

Bon Secours Richmond
Pharmacy and Therapeutics Committees
NeoProfen® Ibuprofen Lysine Injection for Closure of Patent Ductus Arteriosus
September 2006

Recommendations:

The neonatologists and pediatric cardiologists decided against the use of this agent as it can not be used for prophylaxis of intraventricular hemorrhage.

NeoProfen® is recommended for formulary inclusion to replace indomethacin IV as the preferred treatment of patent ductus arteriosus closure in premature infants.

- NeoProfen demonstrated efficacy when compared to placebo, 25% versus 48%, requiring rescue therapy (table 1)
- NeoProfen demonstrates comparable efficacy to indomethacin, PDA closer in 70% versus 66% (table 2)
- NeoProfen benefits include:
 - Urine output was significantly higher in the ibuprofen group on days 3-7, $p < 0.001$, figure 2
 - Oliguria (urine output < 1 ml/kg/hour) develops in significantly fewer infants treated with ibuprofen (6.76% versus 18.9%) than indomethacin
 - Serum creatinine does not increase as much after treatment with ibuprofen as compared to indomethacin ($p=0.04$ on treatment days 4-8, figure 3)
 - Outcome variables other than closure of PDA were not significantly different (table 4)
 - Less impact on mesenteric blood flow, renal perfusion, and cerebral blood flow
- Pharmacy will compound Ibuprofen to minimize wastage (see Pharmacy Compounding Instructions)

Efficacy and Outcomes Analysis

NeoProfen Package Insert Data

One hundred and thirty-six premature infants received either placebo or NeoProfen (10 mg/kg on the first dose and 5 mg/kg at 24 and 48 hours). Mean birth age was 1.5 days (range: 4.6 – 73.0 hours), mean gestational age was 26 weeks (range: 23 – 30 weeks), and mean weight was 798 g (range: 530 – 1015 g). All infants had a documented PDA with evidence of ductal shunting. As shown in Table 1, 25% of infants on NeoProfen required rescue therapy versus 48% of infants on placebo ($p=0.003$ from logistic regression controlling for site).

Table 1. Summary of Efficacy Results, n (%)	NeoProfen N=68	Placebo N=68
Required rescue through study day 14		
Total	17 (25)	33 (48)
By age of treatment		
Birth to < 24 hours	3/14 (21)	8/16 (50)
24-48 hours	9/32 (28)	16/37 (43)
> 48 hours	5/22 (23)	9/15 (60)
Echocardiographically proven PDA prior to rescue	17 (100)	32 (97)
Reasons for Rescue		
Hemodynamically significant PDA per neonatologist	14 (82)	25 (76)
Bounding pulse	6 (35)	12 (36)
Systolic murmur	6 (35)	15 (45)
Pulmonary Edema	3 (18)	5 (15)
Hyperdynamic precordium	2 (12)	3 (9)
Increased cardiac silhouette	1 (6)	5 (15)

Of the infants requiring rescue within the first 14 days after the first dose of study drug, no statistically significant difference was observed between the NeoProfen and placebo groups for mean age at start of first rescue treatment (8.7 days, range 4–15 days, for the NeoProfen group and 6.9 days, range 2–15 days, for the placebo group).

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.

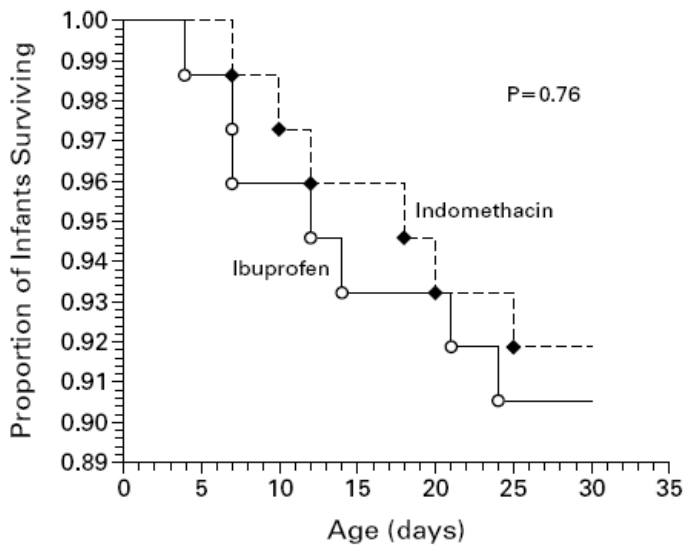


Figure 1. Kaplan–Meier Estimates of Survival at One Month in the Indomethacin and Ibuprofen Groups. The analysis of death rates covered only 30 days.

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.

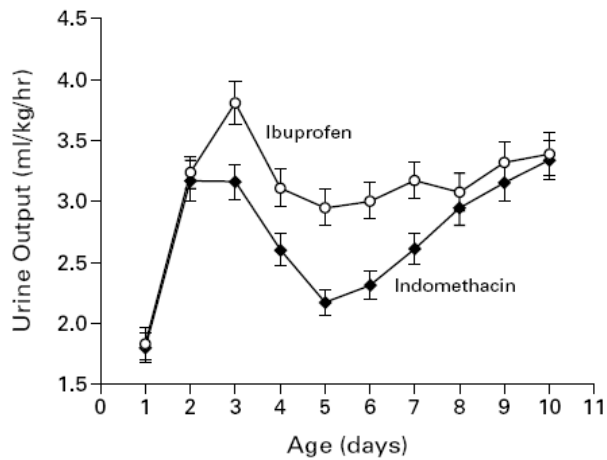


Figure 2. Urine Output in the Indomethacin and Ibuprofen Groups.

