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Increased Risk of Necrotizing Enterocolitis in Premature Infants with Patent Ductus Arteriosus Treated with Indomethacin

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Objective
The authors evaluated the risk of necrotizing enterocolitis (NEC) in very low birth weight infants receiving indomethacin (INDO) to close patent ductus arteriosus (PDA).

Background Data
Controversy exists regarding the best method of managing very low birth weight infants with PDA and whether to employ medical management using INDO or surgical ligation of the ductus.

Methods
Two hundred fifty-two premature infants with symptomatic PDA were given intravenously INDO 0.2 mg/kg every 12 hours × 3 in an attempt to close the ductus. Patients were evaluated for sex, birth weight, gestational age, ductus closure, occurrence of NEC, bowel perforation, and mortality.

Results
There were 135 boys and 117 girls. The PDA closed or became asymptomatic in 224 cases (89%), whereas 28 (11%) required surgical ligation. Ninety infants (35%) developed evidence of NEC after INDO therapy. Fifty-six were managed medically; surgical intervention was required in 34 of 90 cases (37.8%) or 13% of the entire PDA/INDO study group. Bowel perforation was noted in 27 cases (30%). Factors associated with the onset of NEC included gestational age < 28 weeks, birth weight < 1 kg, and prolonged ventilator support. The overall mortality rate was 25.5%, but was higher in infants with NEC *versus* those without. The highest mortality was noted in perforated NEC cases. The PDA/INDO patients were compared with a control group of 764 infants with similar sex distribution, birth weights, and gestational ages without PDA who did not receive INDO. Necrotizing enterocolitis occurred in 105 of 764 control patients (13.7%), including 13 (12.3%) with perforation. The overall mortality rate for controls was 25%, which was similar to the overall 25.5% mortality rate in the PDA/INDO study group.

Conclusion
These data indicate that there is increased risk of NEC and bowel perforation in premature infants with PDA receiving INDO. Mortality was higher in the PDA/INDO group with NEC than those PDA/INDO infants without NEC.

Very low birth weight infants with respiratory distress syndrome and hypoxemia frequently demonstrate continued patency of the ductus arteriosus.[1-3] Infants that develop a significant left-to-right shunt through the ductus are at risk for heart failure development, further aggravating the already-present respiratory embarrassment, and tend to require prolonged ventilator support, have an increased risk of infection and bronchopulmonary dysplasia.[4] Patent ductus arteriosus (PDA) also is associated with an increased risk of necrotizing enterocolitis (NEC), resulting from diminished perfusion of the gastrointestinal tract.[4,5] There is some controversy as to the most appropriate treatment for very low birth weight infants with PDA; however, treatment with indomethacin (INDO; a nonsteroidal anti-inflammatory agent, prostaglandin inhibitor, and potent vasoconstrictor) has been a useful method of achieving pharmacologic closure of the PDA.[1-4] Although INDO treatment is highly effective, it may be associated with a number of complications, including alterations in cerebral blood flow, renal dysfunction, prolonged bleeding time, and a number of gastrointestinal complications including gastrointestinal bleeding, isolated ileal perforation, gastric perforations, and NEC.[4-13] This report evaluates the efficacy of INDO therapy and the risk of developing NEC in premature infants with PDA.[1-4]

MATERIALS AND METHODS

Two hundred fifty-two premature infants with PDA were treated at the James Whitcomb Riley Hospital for Children at Indiana University Medical Center from January 1990 through May 1995. The diagnosis of PDA was suspected by the presence of bounding peripheral pulses, and confirmed by two-dimensional Doppler echocardiography. A continuous systolic murmur sometimes was apparent on auscultation. Patients were evaluated for sex, birth weight, gestational age, response to INDO, occurrence of NEC, incidence of perforation, duration of ventilator support, and mortality. Data were evaluated by chi-square analysis, with a p value < 0.05 considered statistically significant.

