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CASE REPORT

Repeated Bowel Perforations with Ibuprofen Lysine: A Case Report

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Non-steroidal anti-inflammatory drugs (NSAID) have been used to close the patent ductus arteriosus in neonates for over two decades. Ibuprofen lysine, a parenteral NSAID, is labeled for the treatment of patent ductus arteriosus in neonates who do not respond to conventional medical management. While sharing many of the same adverse effects as indomethacin, spontaneous bowel perforation has not been reported. We describe a premature infant that experienced isolated bowel perforations after treatment with ibuprofen lysine for symptomatic patent ductus arteriosus.

KEYWORDS adverse effect, bowel, ibuprofen lysine, NSAID, PDA, perforation

J Pediatr Pharmacol Ther 2008;13:166-169

INTRODUCTION

Indomethacin was the first non-steroidal anti-inflammatory (NSAID) used to close a patent ductus arteriosus (PDA).[1] In April of 2006, the Food and Drug Administration approved the use of ibuprofen lysine injection (NeoProfen, Ovation Pharmaceuticals, Deerfield, Illinois) for pharmacological closure of a PDA that is unresponsive to conventional medical management.[2] The medication is labeled specifically for premature neonates born at less than 32 weeks gestational age and who weigh between 500 and 1500g.[1,3] The non-specific inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) caused by ibuprofen lysine is believed to close the PDA by inhibiting prostaglandin synthesis. [1,3]

The most common adverse reactions reported with ibuprofen lysine include sepsis, anemia, intraventricular hemorrhage, gastrointestinal disorders, and renal insufficiency. Although studies have been done that suggest a reduced adverse effect profile with ibuprofen lysine, compared to indomethacin, its use does not come without risks.[4]

ABBREVIATIONS COX, cyclooxygenase inhibitor eNOS, endothelial nitric oxide syntetase;FiO2, fraction of inspired oxygen; IV, intravenous; NEC, necrotizing enterocolitis; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory; PDA, patent ductus arteriosus; SIMV, synchronized intermittent mechanical ventilation; UAC, umbilical arterial catheter; UVC, umbilical venous catheter

CASE REPORT

A premature male infant born at twenty-five weeks gestational age with a birth weight of 730 grams and length of 30.5 centimeters was delivered via cesarean section and admitted to the neonatal intensive care unit in our institution. The infant's mother received one dose of betamethasone prior to delivery. APGAR scores following birth were 8 and 9 at one

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and five minutes, respectively. The infant was given one dose of surfactant (Infasurf, Forrest Pharmaceuticals, St. Louis, MO) after delivery due to pulmonary immaturity, but did not receive postnatal steroids. An umbilical venous catheter (UVC) and umbilical arterial catheter (UAC) were inserted. At 48 hours of life, an echocardiogram confirmed that the neonate had a moderate PDA. The infant was receiving synchronized intermittent mechanical ventilation with fraction of inspired oxygen (FiO_2) ranging from 25-30%. His respiratory status at the time was relatively unremarkable for a 48 hour old premature newborn. Arterial blood gases read as follows: pH 7.262, pCO_2 49, pO_2 75.7, HCO_3 22, BE -5, and oxygen saturation of 93%. Blood pressure and pulse were normal for an infant of his corrected gestational age. Urine output was adequate with a serum creatinine of 0.9 mg/dL (79.6 µmol/L). He was in an incubator and was receiving parenteral nutrition, intravenous (IV) antibiotics (i.e., ampicillin, gentamicin), and IV caffeine. Sodium bicarbonate, 1 mEq IV, was administered one time for mild acidosis. Abdominal X-rays up to this time had shown unremarkable bowel gas patterns. The UVC and UAC remained in place.

The decision was made to employ early intervention and close the PDA pharmacologically with ibuprofen lysine. An intravenous loading dose of 7.3 mg (10 mg/kg) was given on day one of treatment and was followed twenty-four hours later with a 3.65 mg maintenance dose (5 mg/kg). These are the recommended doses for ibuprofen lysine and both doses were infused over 15 minutes, as recommended by the manufacturer.

Less than 18 hours after the second dose of ibuprofen lysine, an abdominal X-ray revealed free intra-peritoneal air. The presence of free air was confirmed by a left lateral decubitus X-ray. In light of the radiographic finding and due to concerns of gastrointestinal perforation, the ibuprofen lysine was abruptly stopped. Surgical intervention was initiated in order to place an abdominal drain and remove the free air. The procedure revealed no evidence of gross peritonitis or visual bowel perforation. Piperacillin/tazobactam (ZOSYN, Wyeth Pharmaceuticals Inc., Philadelphia, PA) was added to the infant's antimicrobial regimen, and the infant's bowel status was followed closely using serial abdominal X-rays.