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

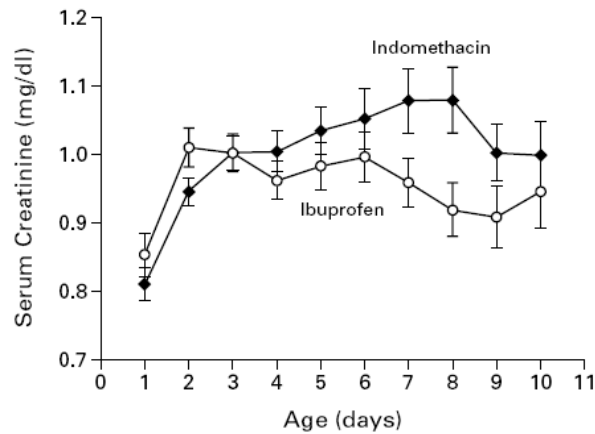


Figure 3. Serum Creatinine Concentrations in the Indomethacin and Ibuprofen Groups.

The values shown are means \pm 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.

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 \pm 8	21 \pm 9	0.46
Time to full enteral feeding (days)	27 \pm 14	30 \pm 16	0.31

*Plus-minus values are means \pm 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.

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).

	Indomethacin (Indocin® IV)	Ibuprofen Lysine(NeoProfen®)
Class	Acetic Acid (class) Analgesic NSAID	Propionic Acid (class) Analgesic NSAID
FDA indications	PDA closure in premature infants weighing between 500-1750gm Unlabeled uses: prophylactic treatment for prevention of PDA in at-risk premature infants	PDA closure in premature infants weighing between 500-1500gm who are no more than 32weeks gestational.
Dose (PDA closure)	Pts less-than 48hrs old: 0.2mg/kg iv followed by 0.1mg/kg iv q12-24 hours x2 doses 2-7 days old: 0.2mg/kg IV every 12-24hours x3 doses Greater than 7 days: 0.2mgkg IV followed by 0.25mg/kg every 12-24hours x2 doses If ductus arteriosus re-opens, a second course of 1-3 doses may be given	Pts 500-1500gm and not more than 32wks gestational age: 10mg/kg IV on day 1, followed by 5mg/kg IV after 24 and 48 hours for 3 total doses; based on birth weight If ductus arteriosus fails to close or reopens, a second course of NeoProfen may be given.
Dose Adjustments	Renal impairment: severe (ClCr less-than 15mL/min), initiate with lowest recommended dosage, monitor patient closely and reduce dosage if necessary Liver disease: Child-Pugh Class III, initiate with lowest recommended dose, monitor closely and reduce dose if necessary	Anuria or marked oliguria (urine output less-than 0.6mL/kg/hr): hold dose until renal function returns to normal
Administration	Reconstitute just prior to administration with 1 to 2mL preservative-free NS or sterile water for injection; do not dilute further Do not add any diluent containing preservative infuse over 20-30minutes - use caution to avoid extravasation After first withdrawal from vial, remaining solution must be discarded as product contains no preservatives.	Dilute to an appropriate volume with dextrose or saline and administer within 30 minutes of preparation Infuse continuously over 15 minutes - administer carefully to avoid extravascular injection or leakage, as solution may be irritating to tissue After first withdrawal from vial, remaining solution must be discarded as product contains no preservatives.
Pharmacokinetics	<u>Distribution</u> Protein binding = 99% <u>Metabolism</u> Metabolites desmethyl, desbenzoyl and desmethyl-desbenzoyl (all unconjugated) <u>Excretion</u> Fecal: 33%, 1.5% unchanged Renal: about 60%, 26% as unchanged drug and metabolite <u>Elimination half-life</u> 4.5hours (mean)	<u>Distribution</u> Protein binding: pre-term infants (22-31weeks) and mean weight of 944.7gms = 95% Volume of distribution: pre-term infants (less-than 30weeks gestational age and weight of 500-1000gm) = 320mL/kg Volume of distribution: 3 days and very low-birth-weight infants (10mg/kg) + 357+/- 121mL/kg Volume of distribution: postnatal age of 5 days and very low-birth-weight infants (5mg/kg) = 349 +/- 152mL/kg <u>Metabolism</u> Hepatic, primarily by CYP2C9 <u>Excretion</u> Renal (adults): 80% changed, 10-15% unchanged <u>Elimination half-life</u> Postnatal age of 0-3 hours and infants: 30.5 hours Postnatal age of 3days and very low-birth-weight infants: 43hours Postnatal age of 5days and very low-birth-weight infants: 26hours
Contraindications	Known or high suspicion of untreated infection Congenital heart disease in whom patency of PDA is necessary for satisfactory pulmonary or systemic blood flow Active bleeding, especially those with active intercranial hemorrhage or gastrointestinal bleeding Thrombocytopenia or coagulation defects Known or high suspicion of necrotizing enterocolitis Impaired renal function	
Warnings	Potential for intraventricular bleeding may be increased due to inhibition of platelet aggregation Decrease urine output	No long-term evaluation of infants greater than 36 weeks post-conceptual age treated with ibuprofen NSAIDs can inhibit platelet aggregation, therefore close monitoring for signs of bleeding is required. Ibuprofen may alter signs of infection Effects on neuro-developmental outcomes, growth, or disease processes associated with prematurity have not been assessed
Adverse Events	Intercranial and GI bleeding, hyponatremia, hyperkalemia, retrolental fibroplasia	sepsis, anemia, total bleeding, intraventricular hemorrhage, apnea, gastrointestinal disorders (non-necrotizing enterocolitis), renal dysfunction, respiratory infection, skin lesion/irritation, hypoglycemia, hypocalcemia, respiratory failure, UTI, adrenal insufficiency, hypernatremia, edema and atelectasis
How supplied	Powder for reconstitution Indocin® IV 1mg	Intravenous solution: NeoProfen® 10mg/mL
Cost per Agent	Indocin® Injection: \$485.80 per vial (1mg/vial)	Neoprofen®: \$469.60 per vial (10mg/mL - 2mL vial)
Cost per Therapy	0.2mg/kg x3 doses =	10mg/kg x1 dose plus 5mg/kg x2 doses =