RESULTS

There were 135 boys and 117 girls. Between 3 and 7 days of age, infants were given intravenously INDO sodium trihydrate 0.2 mg/kg every 12 hours × 3. Each dose was slowly administered intravenously for a period of 20 to 30 minutes. Closure was determined by resolution of clinical findings, echocardiography, or both. Further courses of INDO were considered if a large left-to-right shunt persisted on echocardiography. Surgical therapy (ligation) was initiated if the PDA remained patent after two courses or adverse events related to treatment occurred. Patent ductus arteriosus closure or near closure occurred after INDO therapy in 224 cases (89%), whereas surgical ligation was necessary in 28 (11%). In 90 infants (45 boys and 45 girls; 35%), clinical evidence of NEC developed (pneumatosis intestinalis, fixed bowel loops, free-air on abdominal roentgenogram, thrombocytopenia, rectal bleeding). Fifty-six of the 90 infants were managed medically, and surgical intervention was required in 34 patients (37.5%). These patients represented 13.5% of the entire PDA/INDO study group. Bowel perforation was noted in 27 cases (30%). Necrotizing enterocolitis developed in 9 of the 28 infants requiring ligation of PDA.

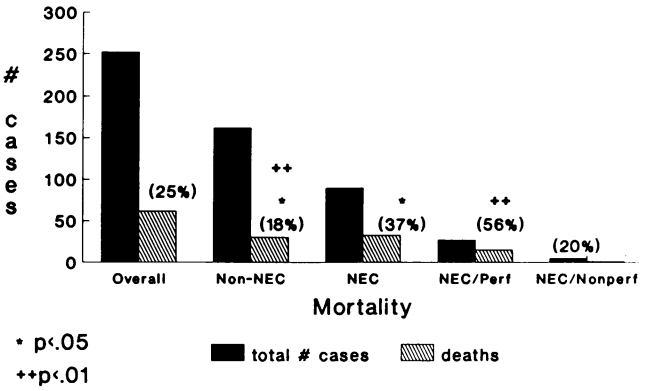

Figure 1. Bar graph demonstrates that there was an increased mortality in indomethacin-treated infants with patent ductus arteriosus (PDA) in whom necrotizing enterocolitis (NEC) developed when compared with infants without NEC. The mortality rate in infants with perforation was 56%.

Factors associated with the onset of NEC included gestational age (26.9 ± 0.27 weeks for infants with NEC *vs.* 28.1 ± 0.20 weeks for those without NEC; $p < 0.04$), birth weight (936.82 ± 38.8 g for infants with NEC *vs.* 1128.56 ± 38.9 g for those without NEC; $p < 0.001$), and prolonged ventilator support (46.7 ± 3.1 days for infants with NEC *vs.* 34.8 ± 3.19 days for those without NEC; $p < 0.02$). The overall mortality rate in the PDA/INDO group was 25% (63/252), but was higher in infants with NEC (37%; 33/90) *versus* those without (18%; 39/162; $p < 0.003$; Fig. 1). The highest mortality rate was noted in perforated NEC cases (56%; 15/27; $p < 0.01$). Four of nine infants in whom NEC developed after ligation of PDA died (44.4%); 7 of 19 (39.2%) infants without NEC also died after PDA ligation.

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Table 1. PATIENT CHARACTERISTICS: PATENT DUCTUS ARTERIOSUS/ INDOMETHACIN *VERSUS* NO PATENT DUCTUS ARTERIOSUS/INDOMETHACIN

Factor	PDA/Indomethacin	No PDA/ Indomethacin
No. of patients	252	764
Sex [no. (%)]		
Boys	135 (53.6)	432 (56.5)
Girls	117 (46.4)	332 (43.5)
Gestational age (wk)	27.8 ± 2.3	28.7 ± 2.3
Birth weight (g)	1032 ± 69	1061 ± 258

PDA = patent ductus arteriosus.

