

Closure of Patent Ductus Arteriosus With Oral Ibuprofen Suspension in Premature Newborns: A Pilot Study

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ABSTRACT. *Objective.* Patent ductus arteriosus (PDA), a common finding among premature infants, is conventionally treated by intravenous indomethacin. Intravenous ibuprofen was recently shown to be as effective and to have fewer adverse reactions in preterm infants. If equally effective, then oral ibuprofen for PDA closure would have several important advantages over the intravenous route. This study was designed to determine whether oral ibuprofen treatment is efficacious and safe in closure of a PDA in premature infants with respiratory distress syndrome.

Methods. Twenty-two preterm newborns (gestational age: 27.5 ± 1.75 [range: 23.9–31 weeks]; weight: 979 ± 266 [range: 380–1500 g]) with PDA and respiratory distress syndrome were studied prospectively. They received oral ibuprofen suspension 10 mg/kg/body weight for the first dose, followed at 24-hour intervals by 2 additional doses of 5 mg/kg each, if needed, starting on the second day of life. Echocardiography was performed before treatment and 24 hours after each dose. Every child underwent cranial ultrasonography before and after each ibuprofen dose. The rate of ductal closure, the need for additional treatment, side effects, complications, and the infants' clinical courses were recorded.

Results. Ductal closure was achieved in all newborns except for 1 (95.5%), in whom clinically nonsignificant ductal shunting persisted. No infant required surgical ligation of the ductus. There was no reopening of the ductus after closure had been achieved. Fourteen newborns were treated with 1 dose of ibuprofen, 6 were treated with 2 doses, and the remaining 2 were treated with 3 doses. The survival rate at 1 month was 86.4% (19 of 22). Three (13.6%) infants died from the following causes: 1 who was born at 24 weeks' gestation with a birth weight of 380 g died as a result of extreme prematurity complications, necrotizing enterocolitis, and low birth weight; 1 died as a result of *Candida* sepsis; and the third died as a result of *Klebsiella* sepsis. Intraventricular hemorrhage was observed in 7 infants. The classification was changed from grade 2 to grade 3 in 1 and from grade 0 to grade 1 or higher in 3 others. The rate of survival to discharge was 86.4% (19 of 22). No bronchopulmonary dysplasia was observed in the study group, and there was no case of tendency to bleed. There were no significant

differences in the levels of serum creatinine before and after treatment with oral ibuprofen.

Conclusions. Oral ibuprofen suspension may be an effective and safe alternative for PDA closure in premature infants with PDA. However, larger comparative studies are warranted. *Pediatrics* 2003;112:e354–e358. URL: <http://www.pediatrics.org/cgi/content/full/112/5/e354>; oral ibuprofen, patent ductus arteriosus, premature newborns.

ABBREVIATIONS. PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

The incidence of patent ductus arteriosus (PDA) in premature infants who weigh between 500 and 1500 g at birth is approximately 30% on the third day of life.¹ Closure is often warranted in preterm infants with respiratory distress syndrome (RDS), as significant left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, and death.^{2,3} Pharmacologic closure of the ductus arteriosus in premature infants with symptomatic left-to-right shunting has been shown to decrease morbidity.^{4,5} Indomethacin, a prostaglandin synthesis inhibitor, has been used widely in the prophylaxis and treatment of hemodynamically significant PDA.^{6,7} Treatment with indomethacin, however, may be associated with adverse reactions, such as reduced renal,⁸ mesenteric,^{9,10} and cerebral perfusion.^{11–14} Decreased perfusion to these vascular beds may lead to renal dysfunction, NEC, gastrointestinal hemorrhage, and IVH or periventricular leukomalacia. Ibuprofen, another prostaglandin synthesis inhibitor, has been shown to be as effective as indomethacin in ductal closure by several investigators who administered it intravenously.^{15–17} In contrast to indomethacin, ibuprofen does not affect basal cerebral blood flow,^{16–21} cerebral metabolic rate,^{18,20} or intestinal or renal hemodynamics.^{17,22}

If it could be shown to be as efficacious and as safe as the intravenous route, then oral ibuprofen would afford several important advantages: 1) intravenous ibuprofen is not available in the United States or in many other countries, 2) the required oral dose is of minimal volume (0.25–0.5 mL for infants who weigh 500–1000 g), 3) oral administration is extremely simple, and 4) the oral form of the drug is less expensive than the intravenous one. This study was designed to determine whether oral ibuprofen treatment is effi-

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cacious and safe in closure of a PDA in premature infants with RDS.