	Indomethacin (Indocin® IV)	Ibuprofen Lysine(NeoProfen®)
	485.80 x 3 = 1457.40	469.60 x 3 = 1408.80

- **Pharmacy Compounding Instructions**

- Rounded patient weight up or down (25 gram maximum round) to the closest weight on the chart
- Patients weighing 1024 grams or less
 - Draw up the loading dose and dilute in appropriate fluid for administration (Dextrose or NS).
 - Draw up both maintenance doses from the same vial and place into syringes for use in compounding on day 2 and 3, label and store as appropriate.
 - If the vials are over filled the weight allowing all four doses to be obtained from one vial may be higher than 1024 grams. (see total ml required on chart below).
- Patients weighing greater than 1025 grams to 1324 gm
 - Draw up the loading dose from the vial at start of therapy and dilute in appropriate fluid for administration (Dextrose or NS).
 - Draw up one maintenance dose from the same vial and place into a syringes for use in compounding on day two of therapy. Discard the remainder of vial.
 - The third dose will be drawn up from a separate vial.
- Patients weighing greater than or equal to 1325 grams
 - Draw up the loading dose from one vial at start of therapy and dilute in appropriate fluid for administration (Dextrose or NS). Discard the remainder of vial.
 - Draw up both maintenance doses on day two of therapy, dilute one dose in the appropriate fluid for administration (Dextrose or NS) on day 2, place the other dose in a syringe for use in compounding on day 3 of therapy. Discard the remainder of vial.

Weight grams	Loading Dose 10 mg/kg	Loading Dose ml	Maintenance Dose 5 mg/kg	Maintenance Dose ml	Total ml Required For LD & 1 MD	Total ml Required For All Doses
500	5	0.5	2.50	0.25	0.75	1.00
550	5.5	0.55	2.75	0.28	0.83	1.11
600	6	0.6	3.00	0.30	0.90	1.20
650	6.5	0.65	3.25	0.33	0.98	1.31
700	7	0.7	3.50	0.35	1.05	1.40
750	7.5	0.75	3.75	0.38	1.13	1.51
800	8	0.8	4.00	0.40	1.20	1.60
850	8.5	0.85	4.25	0.43	1.28	1.71
900	9	0.9	4.50	0.45	1.35	1.80
950	9.5	0.95	4.75	0.48	1.43	1.91
1000	10	1	5.00	0.50	1.50	2.00
1050	10.5	1.05	5.25	0.53	1.58	2.11
1100	11	1.1	5.50	0.55	1.65	2.20
1150	11.5	1.15	5.75	0.58	1.73	2.31
1200	12	1.2	6.00	0.60	1.80	2.40
1250	12.5	1.25	6.25	0.63	1.88	2.51
1300	13	1.3	6.50	0.65	1.95	2.60
1350	13.5	1.35	6.75	0.68	2.03	2.71
1400	14	1.4	7.00	0.70	2.10	2.80
1450	14.5	1.45	7.25	0.73	2.18	2.91
1500	15	1.5	7.50	0.75	2.25	3.00
grams	mg	ml	mg	ml	ml	Total ml

Review of the Literature

Randomized controlled trials

1: N Engl J Med. 2000 Sep 7;343(10):674-81

A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus.

Van Overmeire B., et al.

Department of Pediatrics, University Hospital Antwerp, Belgium.

BACKGROUND: Indomethacin is the conventional treatment for hemodynamically important 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, hemodynamically important 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.

2: Eur J Pediatr. 2002 Apr;161(4):202-7.

Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial.

Lago P, et al.

Neonatal Intensive Care Unit, Department of Paediatrics, University of Padova, Italy.

Indomethacin (INDO) and, more recently, ibuprofen (IBU) have been used to treat haemodynamically significant patent ductus arteriosus (PDA) in preterm infants. Both are cyclo-oxygenase blockers, but seem to have a different influence on regional circulation. In a prospective, randomised, controlled study, we compared INDO and IBU with regard to efficacy and safety for the early non-invasive treatment of PDA. Doppler echocardiography was used to study 232 preterm infants (gestational age 23-34 weeks) with respiratory distress syndrome of whom 175 had persistent, haemodynamically significant PDA at 48-72 h of life. They were randomised to receive three intravenous doses of either INDO (0.2 mg/kg, at 12 h intervals) or IBU (a first 10 mg/kg dose followed by two doses of 5 mg/kg at 24 h intervals), recording rate of ductal closure, need for additional treatment, side-effects and clinical course. The efficacy of the pharmacological treatment was similar in the two groups (56/81, 69% INDO; 69/94, 73% IBU). Patients treated with INDO showed a significant increase in serum creatinine (89 +/- 24 versus 82 +/- 20 mmol/l, $P = 0.03$) and a near-significant tendency for a lower fractional excretion of sodium (3 +/- 3 versus 4 +/- 2%, $P = 0.08$); moreover, 12/81 (15%) INDO patients versus 1/94 (1%) IBU patients became oliguric (< 1 ml/kg per h) during treatment ($P = 0.017$). **CONCLUSION:** Our findings confirm that, by comparison with indomethacin, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome. In particular, no increased incidence of intracranial haemorrhage was observed after ibuprofen treatment.