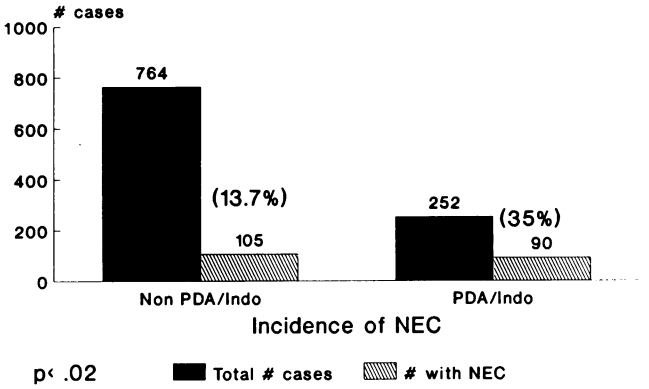

Figure 2. Bar graph demonstrates that there is an increased risk of necrotizing enterocolitis (NEC) in infants with patent ductus arteriosus (PDA) treated with indomethacin (INDO; 35%) *vs.* a 13% incidence of NEC in infants without PDA not treated with INDO.

The PDA/INDO-treated patients then were compared with another control group consisting of 764 premature infants who did not have PDA or did not receive INDO who were treated in the neonatal intensive care facility during the same time frame as the study group. There were 302 girls (43.5%) and 432 boys (56.5%), which is very similar to the sex distribution in the study group (46.4% girls; 53.6% boys). Additionally, the mean gestational age in this latter group was 28.7 ± 0.25 weeks, and the mean birth weight was 1061 ± 30.15 g, which also was similar to the study group (Table 1). Infants without PDA had a shorter duration of ventilator support, with a mean value of 27.38 ± 0.34 days compared with 46.7 ± 3.1 days in the PDA/INDO study group ($p < 0.05$). Hospital length of stay was 53.01 ± 4.8 days for the control group *versus* 77.63 ± 5.4 days for infants with PDA. The overall mortality rate in the control group was 25.5% (195/764), which is similar to the 25% mortality rate (63/252) noted in the study group. Necrotizing enterocolitis developed in 105 of 764 (13.7%) patients in the control group compared with a 35% incidence (90/252) in the study group ($p < 0.02$; Fig. 2). Thirty-nine of 105 control patients with NEC required surgical intervention, which is similar to the surgical intervention rate (34/90; 37%) in infants with PDA treated with INDO. Thirteen of 105 NEC control patients (12.3%) had a perforation, which is much lower than the 30% (27/90) incidence of perforation in the PDA/INDO-treated patients ($p < 0.05$; Table 2). However, the mortality in patients with NEC in the two groups was similar.

DISCUSSION

Very low birth weight infants have immature pulmonary function associated with decreased numbers of terminal bronchioles and alveoli and reduced levels of surfactant production from type II pneumocytes. These infants often require ventilatory support and are hypoxemic. Low arterial partial pressure of oxygen (pO_2) concentrations in the newborn influences the ductus arteriosus to remain patent. In many instances, a hemodynamically significant ductus arteriosus results in a number of problems, including a left-to-right shunt, heart failure, increased duration of ventilator dependency, an increased risk of bronchopulmonary dysplasia, and reduced blood flow to the mesenteric vascular bed.[1,2,4,12,13] Patency of the ductus arteriosus is much more common in infants of low gestational age and birth weight. Indomethacin has proven efficacy in regard to pharmacologic closure of PDA. This is confirmed in the current study, in which 89% of the patients with PDA had successful closure. Although closure of the PDA usually is achieved in the mature infant, INDO therapy has been less effective in the very low birth weight infant, both at the primary attempt at closure or after late reopening of the ductus.[4]

Table 2. INCIDENCE AND OUTCOME

Factor	PDA/ Indomethacin [no. (%)]	No PDA/Indomethacin [no. (%)]
Incidence	90/252 (35)*	105/764 (13.7)
Surgical therapy	34/90 (37.5)	39/105 (37.1)
Perforation	27/90 (30)*	13/105 (12.3)
Mortality		
Overall	63/252 (25)	195/764 (25.5)
NEC	33/90 (36.6)	33/105 (31.4)
Perforation	15/27 (56)	7/13 (53.8)

PDA = patent ductus arteriosus; NEC = necrotizing enterocolitis.
* $p < 0.05$.

