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A COMPARISON OF IBUPROFEN AND INDOMETHACIN FOR CLOSURE OF PATENT DUCTUS ARTERIOSUS

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ABSTRACT

Background Indomethacin is the conventional treatment for patent ductus arteriosus in preterm infants. However, its use is associated with various side effects. In a prospective study, we compared ibuprofen and indomethacin with regard to efficacy and safety for the early treatment of patent ductus arteriosus in preterm infants.

Methods We studied 148 infants (gestational age, 24 to 32 weeks) who had the respiratory distress syndrome and an echocardiographically confirmed patent ductus arteriosus. The infants were randomly assigned at five neonatal intensive care centers to receive three intravenous doses of either indomethacin (0.2 mg per kilogram of body weight, given at 12-hour intervals) or ibuprofen (a first dose of 10 mg per kilogram, followed at 24-hour intervals by two doses of 5 mg per kilogram each), starting on the third day of life. The rate of ductal closure, the need for additional treatment, side effects, complications, and the infants' clinical course were recorded.

Results The rate of ductal closure was similar with the two treatments: ductal closure occurred in 49 of 74 infants given indomethacin (66 percent), and in 52 of 74 given ibuprofen (70 percent) (relative risk, 0.94; 95 percent confidence interval, 0.76 to 1.17; $P=0.41$). The numbers of infants who needed a second pharmacologic treatment or surgical ductal ligation did not differ significantly between the two groups. Oliguria occurred in 5 infants treated with ibuprofen and in 14 treated with indomethacin ($P=0.03$). There were no significant differences with respect to other side effects or complications.

Conclusions Ibuprofen therapy on the third day of life is as efficacious as indomethacin for the treatment of patent ductus arteriosus in preterm infants with the respiratory distress syndrome and is significantly less likely to induce oliguria. (N Engl J Med 2000;343:674-81.)

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PATENT ductus arteriosus remains a frequent problem in premature infants with the respiratory distress syndrome.¹⁻³ In a large network of neonatal intensive care units, the frequency of patent ductus arteriosus in infants weighing 501 to 1500 g was 31 percent.³ Substantial left-to-right shunting through the ductus may increase the risk of intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and death.^{4,5} Therefore, closure of the ductus is indicated. Intravenous indomethacin is the conventional pharmacologic treatment for promoting closure of a patent ductus in premature infants. However, concern remains regarding the safety of indomethacin, which affects renal, gastrointestinal, and cerebral perfusion and may lead to complications such as transient or permanent renal dysfunction,^{6,7} necrotizing enterocolitis, gastrointestinal hemorrhage,⁸ and reduced cerebral intracellular oxygenation.^{9,10}

Ibuprofen has been shown to close the ductus in animals¹¹ without affecting basal cerebral blood flow and intestinal or renal hemodynamics during positive-pressure ventilation,¹² and it has been shown to have different effects on regional circulation from those of indomethacin.¹³⁻¹⁵ Furthermore, ibuprofen enhanced cerebral blood-flow autoregulation and had some neuroprotective effects in animals subjected to oxidative stress.^{16,17} More recently, ibuprofen has been shown to be effective for the closure of patent ductus arteriosus in premature infants,¹⁸⁻²⁰ without reducing mesenteric,

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renal,²¹ or cerebral²² blood flow. These trials, however, included only a small number of infants. Therefore, we conducted a prospective, multicenter trial involving a larger number of patients. The primary objective was to compare the efficacy of ibuprofen with that of indomethacin in inducing closure of patent ductus arteriosus in premature infants with the respiratory distress syndrome. The comparison of the side effects in the two groups was a secondary objective.

METHODS

Patients

Five tertiary neonatal intensive care centers in Belgium participated in the trial (the University Hospital in Antwerp, the University Hospital in Ghent, Queen Paola Children's Hospital in Antwerp, Sint Jan Ziekenhuis in Bruges, and Clinique Saint Vincent in Rocourt). The study was approved by the medical ethics committee of each center. Neonates were enrolled after written informed consent was obtained from their parents. The criteria for enrollment were a gestational age of 32 weeks or less; an age of 2 to 4 days; echocardiographic evidence of patent ductus arteriosus; and the respiratory distress syndrome necessitating respiratory support (all received mechanical ventilation starting at birth). Exclusion criteria were major congenital anomalies; life-threatening infection or hydrops fetalis; recent intraventricular hemorrhage (within the previous 24 hours); urine output below 1 ml per kilogram of body weight per hour during the preceding 8 hours; a serum creatinine concentration of 1.6 mg per deciliter (140 μ mol per liter) or higher; a serum urea nitrogen concentration greater than 40 mg per deciliter (14 mmol per liter); a platelet count of 60,000 per cubic millimeter or less; a tendency to bleed, as revealed by hematuria, blood in the endotracheal aspirate, gastric aspirate, or stools, and oozing from puncture sites; and hyperbilirubinemia necessitating exchange transfusion.