3: Arch Dis Child Fetal Neonatal Ed. 1997 May;76(3):F179-84

Treatment of patent ductus arteriosus with ibuprofen.

Van Overmeire B, et al.

Department of Paediatrics, University Hospital of Antwerp, Belgium.

AIM: To evaluate the efficiency and side effects of ibuprofen for the early treatment of patent ductus arteriosus (PDA) and compare it with indomethacin. **METHODS:** Forty preterm infants with gestational ages of less than 33 weeks, with respiratory distress syndrome (RDS) and echocardiographically confirmed PDA, were randomly assigned at days 2 to 3 of life to receive either intravenous indomethacin 3 x 0.2 mg/kg at 12 hour intervals or intravenous ibuprofen 1 x 10 mg/kg, followed by 5 mg/kg 24 and 48 hours later. **RESULTS:** PDA closed in 15 of 20 patients from the indomethacin group (75%) and in 16 of 20 (80%) from the ibuprofen group. Seven patients (three indomethacin, four ibuprofen) required a second treatment with indomethacin and in five (three in the indomethacin group and two in the ibuprofen group) the duct was ultimately ligated. Ibuprofen patients had a better urinary output and showed no increase in serum creatinine concentrations compared with the indomethacin group. Ibuprofen was not associated with any other side effect. **CONCLUSIONS:** Ibuprofen

treatment seems to be as efficient as indomethacin in closing PDA on the third day of life in preterm infants with respiratory distress syndrome and seems to have fewer renal side effects.

4: Med Wieku Rozwoj. 2005 Jul-Sep;9(3 Pt 1):335-54.

Comparison of the efficacy of ibuprofen and indomethacin in the treatment of patent ductus arteriosus in prematurely born infants

Adamska E, et al.

Klinika Neonatologii i Intensywnej Terapii Noworodka, Instytut Matki i Dziecka, ul. Kasprzaka 17a, 01-211 Warszawa, Poland.

AIM: To assess the efficacy and safety of early treatment with ibuprofen (IBU) and indomethacin (INDO) of patent ductus arteriosus in preterm infants. Prospective study with blind trial. MATERIAL AND METHODS: We studied 35 preterm infants (19 treated with INDO, 16 IBU) (gestation age <33 and birth weight < 1500 g), who had an echocardiographically confirmed patent ductus arteriosus (PDA). The infants were randomly assigned in two groups to receive INDO (0.2-0.2-0.2 mg/kg) or IBU (10-5-5 mg/kg) in first 72 hours of life (average 2 days of life). The rate of ductal closure, the need for surgical ligation, side effects, complications, and the infants clinical course were recorded. RESULTS: The rate of ductal closure was similar in two groups (15/19, 80% INDO; 11/16, 69% IBU). 27 infants (15 INDO, 12 IBU) were treated per protocol (3 doses). For remaining 8 infants we stopped treatment due to side effects. In the IBU group the main reason to stop treatment was pulmonary hemorrhage (3/16, 19%) and pulmonary hypertension (1/16, 6%), but in the INDO group it was increased serum creatinine and urea nitrogen concentrations (3/19, 16%) and intraventricular hemorrhage (IVH IV) grade (1/19 5%). In IBU group vs. INDO, urine output decreased ($p=0.02$), but never before below the level of oliguria (defined as urine output below 1 ml/kg/h). Risk of necrotizing enterocolitis (NEC) grade II was similar in two groups, but only patients treated with INDO showed intestinal perforations ($p=ns$). They received also postnatal hydrocortisone and we showed near significant tendency ($p=0.06$) for intestinal perforation in patients treated with INDO and hydrocortisone. There were no significant differences with respect to IVH or PVL between the groups. CONCLUSIONS: The efficacy of ibuprofen and indomethacin in PDA treatment is similar. Treatment of ibuprofen and indomethacin may cause transient renal dysfunction: diminished urine output and increase of serum creatinine and urea nitrogen concentrations. Indomethacin, especially with concomitant treatment with hydrocortisone, may increase the risk of intestinal perforation.

Meta analysis

5: Eur J Pediatr. 2005 Mar;164(3):135-40. Epub 2004 Dec 10.

A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus.

Thomas RL, et al.

Children's Research Center of Michigan, Children's Hospital of Michigan, 3901 Beaubien Blvd, 48201 Detroit, Michigan, USA.