Indomethacin is associated with a number of adverse effects, including diminished perfusion of the splanchnic bed with an observed 16% to 20% reduction of mesenteric blood flow.[14] Hypoperfusion of the gut with resultant mucosal hypoxia has been implicated in the occurrence of perforations of the stomach, small bowel, and colon, observed in infants receiving INDO.[5,7-10] In addition, NEC also is a significant complication of this form of therapy.[4,5,11-13] Indomethacin may be associated with intraventricular hemorrhage and renal dysfunction, resulting in decreasing glomerular filtration of free-water clearance associated with hyponatremia on a dilutional basis.[4,6] Although INDO is a prostaglandin inhibitor and impairs the synthesis of thromboxane-A-2, relatively few bleeding complications have been associated with its use.[4] At one time, the gastrointestinal complications were thought to be caused by enteral administration of INDO.[4,8] However, similar instances have been noted after intravenous administration of the drug. Very low birth weight infants are at risk for the occurrence of NEC from both the presence of the PDA itself and INDO treatment. Both may cause a reduction in mesenteric blood flow, resulting in hypoperfusion, mucosal hypoxia, ischemia, and ulceration, allowing bacterial invasion to occur.[4,8-10] Although INDO is a very effective medication and results in PDA closure in 89% of cases, these infants are at an increased risk of developing NEC. Cases of NEC that are complicated by perforation continue to have a very high mortality rate (56%).

Very low birth weight preterm infants have immaturity of numerous systems, including the lung, liver, kidney, and especially the immune system. Most premature infants weighing less than 1 kg are relatively immunodeficient.[15] They are particularly vulnerable to infection and have a significantly increased risk of systemic sepsis and death when compared with full-term infants.[15] Polymorphonuclear leukocytes of micropremature infants have diminished chemotaxis and decreased ability to opsonize bacteria. Diminished levels of properdin, severe immunoglobulin deficiency, absent immunoglobulin (Ig) A, low IgM levels, and diminished IgG levels also are found in these micropremature infants when compared with full-term infants.[15] The premature infant also has a relative depletion in the monocyte pool and decreased migration and differentiation into macrophages. Their polymorphonuclear leukocytes also function immaturely—they may have the ability to engulf bacteria, but they may not be able to destroy the organisms. Cell-mediated immunity is deficient in the newborn because of a relatively decreased exposure to antigens, resulting in antigen-specific incompetence. The more premature the infant, the greater the decrease in T-cell production of certain cytokines, which also may adversely influence the very low birth weight infant's ability to respond to any specific antigenic stimulus. The absence of IgA impairs the intestinal mucosal barrier of the premature infant's gastrointestinal tract. This reduces the ability of the mucosa to protect itself from adherence and invasion by microorganisms, leaving these infants at risk for bacterial translocation and systemic sepsis due to gut-derived organisms.[15]

Other factors that may influence the high mortality associated with bowel perforation in NEC patients include the presence of a sparse, flimsy omentum in the premature neonate that rarely can contain and localize infection because of a perforation. Intra-abdominal abscess is a rare event because patients require a functioning immune system to have abscess formation. Therefore, diffuse generalized peritonitis is commonplace in this age group. The ultimate demise of many of these patients is due to multiorgan dysfunction or failure.[16] Although survival of very low birth weight infants has improved as a result of the development of sophisticated neonatal intensive care, the mortality for the premature infant with gastrointestinal perforation and peritonitis remains high despite operative intervention, the use of appropriate antibiotics and nutritional support using total parenteral nutrition.[16] Mortality has reached a plateau for this subset of tiny patients, and little improvement in survival has been observed in recent years.[16]