Study Design

The infants at each unit were randomly assigned to a treatment group by means of cards in sealed opaque envelopes. Each infant received three doses of either indomethacin (Indocid I.V., Merck, West Point, Pa.; 0.2 mg per kilogram at 12-hour intervals) or ibuprofen (an initial dose of 10 mg per kilogram, followed by two doses of 5 mg per kilogram each, after 24 and 48 hours). The medications were infused continuously over a period of 15 minutes. The doses and intervals for ibuprofen were the same as in our earlier trial²⁰ and were in accordance with recommendations for use in infants and neonates that were based on preliminary pharmacodynamic data.^{23,24} Ibuprofen was prepared for intravenous use from a commercially available product intended for parenteral administration (Imbun I.M., Merckle, Blaubeuren, Germany), delivered in vials containing 400 mg of dry, sterile powder of ibuprofen as a lysine salt, corresponding to 234 mg of ibuprofen. The contents of one vial were aseptically reconstituted with 23.4 ml of water for injection, yielding a sterile and pyrogen-free solution of 10 mg of ibuprofen per milliliter. This solution was aseptically dispersed in pyrogen-free ampules containing 2 ml each. Chromatographic analysis showed no appreciable degradation of the product after three months when it was stored at -20°C . All vials were prepared in a single pharmacy and distributed to the participating centers.

When the ductus arteriosus was still patent after the randomly assigned treatment in a patient in either group who was receiving mechanical ventilation, indomethacin (three doses of 0.2 mg per kilogram at 12-hour intervals) was given as a nonrandomized rescue treatment. If this therapy also failed to promote ductal closure and the patient continued to receive mechanical ventilation, or if there was a contraindication to the second pharmacologic treatment, surgical ligation of the ductus was performed.

Echocardiography

In all infants, color Doppler echocardiography (Sonos 1500 imaging system, Hewlett-Packard, Andover, Mass., or Ultramark 4 Plus, Advanced Technology Laboratories, Bothell, Wash., with a 7.5-MHz or 10-MHz transducer) was performed by physicians who were unaware of the infants' treatment assignments. The purpose was to evaluate patency of the ductus arteriosus and shunting at the time of inclusion and after the last dose of the study drug was given. The internal ductal diameter, the maximal shunt velocity, the ratio of the diameter of the left atrium to that of the aortic root (left-atrium-to-aortic-root ratio), and the degree of shunting were recorded as described earlier.²⁵ Shunting was graded as moderate if a disturbed diastolic flow was easily detectable in the main pulmonary artery and there was a diastolic backflow in the aorta immediately beneath the ductus arteriosus and a forward flow above the ductal insertion; it was graded as severe if a diastolic backflow was easily detectable in the pulmonary trunk and in the aorta and if dilatation of the left atrium was present, with a left-atrium-to-aortic-root ratio above 1.6. The second evaluation was performed no more than 24 hours after the last dose of the assigned treatment. A third echocardiographic evaluation was performed to evaluate the effect of a second nonrandomized rescue treatment or whenever there was suspicion on clinical grounds that the ductus had reopened after closure.

Concomitant Treatment

Fluid intake was guided by the body weight, serum sodium concentration, and serum osmolality. For infants with a gestational age of 26 weeks or less, the daily fluid intake began at 80 ml per kilogram and was increased by 20 ml per kilogram each day to a maximum of 130 ml per kilogram per day. For infants with a gestational age of 27 or 28 weeks, the fluid intake began at 70 ml per kilogram, and for those with a gestational age of 29 weeks or more it began at 60 ml per kilogram, with increases of 10 ml per kilogram each day to a maximum of 120 ml per kilogram per day by the end of the first week. The use of furosemide was restricted during the first week. When there was hypotension refractory to fluid-replacement therapy, a dopamine infusion was started. For treatment of the respiratory distress syndrome, infants received respiratory support (conventional or primary high-frequency oscillatory ventilation), oxygen supplements, and early rescue therapy (given from 2 to 18 hours after birth; mean, 6 hours) with surfactant (Survanta, Abbott Laboratories, Brussels, Belgium, or Alvofact, Boehringer Ingelheim Pharma, Biberach an der Riss, Germany) in doses of 100 mg per kilogram. Prophylactic antibiotics were administered from admission to the neonatal intensive care unit and stopped after three to four days if the results of the bacterial cultures (of blood, tracheal aspirate, and urine) remained negative.