Ibuprofen (IBU) has previously been shown to be as effective as indomethacin (INDO) in closing the patent ductus arteriosus (PDA) of preterm infants, without severely affecting renal hemodynamics or basal cerebral blood flow. We conducted a meta-analysis of randomized trials to compare the efficacy and safety of IBU and INDO for treatment of PDA. Data from the nine relevant trials ($n=566$), showed no significant difference in the efficacy of IBU and INDO in PDA closure ($P=0.70$). However, five trials ($n=443$) provided serum creatinine concentration data that revealed a significantly lower increase favoring IBU ($P<0.001$), and urine output data that showed a significantly lower decrease favoring IBU ($P<0.001$). In two trials ($n=188$) the proportion of infants who required postnatal oxygen therapy at 28 days (defined as chronic lung disease) was significantly higher with IBU (52/94; 55.3%) than with INDO (38/94; 40.4%, $P<0.05$). No statistically significant differences were found in mortality, intraventricular hemorrhage, necrotizing enterocolitis, surgical ligation, sepsis, retinopathy of prematurity, periventricular leukomalacia, length of hospital stay, gastrointestinal bleeding, re-opening of PDA, back-up treatment, surfactant therapy, or days on a ventilator. Conclusion: ibuprofen and indomethacin have similar efficacy in patent ductus arteriosus closure, but preterm infants treated with ibuprofen experience lower serum creatinine values, higher urine output, and less undesirable decreased organ blood flow and vasoconstrictive adverse effects.

- [Pediatrics](#). 2005 Jun;115(6):1529-35.

Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study.

[Dani C](#), [Bertini G](#), [Pezzati M](#), [Poggi C](#), [Guerrini P](#), [Martano C](#), [Rubaltelli FF](#); [IntraVentricular Ibuprofen Study Group](#).

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OBJECTIVE: Ibuprofen enhances cerebral blood flow autoregulation and was shown to protect neurologic functions

after oxidative stresses in an animal model. For these reasons, we hypothesized that the prophylactic use of ibuprofen would reduce the occurrence of intraventricular hemorrhage (IVH) and its worsening toward grades 2 to 4 among preterm infants. To confirm this hypothesis, we planned the present prospective study. **METHODS:** This was a double-blind, randomized, controlled trial in which preterm infants with gestational ages of <28 weeks received ibuprofen or placebo within the first 6 hours of life. The infants were assigned randomly, at 7 neonatal care units, to receive ibuprofen (10 mg/kg, followed by 5 mg/kg after 24 and 48 hours) or placebo. Serial echoencephalography was performed 24 and 48 hours after the initial cerebral ultrasound study, on postnatal days 7, 15, and 30, and at 40 weeks' postconceptional age. Grade 1 IVH or no IVH was considered a successful outcome, whereas grade 2 to 4 IVH represented failure. The rates of ductal closure, side effects, and complications were recorded. **RESULTS:** We studied 155 infants. Grade 2 to 4 IVH developed for 16% of the ibuprofen-treated infants and 13% of the infants in the placebo group. The occurrence of patent ductus arteriosus was less frequent only on day 3 of life in the ibuprofen group. There were no significant differences with respect to other complications or adverse effects. **CONCLUSIONS:** Our study demonstrated that prophylactic ibuprofen is ineffective in preventing grade 2 to 4 IVH and that its use for this indication cannot be recommended.

- [Lancet](#). 2004 Nov 27-Dec 3;364(9449):1945-9
Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial.

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BACKGROUND: Ibuprofen is used for treatment and prevention of patent ductus arteriosus in low-birthweight infants. Its effects on regional circulations differ from those of indometacin. Because prophylactic indometacin reduces the frequency of severe intraventricular haemorrhage and patent ductus arteriosus, we aimed to study the efficacy of early ibuprofen in reducing these outcomes in a double-blind, multicentre trial. **METHODS:** Within 6 h after birth, 415 low-birthweight infants (gestational age <31 weeks) were randomly allocated ibuprofen-lysine (10 mg/kg then two doses of 5 mg/kg after 24 h and 48 h) or placebo intravenously. The primary outcome was occurrence of severe intraventricular haemorrhage; secondary outcomes were occurrence of patent ductus arteriosus and possible adverse effects of ibuprofen. Analysis was by intention to treat. **FINDINGS:** 17 (8%) of 205 infants assigned ibuprofen and 18 (9%) of 210 assigned placebo developed severe intraventricular haemorrhage (relative risk 0.97 [95% CI 0.51-1.82]). In 172 (84%) infants of the ibuprofen group, the ductus was closed on day 3 compared with 126 (60%) of the placebo group (relative risk 1.40 [1.23-1.59]). No important differences in other outcomes or side-effects were noted; however, urine production was significantly lower on day 1 and concentration of creatinine in serum was significantly higher on day 3 after ibuprofen. **INTERPRETATION:** Ibuprofen prophylaxis in preterm infants does not reduce the frequency of intraventricular haemorrhage, but does decrease occurrence of patent ductus arteriosus.

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Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial.