Some authors have recommended that initial surgical ligation is the therapy of choice for the very low birth weight premature infant with PDA to avoid the complications associated with INDO administration.[17,18] However, this remains a controversial issue; Robie et al.[19] recently reported an increased risk of NEC after initial ductus ligation when compared with infants receiving INDO alone or before ligation. Although some studies suggest that INDO is less effective in the micropremature infant with PDA, the current study documents an 89% success rate after INDO treatment.[4,17,18]

This study shows that INDO therapy is a highly effective method of achieving ductus closure (89%). However, this treatment is associated with an increased risk of NEC and bowel perforation. The actual mortality rate for NEC is similar among preterm babies with PDA treated with INDO and age- and weight-matched controls. This most likely reflects the inability of the micropremature infant to respond to sepsis and generalized peritonitis because of an immature immune system. These observations suggest that very low birth weight infants with PDA in whom INDO therapy is planned may benefit from some type of prophylactic intervention, employing potentially protective immunomodulation to improve the immune status and hopefully reduce the risk of NEC. Halac et al.,[20] in a prospective study from Argentina, showed that maternally administered dexamethasone in 466 high-risk pregnancies significantly re-

duced the incidence of NEC postgestation. Gillan et al.[21] described the efficacy of recombinant human granulocyte colony-simulating factor in raising the peripheral polymorphonuclear leukocyte and macrophage counts and reducing the incidence of systemic sepsis in high risk premature infants. In a series of experiments concerning gut-derived sepsis, Gennari et al.[22] showed that granulocyte colony-simulating factor improved survival and gut barrier function. In another prospective clinical study, Eibl and colleagues[23] showed that adding exogenous immunoglobulins IgA and IgG to the enteral diets of infants at risk prevented the occurrence of NEC. Laboratory studies by Maxson et al.[24] further document the benefit of exogenous IgA in improving the bowel mucosal barrier and reducing the incidence of bacterial translocation. A number of recent experimental studies document the efficacy and versatility of the cytokine interleukin-11, a bone marrow-derived growth factor that 1) stimulates myelopoiesis resulting in increased production of polymorphonuclear leukocytes and platelets, 2) has a trophic effect on bowel mucosal adaptation in short-bowel syndrome, 3) protects the bowel lining after cytoablative chemoradiation, 4) reduces mortality and preserves intestinal cytoarchitecture in bowel ischemia, and 5) reduces mortality, bone marrow suppression, and bacterial translocation in major burns.[25-28]

In addition, both experimental and preliminary clinical studies have demonstrated that ibuprofen (also a nonsteroidal anti-inflammatory drug) at 10 mg/kg taken intravenously × 3 reduces the incidence of PDA in preterm neonates.[29,30] Ibuprofen also is efficacious in improving survival of laboratory animals with experimental bowel ischemia in contrast to the findings noted with INDO treatment.[14] Although these adjuncts may have potential utility in low birth weight infants at risk for NEC, carefully controlled prospective multicenter studies must be performed to confirm their efficacy before recommending their clinical use.

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Discussion

DR. JAMES A. O'NEILL, JR. (Nashville, Tennessee): I must say I thought that the question about whether indomethacin increases the incidence of necrotizing enterocolitis in preterm infants with patent ductus had been answered negatively until I read this paper.

The first reported use of this drug was just 20 years ago. In 1978, Cotton, Stahlman, and Harvey Bender of this Association from Vanderbilt reported the first randomized trial of surgery *versus* indomethacin, and in that study found no increased incidence of necrotizing enterocolitis (NEC) over the 3% to 6% incidence of that disorder in preemies which our group reported to this Association from that same institution in 1976.