Clinical Course and Outcome

Biologic data, demographic information, and clinical outcomes, including death, were prospectively recorded on data sheets especially designed for this study.

The dose of antenatal indomethacin or glucocorticoid treatment and the interval between the administration of the last antenatal dose and delivery were noted. Gestational age, birth weight, daily fluid intake, urine production, and body weight were also recorded. Urine was collected in adhesive urine bags. Oliguria was defined as a urine output of 1 ml per kilogram per hour or less during a 24-hour collection period. A tendency to bleed was defined according to the criteria used for exclusion from the study. During the first week, urine was screened daily for microscopic hematuria with use of a color-reagent test strip (Multistix, Bayer, Tarrytown, N.Y.). When the test strip indicated more than 5 to 20 red cells per microliter of urine, or when microscopy revealed more than 5 red cells per microliter, microscopic hematuria was diagnosed.

Cranial ultrasound scans were performed during the first three to four days of life, at the end of the first week, and weekly thereafter. All five centers used similar techniques. Infants were assessed

for intraventricular hemorrhage (grade 1 to 4) and for periventricular leukomalacia (grade 1 to 3), which were graded according to standard classification systems (higher grades indicated greater severity).²⁶⁻²⁸ The serum creatinine concentration, serum sodium concentration, hematocrit, and platelet count were recorded during the first week.

The outcome in surviving patients was evaluated on the basis of clinical symptoms, the need for respiratory support (days during which mechanical ventilation and supplemental oxygen were needed), and the time required for the infant to regain his or her birth weight and to be ready for full enteral feeding. Bronchopulmonary dysplasia was defined by the need for supplemental oxygen after 28 days of life, in association with typical radiographic findings. Necrotizing enterocolitis was diagnosed when the clinical signs and radiographic findings generally accepted as characteristic of this condition were present.²⁹

Statistical Analysis

We calculated that a study group of 140 neonates would be necessary for the study to be able to detect a difference of at least 20 percentage points in the closure rate between the ibuprofen and indomethacin groups, assuming a closure rate of 80 percent with indomethacin, with a P value of 0.05 and a power of 80 percent. The t-test, Mann-Whitney U test, and chi-square test or Fisher's exact test were used to compare continuous normally distributed data, nonparametric continuous data, and categorical data, respectively. All reported P values are two-tailed.

To assess the occurrence of side effects in the groups, repeated-measures analysis of variance was performed, with time as the within-subject variable and treatment allocation as the between-subject variable. To evaluate the difference in the rates of death, we performed Kaplan-Meier analysis with log-rank testing. Relative risks were used to indicate the efficacy of treatment and odds ratios to evaluate the probability of ductal closure. Multiple logistic regression was performed to assess the influence of predictive factors on the rate of closure of the ductus and the occurrence of oliguria; the factors we analyzed were sex, birth weight, gestational age, use or nonuse of antenatal glucocorticoid or indomethacin therapy, assignment to indomethacin or ibuprofen, the degree of increase in the serum creatinine concentration before treatment for patent ductus arteriosus, fluid balance and respiratory status before treatment, ductal diameter, maximal velocity of the left-to-right ductal shunt, severity of shunting before treatment, and use or nonuse of high-frequency oscillatory ventilation. We used Statistica '99 software (StatSoft, Tulsa, Okla.) and SPSS software (version 9.0, SPSS, Chicago).

RESULTS

Efficacy of Treatment

We studied 148 infants, 74 of whom were assigned to each group. There was no significant difference between the two groups in base-line clinical and echocardiographic characteristics (Table 1). The rate of closure of the patent ductus arteriosus was similar in the indomethacin and ibuprofen groups, as was the need for rescue treatment (Table 2). No reopening of the ductus after closure was observed. The ductus was surgically ligated because of the presence of contraindications to a second pharmacologic treatment in four infants in the indomethacin group and in three infants in the ibuprofen group. The final numbers of infants who underwent ductal ligation for any reason were also similar in the two groups (Table 2). If there was only minor ductal shunting after therapy in a patient who did not require respiratory support, no further treatment of the ductus was attempted; in all such cases the ductus closed spontaneously before discharge.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE INFANTS.*