METHODS

Twenty-two premature newborns who were treated at the neonatal intensive care unit at the Assaf Harofeh Medical Center between November 2000 and April 2002 were recruited prospectively. The study was approved by the ethics committee of the Ministry of Health, and the infants were enrolled in the study only after written parental consent had been obtained.

Neonates who were admitted to the study were enrolled when the following criteria were met: 1) gestational age <32 weeks and <1500 g; 2) postnatal age between 48 and 96 hours; 3) RDS on chest radiograph necessitating treatment with surfactant, mechanical ventilation, and need for oxygen supplementation above 25%; and 4) echocardiographic evidence of hemodynamically significant PDA (left atrium/aortic root diameter ratio >1.4 or ductal size >1.5 mm).²³ Exclusion criteria included the presence of major congenital anomalies, IVH of grade 3 according to the classification by Papile et al²⁴ within the previous 24 hours, serum creatinine level ≥ 1.5 mg%, serum urea nitrogen concentration >50 mg%, platelet count $\leq 60\,000/\text{mL}^3$, a tendency to bleed (defined by the presence of hematuria, blood in the endotracheal aspirate, gastric aspirate, or stools and/or oozing from puncture sites), or hyperbilirubinemia necessitating exchange transfusion.

Study Design

All infants who were born between November 2000 and April 2002 and met the entry criteria first underwent echocardiography and cranial ultrasonography, after which they were treated with ibuprofen (Nurofen for children, Boots Healthcare International, Nottingham, England) 10 mg/kg administered through a feeding tube. The 2 imaging procedures were again performed 24 hours after each ibuprofen dose. When the PDA was still hemodynamically significant, as demonstrated by echocardiography, and there was no evidence of deterioration in brain ultrasonography, a second dose of ibuprofen 5 mg/kg was administered. A third equivalent dose was given after another 24 hours if deemed necessary. Cranial ultrasound was repeated 1 week after the last ibuprofen dose and again before discharge from the ward. Hematochemical analyses were performed daily in the unit during the first days of life.

RDS was treated with respiratory support (intermittent mechanical ventilation or high-frequency ventilation), oxygen supplements, and surfactant (Curosurf, Teva Group, Phospholipid fraction from porcine lung 80 mg/ml) 100 mg/kg. Treatment of PDA in preterm infants with RDS is indicated before a significant left-to-right shunting occurs.^{2,5} Surfactant was administered during the first 24 hours on the basis of the need for oxygen and respiratory support, ie, fraction of inspired oxygen $\geq 40\%$ and mean airway pressure of ≥ 8 , and chest radiographs compatible with the diagnosis of RDS. Prophylactic antibiotics were started on admission and stopped after 5 days if blood cultures were negative. Birth weight, gestational age, and clinical outcomes were recorded prospectively.

Echocardiography

Color Doppler echocardiography (Ving Med Sound Flex Scan T57S Color Display Monitor, System 5, Transducer FPA 10 MHz; GE Ultrasound, Horton, Norway) was performed on all infants who were clinically suspected of having PDA. This was conducted by a technician under the supervision of a cardiologist who was blind to the child's name and the treatment being given. Patients with clinical signs of PDA such as tachycardia (>160 beats/min), presence of a murmur, and bounding pulses were eligible for the study and underwent an echocardiographic evaluation before entry to the study.¹⁶ PDA was considered echocardiographically significant when the ductal size was >1.5 mm or the left atrial-to-aortic root ratio was >1.4. We evaluated these parameters before the first dose and 24 hours after each dose of ibuprofen, never exceeding 3 doses in total.