In 1983 a multicenter prospective randomized trial was done. [Slide] In this you see usual medical therapy, usual medical therapy and surgery, usual medical therapy/indomethacin. The percentage incidence of NEC was 6% in all groups so there was no increased incidence or correlation with indomethacin and there was no difference whether the infants were large or small, at least in terms of 1000 g. In 1987, Cotton reported the prophylactic use of indomethacin in 32 patients, and there were no instances of NEC.

Nonetheless, during this time, there have been many reports of isolated perforations, suggesting that the modest decreases in superior mesenteric flow, which have been noted by the Dutch and others in recent studies in the last couple of years, suggest that this is a phenomenon more of localized or regional ischemia than generalized ischemia associated with NEC. These questions then come to mind:

Dr. Grosfeld, your institution was part of that multi-institution study along with ours. Why are you now seeing an increase in the incidence of NEC whereas you did not before? The age and weight of the populations appear to have been identical.

Number two, and perhaps most importantly, is this a dose effect? Reports over the last 2 years from the obstetric literature, where indomethacin is used as a tocolytic agent and the fetus is exposed to massive doses of indomethacin, report a very large incidence of necrotizing enterocolitis. Your group uses O.2 mg/kg × 3. Our group uses only the one dose at the beginning and then 0.1, or half of that, after that, and now only one dose.

Is it one of the periodic variations we see in the incidence of this disorder or perhaps a special pathogen effect? Your incidence of 14% overall is more than twice what most of us are currently seeing. Thirty-five percent of patients with patent ductus and NEC treated with and indomethacin is well above the 6% to 8% reported elsewhere. So do you have a special population?

Regardless of my questions, which really relate to mechanisms, you and your group have highlighted an important phenomenon. We are indebted to you for reporting this remarkably large experience and excellent mortality, and for analyzing it so well.

DR. ARNOLD G. CORAN (Ann Arbor, Michigan): Dr. Grosfeld has shown us in this presentation that premature infants with a patent ductus arteriosus (PDA) treated with indomethacin developed necrotizing enterocolitis (NEC) at a higher frequency than a comparable group of premature infants without PDA. This higher incidence was also associated with a higher perforation rate. However, the mortality in this group of infants was not increased.

In our children's hospital, the C. S. Mott Children's Hospital at the University of Michigan, we see approximately 30 cases each year of NEC in premature infants out of 400 premature admissions to our neonatal intensive care unit; the overall admission rate being approximately 700 to 800. Two thirds are treated medically and one third require surgery. We also treat 90 premature infants with hemodynamically significant PDAs per year, of which approximately 80 are effectively closed with indomethacin and 10 require a subsequent surgical ligation. These data, as you can see, are quite similar to the data presented by Dr. Grosfeld.

However, the incidence of NEC in this latter group of babies with PDA treated with indomethacin is not much higher than that seen in the general population of premature infants in our neonatal intensive care unit, namely somewhere around 10% to 12%. In addition, the incidence of NEC in the babies undergoing subsequent PDA ligation was the same as those treated solely with indomethacin. This was also true in Dr. Grosfeld's series. I calculated these numbers from his data, and the incidence of NEC after PDA ligation was 9 of 28, or 35%, the same as the incidence of NEC in the indomethacin group.

The real question one needs to answer is whether treatment with indomethacin is a separate risk factor for the development of NEC in premature infants with PDA? It could well be that NEC develops in premature infants with PDA regardless of the therapy used for the ductus.

One could explain this physiologically on the basis of major mesenteric ischemia secondary to the steal created by the large left-to-right shunt through the PDA. In fact, this is my own personal bias. Dr. Grosfeld implies in his paper that indomethacin is the culprit. However, I do not believe his data can completely support that contention.

Obviously the best way to answer this question is to carry out a large prospective study in which premature infants with PDA would be stratified on the basis of the number of courses and doses of indomethacin they receive. However, I believe the data presented today could also be used to answer this question by