CHARACTERISTIC	INDOMETHACIN GROUP (N=74)	IBUPROFEN GROUP (N=74)
Birth weight (g)	1230±380	1230±390
Gestational age (wk)	29.0±2.1	29.0±2.3
Gestational-age category (no.)		
≤26 wk	10	13
27-28 wk	17	18
29-30 wk	22	23
31-32 wk	25	20
Antenatal indomethacin (no.)	11	13
Antenatal glucocorticoids (no.)	33	38
Surfactant treatment (no.)	63	56
1 Dose	25	21
2 Doses	24	22
≥3 Doses	14	13
High-frequency oscillatory ventilation (no.)	31	30
Mean airway pressure (cm of water)†	9.0±2.7	9.8±3.0
Inspired oxygen (%)†	41.7±15.3	42.1±14.8
Intraventricular hemorrhage (no.)		
Grade 1	10	4
Grade 2	7	9
Grade 3	3	2
Ductal diameter (mm)†	2.5±0.7	2.5±0.9
Maximal shunt velocity (m/sec)†	1.52±0.49	1.53±0.57
Left-atrium-to-aortic-root ratio†	1.54±0.25	1.55±0.26
Degree of ductal shunting (no.)†		
Moderate	44	46
Severe	30	28

*Plus-minus values are means ±SD. There were no significant differences between the groups.

†Values are for the day on which treatment began (the third day of life).

Four factors were shown to be significant independent predictors of the failure of pharmacologic treatment for patent ductus arteriosus (Table 3). In centers that preferentially used high-frequency oscillatory ventilation, overall rates of ductal closure were lower than in other centers. However, in each center the efficacy of indomethacin and ibuprofen remained similar. When patients were stratified according to the four categories of gestational age, closure was found to be less likely to occur in the lowest gestational-age category (≤26 weeks) but there was no difference in effect between the drugs within each category. The antenatal use of indomethacin as a tocolytic agent and a lower ductal shunt velocity on the third day of life (the latter reflecting a higher pulmonary arterial pressure) were independently associated with treatment failure.

Outcome and Side Effects

Survival at one month was similar in the two groups (P=0.76) (Fig. 1). The most common causes of death were refractory hypoxemia and overwhelming sepsis. There was no significant difference between the treat-

TABLE 2. EFFICACY OF TREATMENT.*

VARIABLE AND OUTCOME	INDOMETHACIN GROUP (N=74)	IBUPROFEN GROUP (N=74)	P VALUE	RELATIVE RISK (95% CI)
Randomly assigned treatment				
Age at start of treatment — days	3.1±0.5	3.1±0.6	0.88	
PDA closed — no. (%)	49 (66)	52 (70)	0.41	0.94 (0.76–1.17)
Non-randomly assigned rescue treatment				
Infants — no. (%)	9 (12)	12 (16)	0.48	0.75 (0.34–1.67)
Age at start of rescue treatment — days	6.7±1.1	9.5±3.5	0.02	
PDA closed — no. (%)	3 (33)†	3 (25)†	1.00	1.33 (0.35–5.13)
Ductal ligation — no. (%)	9 (12)	10 (14)	0.81	0.90 (0.39–2.09)

*Plus-minus values are means ±SD. CI denotes confidence interval, and PDA patent ductus arteriosus.

†The percentage is of infants receiving a second treatment.

TABLE 3. FACTORS ASSOCIATED WITH THE FAILURE OF TREATMENT FOR PATENT DUCTUS ARTERIOSUS.*

FACTOR	ODDS RATIO (95% CI)
Gestational age†	
≤26 wk	4.26 (0.98–18.65)
27–28 wk	0.81 (0.25–2.67)
29–30 wk	0.58 (0.18–1.87)
31–32 wk‡	1.00
Antenatal indomethacin ≤48 hr before birth	5.29 (1.52–18.34)
High-frequency oscillatory ventilation	3.46 (1.35–8.88)
Ductal shunt velocity§	0.35 (0.14–0.87)

*The table shows the results of multiple logistic-regression analysis including 134 infants. CI denotes confidence interval.

†Gestational age was significantly associated with the failure of treatment (P=0.04 overall).

‡Infants in this category served as the reference group.

§The odds ratio is for each decrease of 1 m per second.

ment groups in the number of infants with severe neonatal complications (Table 4). The rate of survival to discharge, the rate of bronchopulmonary dysplasia, the proportion needing respiratory support, the time required to regain the birth weight, the time until full enteral feeding was possible, and the rate of microscopic hematuria were similar (Table 4). No difference in the likelihood of a tendency to bleed was noted. No localized irritation, redness, or extravasation was noted during any of the infusions of the study medication.