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BACKGROUND: Patent ductus arteriosus is a common complication of prematurity that frequently requires surgical or medical treatment. The benefit of prophylactic treatment by indometacin, a cyclo-oxygenase inhibitor, remains uncertain compared with curative treatment. This benefit could be improved with ibuprofen, another cyclo-oxygenase inhibitor with fewer adverse effects than indometacin on renal, mesenteric, and cerebral perfusion. We aimed to compare prophylactic and curative ibuprofen in the treatment of this abnormality in very premature infants. **METHODS:** We did a randomised controlled trial in infants younger than 28 weeks of gestation, who were randomly assigned to receive either three doses of ibuprofen or placebo within 6 h of birth. After day 3, symptomatic patent ductus arteriosus was treated first by open curative ibuprofen, then back-up indometacin, surgery, or both. The primary endpoint was need for surgical ligation. Analysis was per protocol. **FINDINGS:** The study was stopped prematurely after 135 enrollments because of three cases of severe pulmonary

hypertension in the prophylactic group. 65 infants received prophylactic ibuprofen, and 66 received placebo. Prophylaxis reduced the need for surgical ligation from six (9%) to zero ($p=0.03$), and decreased the rate of severe intraventricular haemorrhage from 15 (23%) to seven (11%) ($p=0.10$). However, survival was not improved (47 [71%] placebo vs 47 [72%] treatment, $p=1.00$), because of high frequency of adverse respiratory, renal, and digestive events. INTERPRETATION: In premature infants, prophylactic ibuprofen reduces the need for surgical ligation of patent ductus arteriosus, but does not reduce mortality or morbidity. Therefore, it should not be preferred to early curative ibuprofen.

- [Pediatr Int.](#) 2003 Dec;45(6):665-70.

Comparison of ibuprofen and indomethacin therapy for patent ductus arteriosus in preterm infants.

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BACKGROUND: Patent ductus arteriosus (PDA) is commonly found in very low-birthweight (VLBW) infants. The presence of respiratory distress syndrome (RDS) is also associated with increased frequency of significant PDA. Intravenous indomethacin has been used to treat and to prevent PDA in premature infants since 1976. However, concern remains regarding the safety of indomethacin, which affects renal, gastrointestinal and cerebral perfusion. Intravenous ibuprofen has recently been used to treat and to prevent PDA premature infants with PDA without reducing cerebral blood flow or affecting intestinal or renal hemodynamics. The aim of the present study is to compare intravenous ibuprofen and indomethacin with regard to efficacy and safety for the early treatment of PDA in preterm infants. **METHODS:** A total of 63 preterm infants with RDS who had a birthweight of $< \text{or} = 1500$ g and gestational age of $< \text{or} = 32$ weeks, were enrolled in the present study. All patients were treated with nasal continuous positive airway pressure with additional oxygen supply in inspired air $> 30\%$, or with mechanical ventilation. The patients' serum platelet counts were $> 100,000/\mu\text{L}$, and serum creatinine values were < 1.5 mg/dL. There were no 3-4 grade intraventricular hemorrhages before randomization, and all patients were aged 2-7 days and had echo-cardio-graphic evidence of significant PDA. Patients were randomized into two groups: the first group of neonates (group A, $n = 32$) received intravenous ibuprofen lysine 10 mg/kg, followed by 5 mg/kg after 24 and 48 h; the second group (group B, $n = 31$) received intravenous indomethacin 0.2 mg/kg every 12 h for three doses. **RESULTS:** Patent ductus arteriosus closed in 27 patients from the ibuprofen group (84.4%) and in 25 patients from the indomethacin group (80.6%). PDA reopened in three patients from the ibuprofen group (9.4%) and in three patients from the indomethacin group (9.7%). One patient in the ibuprofen group and two patients in the indomethacin group required ductal ligation. Serum creatinine and blood urea nitrogen (BUN) concentrations were lower in the ibuprofen group than in the indomethacin group. Urine output and creatinine clearance values were higher in the ibuprofen group than in the indomethacin group. **CONCLUSIONS:** Ibuprofen therapy is as efficacious as indomethacin for the treatment of PDA in preterm infants. Infants treated with ibuprofen have higher creatinine clearance and urine output and lower serum creatinine and BUN values than infants treated with indomethacin.

[Lancet.](#) 2002 Aug 10;360(9331):492.

Ibuprofen prophylaxis in preterm neonates.

[Schmidt B](#), [Wright LL](#), [Davis P](#), [Solimano A](#), [Roberts RS](#); [Indomethacin Prophylaxis in Preterms Investigators](#).

- [Eur J Pediatr.](#) 2002 Apr;161(4):202-7.

Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial.

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Indomethacin (INDO) and, more recently, ibuprofen (IBU) have been used to treat haemodynamically significant patent ductus arteriosus (PDA) in preterm infants. Both are cyclo-oxygenase blockers, but seem to have a different influence on regional circulation. In a prospective, randomised, controlled study, we compared INDO and IBU with regard to efficacy and safety for the early non-invasive treatment of PDA. Doppler echocardiography was used to study 232 preterm infants (gestational age 23-34 weeks) with respiratory distress syndrome of whom 175 had persistent, haemodynamically significant PDA at 48-72 h of life. They were randomised to receive three intravenous doses of either INDO (0.2 mg/kg, at 12 h intervals) or IBU (a first 10 mg/kg dose followed by two doses of 5 mg/kg at 24 h intervals), recording rate of ductal closure, need for additional treatment, side-effects and clinical course. The efficacy of the pharmacological treatment was similar in the two groups (56/81, 69% INDO; 69/94, 73% IBU). Patients treated with INDO showed a significant increase in serum creatinine (89 +/- 24 versus 82 +/- 20 mmol/l, P = 0.03) and a near-significant tendency for a lower fractional excretion of sodium (3 +/- 3 versus 4 +/- 2%, P = 0.08); moreover, 12/81 (15%) INDO patients versus 1/94 (1%) IBU patients became oliguric (< 1 ml/kg per h) during treatment (P = 0.017). **CONCLUSION:** Our findings confirm that, by comparison with indomethacin, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome. In particular, no increased incidence of intracranial haemorrhage was observed after ibuprofen treatment.