Cranial Ultrasonography

Cranial ultrasound scans were performed before treatment was started, after each dose of ibuprofen, before any additional doses,

1 week after the last dose, and before discharge from the ward. The study infants were assessed for IVH (grades 1–4) and for periventricular leukomalacia (grades 1–3), which were graded according to standard classification systems.^{24–26}

Statistical Analysis

Continuous data, such as weight, gestational age, various treatment modalities, IVH, and age at start of treatment, are presented as mean \pm standard deviation. Changes in serum creatinine concentrations were compared using *t* test.

RESULTS

A total of 117 premature infants at gestational age <32 weeks and birth weight <1500 g were born in the Assaf Harofeh Medical Center neonatal intensive care unit during the study period. Fifty-two of them were eligible for entry in the study and underwent an echocardiographic-Doppler ultrasound evaluation at the age of 48 to 96 hours. Thirty infants were excluded because of spontaneous ductal closure or PDA with minor shunting.

Fluid intake began at 70 to 80 mL/kg/d and was increased by 20 to 30 mL/kg/d to a maximum of 160 mL/kg/d by the end of the first week, adjusted according to body weight. Most patients received packed red blood cells as well as fresh-frozen plasma transfusion. Hypotension was treated with fluid replacement. Dopamine was used in cases in which fluid treatment failed. Furosemide was not used during the first week of life.

The baseline characteristics of the 22 studied premature infants are presented in Table 1. The rate of PDA closure was 95.5% (21 of 22 cases). There was no reopening of the ductus after closure had been achieved. No infant required surgical ligation of the ductus (Table 2). Fourteen newborns were treated with 1 dose of ibuprofen, 6 were treated with 2 doses, and the remaining 2 were treated with 3 doses.

Outcome and Side Effects

The survival rate at 1 month was 86.4% (19 of 22; Table 3). The causes of death are as follows: 1 infant

TABLE 1. Baseline Characteristics of the Study Infants

Birth weight (g)	979 \pm 266 (range: 380–1500)
Gestational age (wk)	27.4 \pm 1.7 (range: 24–31)
<26	4
27–28	14
29–30	2
31	2
Antenatal indomethacin (<i>n</i>)	0
Antenatal glucocorticoids (<i>n</i>)	9
Surfactant treatment (<i>n</i>)	11
1 dose	4
2 doses	7
3 doses	2
High-frequency oscillatory ventilation (<i>n</i>)	6 (27.3%)
Mean airway pressure (cm H ₂ O)	9.8 \pm 1.9 (range: 7–13)
Inspired oxygen (%)	40 \pm 13 (range: 25–70)
IVH (<i>n</i>)	
Grade 1	3 (13.6%)
Grade 2	2 (9%)
Grade 3	2 (9%)
Ductal diameter (mm)	2.1 \pm 0.79 (range: 1.5–3.9)
Degree of ductal shunting (<i>n</i>)	
Moderate	17 (77.3%)
Severe	5 (22.7%)

TABLE 2. Efficacy of Treatment by Ibuprofen

Variable	
Age at start of treatment (d)	2.5 ± 0.6 (range: 2–4)
No. of closed PDA (%)	21/22 (95.5%)
No. of ibuprofen doses	1.45 ± 0.67 (range: 1–3)
Surgical ligation	0

TABLE 3. Outcome of the Study Infants (*n* = 22)