Renal Function

Oliguria developed in 14 infants in the indomethacin group and in 5 infants in the ibuprofen group dur-

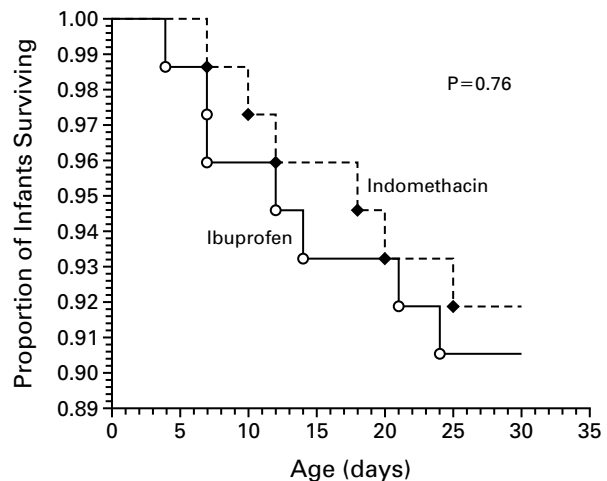


Figure 1. Kaplan-Meier Estimates of Survival at One Month in the Indomethacin and Ibuprofen Groups.

The analysis of death rates covered only 30 days.

ing the three days beginning with the start of treatment (P=0.03). Urine output was significantly lower from day 3 to day 7 in the indomethacin group than in the ibuprofen group (P<0.001), whereas the base-line values were similar (Fig. 2). The increase in the serum creatinine concentration from day 4 to day 8 in the indomethacin group was significantly greater than that in the ibuprofen group (P=0.04) (Fig. 3). The rate of administration of furosemide and the pattern of changes in daily weight were similar in the two groups (data not shown). Fifteen infants assigned to indomethacin and 14 assigned to ibuprofen received an infusion of dopamine during the first week of life, at similar doses.

Patients in whom oliguria developed were more

TABLE 4. OUTCOME OF INFANTS ACCORDING TO TREATMENT GROUP.*

OUTCOME VARIABLE	INDOMETHACIN GROUP (N=74)	IBUPROFEN GROUP (N=74)	P VALUE
Death within 30 days (no.)	6	7	0.77
Necrotizing enterocolitis (no.)	8	4	0.37
Localized bowel perforation (no.)	1	0	
Sepsis (no.)	2	4	0.68
Extension of IVH during treatment (no.)†			
Change from grade 1 to grade 2	1	0	
Change from grade 2 to grade 3	2	0	
Change from grade 2 to grade 4	3	0	
Change from grade 0 to grade 1 or higher	2	5	0.38
PVL (no.)‡			
Grade 1 (flaring after day 7)	4	3	
Grade 2	2	0	
Grade 3 (cystic)	4	2	0.17
Respiratory outcome			
BPD (no.)§	29	39	0.10
IPPV (days)			
Median	8.5	9	0.78
Range	2–41	2–76	
CPAP (days)			
Median	1	2	0.18
Range	0–33	0–29	
Supplemental oxygen (days)			
Median	19	29.5	0.41
Range	2–110	3–270	
Time to regain birth weight (days)	20±8	21±9	0.46
Time to full enteral feeding (days)	27±14	30±16	0.31

*Plus-minus values are means ±SD. IVH denotes intraventricular hemorrhage, PVL periventricular leukomalacia, BPD bronchopulmonary dysplasia, IPPV intermittent positive-pressure ventilation, and CPAP continuous positive airway pressure.

†IVH was graded from 1 to 4, with higher grades indicating greater severity.

‡PVL was graded from 1 to 3, with higher grades indicating greater severity.

§BPD was defined by the need for supplemental oxygen for more than 28 days.

likely than those in whom this condition did not develop to have received indomethacin treatment for patent ductus arteriosus, to have undergone high-frequency oscillatory ventilation, to have microscopic hematuria during treatment, and to have necrotizing enterocolitis after treatment (Table 5). Moreover, they had significantly higher pretreatment serum creatinine concentrations, a greater increase in creatinine values from the first to the third day after birth, and a lower velocity of the left-to-right shunt through the ductus. When the combined effect of the predictive variables was estimated in a multiple logistic-regression model, four factors were independently and significantly predictive of the development of oliguria: indomethacin treatment rather than ibuprofen treatment (odds ratio, 3.62; 95 percent con-

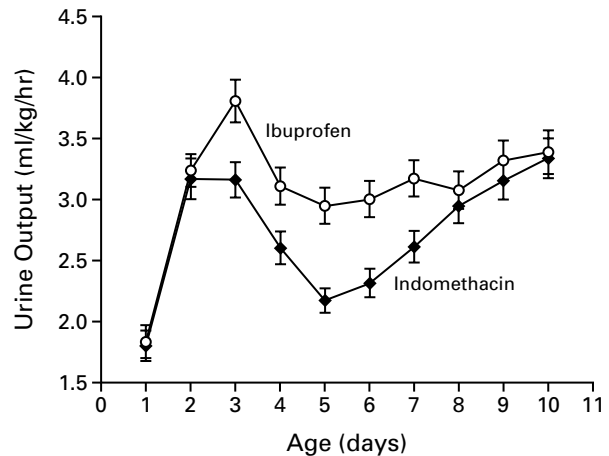


Figure 2. Urine Output in the Indomethacin and Ibuprofen Groups.