- [Acta Paediatr.](#) 2000 Nov;89(11):1369-74.
Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants.

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The aim of our study was to evaluate whether the prophylactic use of ibuprofen would reduce the incidence of significant patent ductus arteriosus (PDA) and to confirm the effectiveness of ibuprofen as rescue treatment in closing PDA. Eighty preterm infants with gestational age less than 34 wk with infant respiratory distress syndrome (iRDS) were randomized to receive intravenous ibuprofen lysine (10 mg/kg, followed by 5 mg/kg after 24 and 48 h) either within 24 h of life (group A) or after echocardiographic diagnosis of PDA (group B). To evaluate the severity of RDS in each patient, we calculated the initial and highest values of Oxygenation Index (O.I. = mean airway pressure x FiO₂ x 100/PaO₂) and Ventilatory Index (V.I. = O.I. x mechanical respiratory rate). Other studied variables were ventilatory support, renal function, biochemical and haematological profiles, frequency of bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP). On the 3rd day of life, 8% (3/40) of patients of group A and 53% of patients (21/40) of group B (p < 0.0001) developed a significant PDA. Between patients of group B who presented PDA at 3 d of life 90% (19/21) had a closure of ductus arteriosus after ibuprofen treatment. Initial and highest values of O.I. and V.I. were similar in both groups A and B. No significant differences between the groups were observed in regard to respiratory support, renal function and frequency of BPD, IVH, NEC and ROP. Ibuprofen was not associated with adverse effects. **Conclusion:** Prophylactic treatment with ibuprofen reduces PDA occurrence in preterm infants with iRDS at 3 d of life in comparison with rescue treatment, but both modes are effective in closing the ductus without significant adverse effects.

[N Engl J Med.](#) 2000 Sep 7;343(10):674-81.

A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus.

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BACKGROUND: Indomethacin is the conventional treatment for hemodynamically important 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, hemodynamically important 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.

[Clin Pharmacol Ther.](#) 2000 Jun;67(6):676-83.

Effects of prophylactic ibuprofen on cerebral and renal hemodynamics in very preterm neonates.

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OBJECTIVE: To evaluate the effects on cerebral and renal blood flow velocities of ibuprofen when used as prophylaxis for patent ductus arteriosus in preterm neonates (gestational age <30 weeks). **METHODS:** Blood flow velocities in the anterior cerebral artery and the renal artery were measured with Doppler ultrasonography in 17 neonates before, during, and 10, 30, and 60 minutes after administration of 10 mg/kg ibuprofen lysine. **RESULTS:** In four (23.6%) neonates without echocardiographic patency of the ductus, no significant modifications in blood flow velocities and Doppler indexes were found either in the anterior cerebral artery or in the renal artery. In 13 (76.4%) neonates, cardiac echocardiographic Doppler showed patency of the ductus and left-to-right shunt. In these neonates diastolic and mean blood velocities rapidly increased both in the anterior cerebral artery and the renal artery ($P < .0001$). Resistance and pulsatility index decreased during the study period ($P < .0001$ and $P < .001$, respectively, in the anterior cerebral artery; $P < .0001$ in the renal artery). **CONCLUSIONS:** Data suggest that ibuprofen does not determine any direct effect on cerebral and renal blood flow velocities; hemodynamic modifications observed in neonates with patency of ductus can be related to closure of the ductus induced by the drug.

[Eur J Pediatr.](#) 2000 May;159(5):364-8.

Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants.

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This study was aimed at evaluating the efficacy of ibuprofen in the prophylaxis of patent ductus arteriosus (PDA) in very preterm neonates and at detecting eventual side-effects. A total of 46 preterm neonates with gestational age under 31 weeks were randomly assigned at 2 h of life: 23 to the prophylaxis group and 23 to the control group. The prophylaxis group received intravenous treatment with ibuprofen lysine (10 mg/kg), followed by 5 mg/kg after 24 h and 48 h. No placebo was given to the control group. No PDA was demonstrated at 72 h of life in 20 of the 23 babies in the ibuprofen group (87%) nor in 7 of the 23 control neonates (30.4%). All neonates with PDA received treatment with indomethacin. One neonate in the prophylaxis group and three in the control group underwent surgical ligation. Prophylaxis with ibuprofen was not associated with any significant side-effect except for food intolerance. **CONCLUSION:** Ibuprofen prophylaxis seems to be efficient in closing patent ductus arteriosus and in reducing indomethacin treatment. No significant early side-effects were found due to ibuprofen.

[Pediatr Res.](#) 2000 Jan;47(1):36-42.

Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus.

