5 mL/100 g/min after the 24-hour dose of ibuprofen ($P < 0.001$). There were no significant changes in mean cerebral oxygen delivery after the 48-hour doses of normal saline and ibuprofen.

CONTRAINDICATIONS AND PRECAUTIONS

Ibuprofen is contraindicated in premature neonates with at least one of the following: 1) proven or suspected infection that is untreated; 2) congenital heart disease in which patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow; 3) active bleeding, especially intracranial hemorrhage or gastrointestinal bleeding; 4) thrombocytopenia; 5) coagulation defects; 6) suspected NEC; or 7) significant impairment of renal function (4).

Ibuprofen can inhibit platelet aggregation, so signs of bleeding should be monitored. Ibuprofen solution may be irritating to the tissue; therefore, it should be administered carefully to avoid extravasation. Ibuprofen is known to displace bilirubin from albumin binding sites and should be used with caution in patients with an elevated total bilirubin level (4). Studies have yet to determine the long-term effects of ibuprofen.

Drug interactions of ibuprofen in neonates have not been assessed (4).

ADVERSE EVENTS

Adverse events associated with ibuprofen include bleeding, skin lesion/irritation, hypoglycemia, hypocalcemia, adrenal insufficiency, and respiratory failure. IVH and renal insufficiency have also been reported (4).

DOSING AND ADMINISTRATION

The regimen for treatment of PDA with ibuprofen comprises three doses. The recommended initial dose is 10 mg/kg intravenously, followed by two doses of 5 mg/kg 24 and 48 hours later. If urine output is <0.6 mL/kg/hr, subsequent dose(s) should be held until renal function has returned to normal. If the ductus arteriosus fails to close or later reopens, a second course of ibuprofen may be given (4).

The available concentration of ibuprofen lysine is 17.1 mg/mL (equivalent to 10 mg/mL ibuprofen). Each single-use vial contains 2 mL of sterile solution. Vials should be stored at room temperature (20°–25°C) and protected from light (4).

Ibuprofen should be used within 30 minutes of preparation. The dose can be infused continuously over 15 minutes. It should not be administered in the same intravenous line with total parenteral nutrition. Since ibuprofen does not contain preservatives, unused solution should be discarded (4).

ECONOMIC ISSUES

At Baylor University Medical Center, the acquisition costs of ibuprofen lysine and indomethacin are comparable. The cost per course of therapy for ibuprofen (three 20-mg vials) is $1409.40, and for indomethacin (three 1-mg vials), $1458.

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