The values shown are means ±SE. There were significant differences between the treatment groups from day 3 to day 7 (P<0.001 overall).

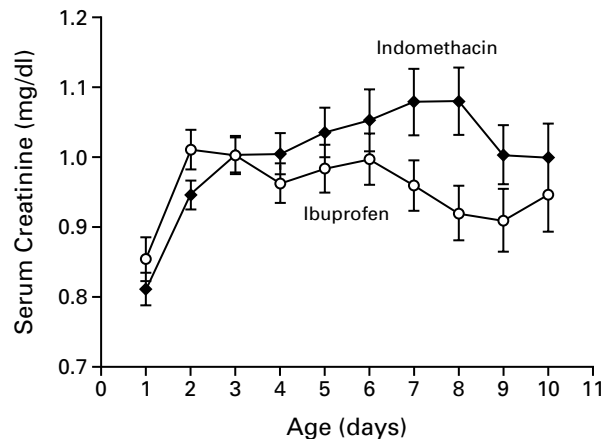


Figure 3. Serum Creatinine Concentrations in the Indomethacin and Ibuprofen Groups.

The values shown are means ±SE. There were significant differences between the treatment groups from day 4 to day 8 (P=0.04 overall). To convert values for creatinine to micromoles per liter, multiply by 88.4.

fidence interval, 1.00 to 13.10); receipt of high-frequency oscillatory ventilation (odds ratio, 5.26; 95 percent confidence interval, 1.45 to 19.07); a greater increase in the serum creatinine concentration from day 1 to day 3 after birth (odds ratio for each increase of 1 percent, 1.01; 95 percent confidence interval, 1.00 to 1.03); and a lower ductal-shunt velocity (odds ratio for each decrease of 1 m per second, 0.14; 95 percent confidence interval, 0.04 to 0.58).

TABLE 5. FACTORS ASSOCIATED WITH THE OCCURRENCE OF OLIGURIA.*

VARIABLE	INFANTS WITH NORMAL URINE OUTPUT (N=129)	INFANTS WITH OLIGURIA (N=19)	P VALUE
Serum creatinine — mg/dl†			
Day 1	0.82±0.19	0.89±0.33	0.21
Day 2	0.96±0.18	1.11±0.28	0.003
Day 3	0.97±0.20	1.18±0.2	<0.001
Pretreatment rise in serum creatinine from day 1 to day 3 — % increase	28±36	49±49	0.04
Maximal velocity of ductal shunt — m/sec	1.57±0.52	1.21±0.45	0.006
High-frequency oscillatory ventilation — no. (%)	46 (36)	14 (74)	0.002
Indomethacin treatment for PDA — no. (%)	60 (47)	14 (74)	0.03
Microscopic hematuria — no./total no. (%)‡			
Day 4	13/87 (15)	9/15 (60)	<0.001
Day 5	8/87 (9)	4/15 (27)	0.06
Day 6	6/87 (7)	4/15 (27)	0.02
Day 7	4/87 (5)	3/15 (20)	0.04
Necrotizing enterocolitis after treatment — no. (%)	7 (5)	4 (21)	0.02
Gestational age — wk	29.1±2.26	28.4±1.90	0.22
Antenatal indomethacin use — no. (%)	17 (13)	3 (16)	0.80

*The table shows the results of univariate analysis. Plus-minus values are means ±SD. PDA denotes patent ductus arteriosus. Oliguria was defined as urine production of ≤1 ml per kilogram per hour during the three days beginning with the start of treatment.

†To convert values to micromoles per liter, multiply by 88.4.

‡Results of daily urinalysis were available for 102 of the 148 patients (87 with normal urine output and 15 with oliguria).

DISCUSSION

On the basis of our findings, it appears that ibuprofen is as effective as indomethacin in promoting ductal closure in premature infants. The rate of closure in the group assigned to indomethacin was similar to rates previously reported. In 15 of 21 infants with birth weights of less than 1750 g (71 percent)³⁰ and in 87 of 113 infants with similar gestational ages and birth weights (77 percent),⁵ a patent ductus arteriosus disappeared after indomethacin treatment at the age of two to seven days. More recently, a ductus arteriosus was closed after prophylactic treatment with indomethacin in 22 of 31 preterm infants (71 percent).³¹ Although we observed differences in the overall rate of ductal closure among the centers participating in our study, the efficacy of the two drugs remained similar in each of the centers.