Variable	<i>N</i>
Death within 30 d (<i>n</i>)	3
NEC (<i>n</i>)	1
Localized bowel perforation (<i>n</i>)	0
Sepsis (<i>n</i>)	4
Extension of IVH during treatment (<i>n</i>)	
Change from grade 1 to grade 2	0
Change from grade 2 to grade 3	1
Change from grade 2 to grade 4	0
Change from grade 0 to grade 1 or higher	3
PVL (<i>n</i>)	3
Grade 1 (flaring after d 7)	1
Grade 2	2
Grade 3 (cystic)	0
Respiratory outcome	
BPD (<i>n</i>)	0
IPPV (d)	mean 11 (range: 3–62)
CPAP (d)	0
Time to regain birth weight (d)	14.8 ± 4.5 (range: 7–23)
Time to full enteral feeding (d)	19.3 ± 6.1 (range: 12–28)

PVL indicates periventricular leukomalacia; BPD, bronchopulmonary dysplasia; IPPV, intermittent positive pressure ventilation; CPAP, continuous positive airway pressure.

who was born at 24 weeks' gestation with a birth weight of 380 g died at the 17 days of age of complications related to extreme prematurity, NEC, and low birth weight; 1 died at 14 days of age as a result of *Candida* sepsis; and the third died at the age of 30 days of age as a result of *Klebsiella* sepsis. Two of the 4 newborns who developed sepsis survived. The rate of survival to discharge was 86.4% (19 of 22; Table 3). No bronchopulmonary dysplasia (oxygen support at 36 weeks of age)²⁷ was observed in the study group, and there was no case of tendency to bleed.

Renal Function

There were no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen (*P* = .35; Table 4).

DISCUSSION

Intravenous ibuprofen has been shown to be as effective as indomethacin in PDA closure.^{15–17} If treatment with oral ibuprofen is both effective and

safe, then it would have the advantages of more widespread availability, simpler administration, and decreased cost. The primary objective of the current study was to determine whether orally administered ibuprofen treatment is efficacious in PDA closure in premature infants with RDS. Our results showed oral ibuprofen to be effective and safe in PDA closure, with 21 of our 22 (95.5%) study infants achieving a successful outcome. This frequency of closure is significantly higher than the 70% figure reported by Van Overmeire's group¹⁷ (*P* = .015), where ibuprofen was administered intravenously, and also significantly higher compared with other studies in which indomethacin was administered for PDA closure with a reported ductal closure rate of between 71% and 77%.^{3,28} Because ductal closure was achieved in all of our infants but 1—and that patient's residual defect was clinically nonsignificant—there was no need for rescue therapy or surgery.

Ibuprofen plasma levels were not measured in our patients. However, ibuprofen pharmacokinetics has been studied among preterm infants with PDA after intravenous administration²⁹ and a large interindividual variability in pharmacokinetics was observed. The peak plasma ibuprofen concentrations after the first and third doses and the pharmacokinetics in the group of patients in whom ductal closure was achieved after treatment were compared with the same parameters in those who did not achieve ductus closure. The results demonstrated that no significant changes for any of the studied parameters could be observed.²⁹ It was concluded that "further studies are needed to identify concentration/ductal response relationship and to clarify the underlying mechanisms of the observed changes."²⁹

The pharmacokinetics of oral ibuprofen among preterm infants and infants older than 3 months have been studied and reported.^{30–32} The findings indicate that ibuprofen is absorbed rapidly after oral administration, and peak concentrations in plasma are observed after 1 to 2 hours. Among infants older than 3 months, the age of the child does not significantly influence the rate of absorption of ibuprofen, the plasma concentration of the drug, or its rate of elimination. With oral administration of ibuprofen, a small interindividual variability in the pharmacokinetics of the drug is observed.^{30–32} It is possible, though, that the slower rate of oral ibuprofen absorption, together with the longer time to peak plasma levels, as compared with the intravenous route, and the prolonged time of contact and exposure of the ductus to ibuprofen, enables ibuprofen to exert its

TABLE 4. Changes in Serum Creatinine (mg/dL)

Day 1 (24 h after ibuprofen administration)	0.87 ± 0.15 (range: 0.7–1.4) 95% CI: 0.8–0.94
Day 2 (48 h after ibuprofen administration)	0.91 ± 0.15 (range: 0.68–1.29) 95% CI: 0.83–0.98
Day 3 (72 h after ibuprofen administration)	0.8 ± 0.14 (range: 0.65–1.2) 95% CI: 0.74–0.87
Pretreatment increase in serum creatinine from d 1 to d 3	<i>P</i> = .35
Comparison of creatinine between d 1 and d 2	<i>P</i> = .44
Comparison of creatinine between d 2 and d 3	<i>P</i> = .37

CI indicates confidence interval.

pharmacologic effect longer and with greater effect than the intravenous route.