The ductus arteriosus remained open, and as care continued, the infant's pulmonary status worsened with a probable left to right shunt. Chest X-ray, arterial blood gases, and poor renal function all indicated that significant respiratory compromise was impacting the clinical status of the infant. A repeat echocardiogram done on the 11th day of life confirmed the continued presence of a PDA. On the neonate's 12th day of life and 10 days after the first suspected perforation, the infant's arterial blood gases had deteriorated considerably. Still on SIMV, the infant's blood gases read: pH 7.229, pCO_2 85, pO_2 45.2, HCO_3 35, BE 4, and an oxygen saturation of 70%. The FiO_2 had increased from 25% to 40% over the previous two days. The serum creatinine was also elevated for a premature newborn at 1 mg/dL (88.4 µmol/L), providing further evidence that poor oxygen perfusion to the organs was likely. The UVC and UAC were no longer in place.

Two treatment options existed. Surgical ligation could be performed, or the less invasive approach, a repeat trial of ibuprofen lysine could be attempted. Due to the infant's deteriorating clinical status, it was decided to proceed with the less invasive method and attempt PDA closure with a repeat trial of ibuprofen lysine. The infant's weight was now 910 grams; therefore, a 9 mg IV loading dose of ibuprofen lysine was administered. At the time, the neonate was also receiving parenteral nutrition, IV antibiotics, gentamicin and piperacillin/tazobactam, IV caffeine, and IV levothyroxine.

The morning following the ibuprofen lysine loading dose, a chest X-ray revealed the infant had a right upper lobe atelectasis with free abdominal air. The presence of free air was again confirmed with a left lateral decubitus X-ray. An immediate surgical intervention revealed two small perforations in the intestines. One of the perforations was 5 centimeters from the ileocecal valve and the other was in the midportion of the small bowel. The perforations were repaired, drainage tubes were placed, and the infant was continued on antibiotics. Ibuprofen lysine was witheld indefinitely. One week after the infant's second perforation, surgical intervention was undertaken in order to close the PDA. Within 48 hours post ligation, the infant's respiratory and renal function both improved considerably.

DISCUSSION

This case shows a strong correlation between the administration of ibuprofen lysine and gastrointestinal perforation, an adverse reaction that is not specified in the package insert nor is it listed as a precaution for use. In both instances bowel perforation occurred less than 24 hours after a dose of ibuprofen, and abdominal X-rays taken prior to administration of ibuprofen showed no signs of free air.

Spontaneous intestinal perforations have been well documented in neonates receiving indomethacin with no clear understanding of the mechanism,[5-7] although effects on prostaglandins and diminished blood flow to the intestine may contribute to the development of intestinal perforations. Gordon et al, have suggested that diminished activity of endothelial nitric oxide syntetase (eNOS), caused by indomethacin, may be a risk factor for development of spontaneous intestinal perforation.[8] Nitric oxide (NO) is a potent vasodilator and diminished concentrations of NO, as a result of decreased eNOS, could lead to intestinal contractions which may precipitate an intestinal perforation. If ibuprofen has similar effects on eNOS to those reported for indomethacin, there may be a similar risk for intestinal perforations.

Clinically significant PDA occurs in approximately 30% of newborns weighing between 500 and 1500 grams and PDA closure remains a critical issue in the management of premature newborns. The left-to-right shunting that may result from a PDA can potentially lead to congestive heart failure, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis (NEC).[4] Early PDA closure in premature newborns has been shown to improve outcomes, including fewer incidences of PDA reopening and better mortality rates.[1] The spontaneous bowel perforation rate in extremely low birth weight infants is reported to be 8.4%, but may be increased with the use of NSAIDs in this population.[9] However, bowel perforations are just one of the risks associated with PDA closure via NSAID treatment.[10]

Surgical intervention, which is typically used for large PDAs, is an alternative to pharmacologic ligation, but it also poses risks to the infant. Hemorrhage, nerve and vessel damage, and infections are all concerns when electing to surgically ligate a PDA.[11] NEC and spontaneous bowel perforations are also a complication following surgical ligation. A comparison of indomethacin and surgical ligation for closure of PDA found no significant differences in the rates of NEC or isolated bowel perforation[12].

SUMMARY

The potential risks of any method need to be carefully considered when deciding to use pharmacologic closure or surgical ligation of a PDA. Practitioners should be aware that while not previously reported, there may be an increase in risk of bowel perforation following ibuprofen lysine administration.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

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