Ibuprofen has been shown to constrict the ductus arteriosus effectively in lambs.¹¹ Earlier, smaller studies suggested that ibuprofen might be effective in the prevention and early treatment of patent ductus arteriosus in human neonates.¹⁶⁻¹⁸ When ibuprofen

was administered within three hours after birth, it reduced the subsequent incidence of patent ductus arteriosus in a preliminary study.¹⁹ In another study, it reduced the incidence of patent ductus arteriosus without altering cerebral blood flow.¹⁸ In 20 premature infants, it seemed to be as effective as indomethacin in closing the ductus arteriosus on the third day of life.²⁰

Since in our earlier trial we observed that urine production was less affected by ibuprofen than by indomethacin,²⁰ we investigated renal function in more detail in the present study. Oliguria (defined as urine output of less than 1 ml per kilogram per hour) developed in significantly fewer infants, and serum creatinine values did not increase, after ibuprofen treatment. Our observations underscore recent findings that ibuprofen does not cause a reduction in renal blood-flow velocity.²¹ Of the two cyclooxygenase isoenzymes that are known (COX-1 and COX-2), COX-1 seems to be primarily involved in basal physiologic processes in the kidney.³² Although both isoforms are inhibited by ibuprofen and indomethacin,

indomethacin is more potent against COX-1.³³ Although it is uncertain whether these findings also apply to preterm infants with patent ductus arteriosus, a difference in the renal effects of the two drugs remains a possibility. In addition, some experimental evidence suggests that there may be mechanisms unrelated to the inhibition of prostaglandins that partly explain the differences in the effects of indomethacin and ibuprofen on regional circulations.^{15,34}

It is remarkable that necrotizing enterocolitis developed in a significantly higher proportion of the infants with oliguria than of those without oliguria (21 percent vs. 5 percent, $P=0.02$), probably reflecting an associated impairment of mesenteric perfusion. Moreover, twice as many infants had necrotizing enterocolitis in the indomethacin group as in the ibuprofen group, although the difference was not statistically significant. In an experimental model of bowel ischemia in rats, animals treated with ibuprofen had a significantly lower incidence of intestinal necrosis, and it was suggested that ibuprofen may have a cytoprotective role in animals at risk for bowel ischemia.¹⁴ In piglets, ibuprofen did not affect intestinal and renal hemodynamics during positive-pressure ventilation with high mean airway pressures¹² and had no significant effects on gastrointestinal vascular resistance.¹⁵ In preterm infants, ibuprofen did not significantly reduce mesenteric blood-flow velocity.²¹ In our patients, however, this lack of effect was not reflected in earlier full enteral feedings or in the rate of weight gain. Feeding guidelines were, however, not strictly specified in the protocol.

A limitation of our trial is the relatively small number of patients, which limited the power of the study to detect significant differences in other clinical effects that we observed — notably, those related to outcomes such as necrotizing enterocolitis, isolated bowel perforation, intraventricular hemorrhage, and periventricular leukomalacia. For the same reason, small differences in the efficacy of the drugs according to gestational age may not have become apparent.

In summary, our data indicate that ibuprofen is as effective as indomethacin in promoting ductal closure on the third day of life in premature infants. However, ibuprofen is associated with significantly less impairment of renal function. No significant differences with regard to other side effects were observed. A lower gestational age (≤ 26 weeks), antenatal indomethacin use, receipt of high-frequency oscillatory ventilation, and an elevated pulmonary-artery pressure increased the risk of treatment failure.