Ibuprofen was administered orally in our study; therefore, there are theoretical concerns about direct gastrointestinal irritability. In our study, the drug was given undiluted through a feeding tube in a very small volume and followed by flushing with distilled water before final dilution in the stomach. The osmolarity of the ibuprofen suspension used in our study was 320 mosmol/L, and the pH was 5.5, both of which are not associated with gastrointestinal irritation. Most of the preterm infants in our study ($n = 14$) received only 1 dose of ibuprofen, 6 patients received 2 doses, and only 2 infants received 3 doses. The administration of several doses of ibuprofen as an antipyretic as presented and studied in other studies^{33,34} was not associated with significant gastrointestinal tract problems.

In the study by Raju et al,³² in which ibuprofen was administered orally or intravenously to 9 preterm infants for the prevention of bronchopulmonary dysplasia, the study drug was withdrawn in 1 infant after 8 days (15 doses) of treatment because of gastrointestinal hemorrhage that occurred 6 hours after the last dose. However, this infant also received steroids and aminophylline, which potentially can cause gastrointestinal bleeding, and it is not clear whether this infant received intravenous or oral ibuprofen.³² Furthermore, gastrointestinal adverse reactions have been observed among preterm and term infants whose mothers were treated with antenatal indomethacin without direct contact of the nonsteroidal anti-inflammatory drugs with the gastrointestinal tract of the newborn.^{35–37}

Serum creatinine levels in our patients were within normal range at all times, so there was no contraindication for a second or third dose of ibuprofen when it was needed. This might be an explanation for the higher rate of pharmacologic ductal closure observed in our study.

The infants in our study were less mature and had a lower birth weight than those reported by Van Overmeire's group¹⁷; however, they were not more clinically ill. The infant who died as a result of extreme prematurity (24th gestational week) and extreme low birth weight (380 g) had no deterioration in serum creatinine or in brain sonography, and only 1 dose of oral ibuprofen had been effective for ductal closure.

IVH was observed in 7 infants (Table 1). The classification was changed from grade 2 to grade 3 in 1 and from grade 0 to grade 1 or higher in 3 others (Table 3). IVH is a common complication during the first days of life in premature infants, and its presence or extension therefore might be the natural history of IVH or a complication of PDA in premature infants, and not necessarily related to ibuprofen treatment.

Gournay et al³⁸ described 3 cases of severe hypoxemia after intravenous ibuprofen administration during prophylactic treatment of PDA in premature infants who were born at <28 weeks of gestation within the first 6 hours after birth, which is earlier than that reported in most previous studies. Their 3

infants had been stable before the prophylactic drug was given and developed refractory hypoxemia within 1 hour after receiving the first dose. Echocardiographic examinations showed severely decreased pulmonary blood flow in all 3 cases. No incidents of severe hypoxemia or decreased pulmonary blood flow on echocardiographic examination after administration of the drug occurred among our study patients.

There are several limitations to our study. This was an open-label, one-arm study, and there was no matched control group. The physicians and nurses were aware of the nature of the study, although the cardiologist who supervised the echocardiographic studies was blind to the status of the infants and whether they were treated with oral ibuprofen. Intravenous ibuprofen has 100% bioavailability; the bioavailability of the oral ibuprofen administered in our study was not measured.

CONCLUSIONS

The results of our study on a small-sized population indicate that oral ibuprofen may be an effective and safe alternative to intravenous ibuprofen for PDA closure in premature infants. Larger comparative studies are needed to validate these findings.

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