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A prospective randomized controlled trial was performed to compare the effects of ibuprofen with indomethacin on cerebral hemodynamics measured using near infrared spectroscopy in preterm infants during treatment for patent ductus arteriosus. Infants were randomly assigned to three intravenous doses of either indomethacin (0.20-0.25 mg/kg, 12 hourly) or ibuprofen (5-10 mg/kg, 24 hourly) and also received a dose of saline. The primary end points of the study were the effects of the first dose on cerebral blood flow (CBF) and cerebral blood volume. Fifteen infants received indomethacin and 18 received ibuprofen. The group mean (SD) values for CBF (mL x 100 g(-1) x min(-1)) before and after the first dose of indomethacin were 13.6 (4.1) and 8.3 (3.1), respectively, the change being significant ($p < 0.001$). In contrast, no significant changes in CBF were observed with the first dose of ibuprofen, the respective before and after values being 13.3 (3.2) and 14.9 (4.7) mL x 100 g(-1) x min(-1). The median (interquartile range) value for change in cerebral blood volume (mL/100 g) after the first dose in the indomethacin group was -0.4 (-0.3 to -0.6) and in the ibuprofen group was 0.0 (0.1 to -0.1), the difference between the two groups being significant ($p < 0.001$). Cerebral oxygen delivery changed significantly after the first dose in the indomethacin group but not in the ibuprofen group. Significant reductions in CBF, cerebral blood volume, and cerebral oxygen delivery also occurred after the 24-h dose of indomethacin, but there were no significant changes after the 48-h dose of saline in the indomethacin group or after the 24- and 48-h doses of ibuprofen. The patent ductus arteriosus closure rates after indomethacin and ibuprofen were 93 and 78%, respectively. We conclude that ibuprofen, unlike indomethacin, has no adverse effects on cerebral hemodynamics and appears to mediate patent ductus arteriosus closure.

[J Pediatr.](#) 1999 Dec;135(6):733-8.

Effects of indomethacin and ibuprofen on mesenteric and renal blood flow in preterm infants with patent ductus arteriosus.

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OBJECTIVE: To evaluate the effect of intravenous ibuprofen and indomethacin for treatment of patent ductus arteriosus (PDA) on mesenteric and renal blood flow velocity in preterm infants. **STUDY DESIGN:** Seventeen mechanically ventilated preterm infants (<33 weeks' gestation) with PDA received either 0.2 mg/kg indomethacin (n = 8) or 10 mg/kg ibuprofen (n = 9), infused over 15 minutes. Mesenteric and renal blood flow velocity were measured by using Doppler ultrasonography. **RESULTS:** Indomethacin caused a significant reduction in mesenteric and renal blood flow velocity 30 minutes after drug administration; mesenteric and renal blood flow velocity did not return to the pretreatment values by 120 minutes. Ibuprofen did not alter blood flow 30 minutes after treatment, and blood flow increased 120 minutes after treatment. Mesenteric and renal blood flow velocity changes were significantly different between the 2 treatment groups. **CONCLUSIONS:** Compared with indomethacin, ibuprofen did not significantly reduce mesenteric and renal blood flow velocity.

[JAMA.](#) 1996 Feb 21;275(7):539-44.

Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants.

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OBJECTIVE--To test whether early postnatal (0 to 3 hours) intravenous administration of ibuprofen will prevent patent ductus arteriosus (PDA) in preterm neonates. **DESIGN--**Prospective sequential controlled trial with three treatment arms. **SETTING--**Level 3 perinatal-neonatal intensive care nursery. **PATIENTS--**Thirty-four premature newborn infants born from February to August 1993 with a mean birth weight of 913 g (range, 565 to 1460 g) and gestational age of 26.9 weeks (range, 22.4 to 31.0). **INTERVENTION--**Infants were consecutively assigned within 3 hours of age to treatment with either one dose of ibuprofen lysine (10 mg/kg intravenously) followed by 5 mg/kg per dose intravenously at 24 and 48 hours of age (n = 12), one dose of ibuprofen lysine (10 mg/kg intravenously; n = 11), or saline (n = 11). **OUTCOME VARIABLES--**Primary outcome variable was the presence of ductus arteriosus by echocardiography and clinical assessments at 3, 7, and 21 days of life. Secondary outcome variables included presence of intraventricular hemorrhage, renal function, ventilatory and oxygen needs, hematologic changes, gastrointestinal function, time to full enteral feeding, duration of hospitalization, and age at discharge. **RESULTS--**The three groups of patients were comparable in birth weight, gestational age, antenatal administration of betamethasone, and other perinatal characteristics. Ibuprofen treatment significantly reduced plasma levels of prostaglandins, and the levels remained low for 72 hours in newborns who received three doses of the drug. The incidence of PDA and other variables did not differ between patients who received a single dose of ibuprofen and those given saline. However, compared with the saline-treated newborns, babies who received three doses of ibuprofen had no PDA (0/12 vs 7/11 for saline; $P < .02$), had lower daily mean airway pressures (mean +/- SD, 5.2 +/- 1.1 cm H₂O vs 8.3 +/- 2.8 cm H₂O for

saline; $P < .02$) and better oxygenation index (2.6 ± 0.6 vs 4.7 ± 1.8 for saline; $P < .02$) at the end of the first week of life, and required fewer days of ventilation (25 ± 14 days vs 44 ± 26 days for saline; $P < .03$). Babies given three doses of ibuprofen tended to tolerate full oral feedings earlier (35 ± 19 days vs 56 ± 34 days for saline; $P = .09$), had shorter duration of hospitalization (71.2 ± 22.6 days vs 127.3 ± 74.7 days for saline; $P < .05$), and were discharged to home at an earlier postconceptional age (37.8 ± 2.0 weeks vs 44.8 ± 9.8 weeks for saline; $P < .05$). ibuprofen treatment in this phase I trial was not associated with any apparent early neurological, intestinal, renal, hepatic, or hematologic complications.

CONCLUSIONS--Administration of three doses of ibuprofen within 3 hours after birth in preterm neonates reduced the incidence of PDA without causing notable early adverse drug reactions in this phase I trial. Early closure of the ductus arteriosus was also associated with better respiratory outcome and earlier discharge from the hospital.