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REFERENCES

- Ramanathan R, Siassi B, Gallagher R, deLemos RA. Outcome of very low birth weight infants <1500 g enrolled in the National Database Network: are there any trends in neonatology? *Pediatr Res* 1997;41:171A. abstract.
- Lagercrantz H, Katz-Salamon M, Forsberg H. The Stockholm Neonatal Project: neonatal mortality and morbidity at the Children's Centre, Karolinska Hospital. *Acta Paediatr Suppl* 1997;419:11-5.
- The Vermont-Oxford Trials Network: very low birth weight outcomes for 1990. *Pediatrics* 1993;91:540-5.
- Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. *J Pediatr* 1978;93:647-51.
- Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983;102:895-906.
- Betkerer MV, Yeh TF, Miller K, Glasser RJ, Pildes RS. Indomethacin and its effects on renal function and urinary kallikrein excretion in premature infants with patent ductus arteriosus. *Pediatrics* 1981;68:99-102.
- van Bel F, Guit GL, Schipper J, van de Bor M, Baan J. Indomethacin-induced changes in renal blood flow velocity waveform in premature infants investigated with color Doppler imaging. *J Pediatr* 1991;118:621-6.
- Rennie JM, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986;61:233-8.
- Edwards AD, Wyatt JS, Richardson C, et al. Effects of indomethacin on cerebral haemodynamics in very preterm infants. *Lancet* 1990;335:1491-5.
- McCormick DC, Edwards AD, Brown GC, et al. Effect of indomethacin on cerebral oxidized cytochrome oxidase in preterm infants. *Pediatr Res* 1993;33:603-8.
- Coceani F, White E, Bodach E, Olley PM. Age-dependent changes in the response of the lamb ductus arteriosus to oxygen and ibuprofen. *Can J Physiol Pharmacol* 1979;57:825-31.
- Malcolm DD, Segar JL, Robillard JE, Chemtob S. Indomethacin compromises hemodynamics during positive-pressure ventilation, independently of prostanoids. *J Appl Physiol* 1993;74:1672-8.
- Feigen LP, King LW, Ray J, Beckett W, Kadowitz PJ. Differential effects of ibuprofen and indomethacin in the regional circulation of the dog. *J Pharmacol Exp Ther* 1981;219:679-84.
- Grosfeld JL, Kamman K, Gross K, et al. Comparative effects of indomethacin, prostaglandin E1, and ibuprofen on bowel ischemia. *J Pediatr Surg* 1983;18:738-42.
- Speziale MV, Allen RG, Henderson CR, Barrington KJ, Finer NN. Effects of ibuprofen and indomethacin on regional circulation in newborn piglets. *Biol Neonate* 1999;76:242-52.
- Chemtob S, Beharry K, Rex J, Varma DR, Aranda JV. Prostanoids determine the range of cerebral blood flow autoregulation of newborn piglets. *Stroke* 1990;21:777-84.
- Chemtob S, Roy MS, Abran D, Fernandez H, Varma DR. Prevention of postasphyxial increase in lipid peroxides and retinal function deterioration in the newborn pig by inhibition of cyclooxygenase activity and free radical generation. *Pediatr Res* 1993;33:336-40.
- Patel J, Marks KA, Roberts I, Azzopardi D, Edwards AD. Ibuprofen treatment of patent ductus arteriosus. *Lancet* 1995;346:255.
- Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. *JAMA* 1996;275:539-44.
- Van Overmeire B, Follens I, Hartmann S, Creten WL, Van Acker KJ. Treatment of patent ductus arteriosus with ibuprofen. *Arch Dis Child* 1997;76:F179-F184.
- Pezzati M, Vangi V, Biagiotti R, Bertini G, Cianciulli D, Rubaltelli FF. Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus. *J Pediatr* 1999;135:733-8.
- Mosca F, Bray M, Lattanzio M, Fumagalli M, Tosoletto C. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. *J Pediatr* 1997;131:549-54.
- Van Overmeire B, Schepens PJ, Langhendries J-P, Touw DJ, van den Anker JN. Ibuprofen pharmacokinetics in premature infants with patent ductus arteriosus. *Pediatr Res* 1999;45:230A. abstract.
- Aranda JV, Varvarigou A, Beharry K, et al. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature infant. *Acta Paediatr* 1997;86:289-93.
- van Overmeire B, Brus F, van Acker KJ, et al. Aspirin versus indomethacin treatment of patent ductus arteriosus in preterm infants with respiratory distress syndrome. *Pediatr Res* 1995;38:886-91.

26. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529-34.
27. Shankaran S, Slovis TL, Bedard MP, Poland RL. Sonographic classification of intracranial hemorrhage: a prognostic indicator of mortality, morbidity, and short-term neurologic outcome. *J Pediatr* 1982;100:469-75.
28. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1-6.
29. Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. *N Engl J Med* 1984;310:1093-103.
30. Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. *N Engl J Med* 1982;306:506-10.
31. Couser RJ, Ferrara TB, Wright GB, et al. Prophylactic indomethacin therapy in the first twenty-four hours of life for the prevention of patent ductus arteriosus in preterm infants treated prophylactically with surfactant in the delivery room. *J Pediatr* 1996;128:631-7.
32. Smith WL, DeWitt DL. Biochemistry of prostaglandin endoperoxide H synthase-1 and synthase-2 and their differential susceptibility to nonsteroidal anti-inflammatory drugs. *Semin Nephrol* 1995;15:179-94.
33. Vane JR, Botting RM. Mechanism of action of anti-inflammatory drugs. In: Sinzinger H, Samuelsson B, Vane JR, Paoletti R, Ramwell P, Wong PY-K, eds. Recent advances in prostaglandin, thromboxane, and leukotriene research. Vol. 433 of *Advances in experimental medicine and biology*. New York: Plenum Press, 1997:131-8.
34. Chemtob S, Beharry K, Barna T, Varma DR, Aranda JV. Differences in the effects in the newborn piglet of various nonsteroidal antiinflammatory drugs on cerebral blood flow but not on cerebrovascular prostaglandins. *Pediatr Res* 1991;30:106-11.