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A Second Course of Ibuprofen Is Effective in the Closure of a Clinically Significant PDA in ELBW Infants

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KEY WORDS

extremely preterm infants, ibuprofen, patent ductus arteriosus

ABBREVIATIONS

DA—ductus arteriosus

PDA—patent ductus arteriosus

ELBW—extremely low birth weight

CLD—chronic lung disease

NSAID—nonsteroidal antiinflammatory drug

OR—odds ratio

CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: A PDA remains a common problem of preterm neonates, and when and how to treat it remains uncertain. Ibuprofen has been shown to be as effective in the treatment of a PDA as indomethacin, with fewer adverse effects.



WHAT THIS STUDY ADDS: Treatment of a PDA with a second course of ibuprofen after failure of initial treatment remains controversial. This is the first study to examine the efficacy of first and second courses of ibuprofen in the most vulnerable preterm population (<1000 g).

abstract

OBJECTIVES: There are few published data on the efficacy of ibuprofen in the most immature infants and no data on repeated courses. Our objectives were to describe PDA closure rates in a population of infants <1000 g birth weight after repeated courses of ibuprofen, to examine the effect of gestation, and to document plasma markers of renal function and platelet counts.

METHODS: This was a single center observational study. We collected data on infants weighing <1000 g at birth who were treated with ibuprofen for a clinically significant PDA. A successful outcome was defined as resolution of clinical symptoms such that no additional treatment was required. Serum biochemistry and hematology data were analyzed and compared with controls.

RESULTS: We identified 160 infants with a mean \pm SD birth weight of 757 ± 127 g and gestation of 25.6 ± 1.4 weeks. Seventy infants closed their PDA after a single course of ibuprofen (45%) and 32/80 (40%) following a second. Infants of <26 weeks' gestation ($n = 83$) were less likely to respond after both the first (27.7% vs 63.6%; $P < .001$) and second (30.9% vs 60.0%; $P = .026$) courses. The postnatal decrease in plasma creatinine was delayed by ibuprofen treatment, while platelet counts and other plasma markers were unaffected.

CONCLUSIONS: In our study population, PDA closure was gestation dependant, with a cumulative closure rate of 65%. A similar proportion of infants closed their PDA following the first and second courses regardless of gestation. These data suggest that a second course of ibuprofen may be effective in closing a PDA in even the most preterm infant. *Pediatrics* 2009;124:e287–e293

The ductus arteriosus (DA) is the blood vessel of fetal life responsible for shunting blood from the pulmonary artery to the aorta. In term infants, the normal physiologic response of the DA to delivery is contraction with functional closure over the first few hours of life, followed by remodeling leading to permanent closure. Preterm infants have a high incidence of persistent patent DA (PDA), with rates in those weighing <1000 g approaching 60%.¹ A clinically symptomatic PDA has been associated with significant morbidity in this high-risk population.^{2,3}

Mechanisms of ductal closure are complex; prostaglandins play a central role in both the active maintenance of ductal patency in utero and in postnatal closure. Pharmacologic treatment with the prostaglandin H synthase inhibitors indomethacin and ibuprofen induce closure of PDAs in premature infants in a dose-dependant manner.⁴ Randomized, controlled trials have demonstrated similar efficacy in ductal closure rates with these 2 agents in infants born at up to 34 weeks' gestation.^{5,6} Indomethacin has been shown to be less effective in closing PDAs with increasing immaturity,⁷ with high recurrence rates in infants weighing <1000 g.⁸ Closure rates of 44% are reported after a second course of treatment with indomethacin in infants of <28 weeks' gestation.⁹ There are, however, no previously published data on the efficacy of a second course of ibuprofen treatment.

Indomethacin treatment in the preterm infant is associated with decreased regional blood flow^{10,11} leading to oliguria and changes in the biochemical markers of renal function. Treatment with ibuprofen causes less renal impairment than indomethacin.^{5,6,11,12} Premature infants are vulnerable to the effects of nephrotoxic drugs,¹³ however, there are few data describing the changes in

standard serum measures of renal function in these infants after exposure to ibuprofen.

Platelet function is reduced by ibuprofen use^{14,15}; however, there have been no data on the effect of ibuprofen treatment for a PDA on platelet counts in infants weighing <1000 g.

In this study, we aimed to describe PDA closure rates after first and second courses of ibuprofen in a population of infants weighing <1000 g at birth, and to document changes in serum sodium, urea, and creatinine levels, and platelet counts during the treatment course.

PATIENTS AND METHODS

Over a 7-year period from 1999 to 2006, data were collected prospectively from a single-center tertiary neonatal unit on all preterm neonates weighing <1000 g, both inborn and outborn with early postnatal transfer (<48 hours of age). Throughout this period ibuprofen was the standard medical treatment for a symptomatic PDA and was prescribed as 10 mg/kg of ibuprofen-base, followed by 2 additional doses of 5 mg/kg on consecutive days.^{11,12} All treated infants had clinical signs of a PDA and the diagnosis was confirmed by an echocardiogram. A PDA was deemed significant and requiring treatment when moderate to large in size with evidence of left to right ductal shunting and an increased left atrium to aortic ratio and if there was failure to wean from mechanical ventilation. No infants received prophylactic treatment with either ibuprofen or indomethacin. Infants who remained clinically symptomatic after a first course and had no contraindications to additional treatment were given a second course of ibuprofen.

Data were analyzed on all infants with a birth weight of <1000 g who received a minimum of 1 course of ibuprofen. A successful outcome was de-

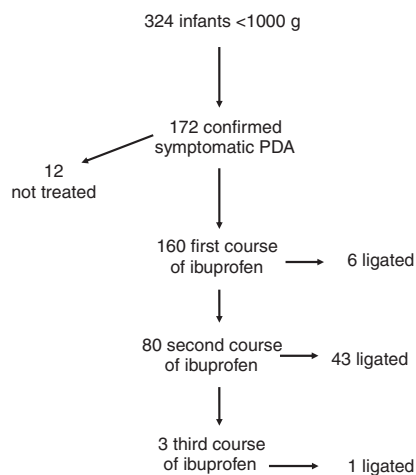
finied as resolution of clinical signs and symptoms such that no additional treatment was required. Data were examined for factors likely to influence treatment outcome including weight, gestational age at birth, gender, and age at the start of treatment.

Changes in blood sodium, urea, creatinine, and platelet levels over the course of treatment were analyzed. These data were collected before the initial dose and then daily after each subsequent dose. Biochemical and hematologic data were collected from a comparison group of 30 infants who did not receive ibuprofen and who matched the study group for gestational and postnatal age. If platelet counts fell below $40 \times 10^9/L$, then a platelet transfusion was given before the next dose of ibuprofen.

Statistical analysis was performed by using SigmaStat 2.0 (Jandel Scientific, San Rafael, CA). Statistical significance was set at the 95% level. Differences between groups were analyzed by using the Student's *t* test and Mann-Whitney test when normality tests failed. Differences in proportions between 2 groups were analyzed by using Fisher's exact test and the χ^2 test. Changes in measurements over time were examined by using analysis of variance for repeated measures. Dichotomous data were correlated by using the point biserial correlation coefficient. Multiple logistic regression was used to describe the relationship between PDA closure, gestational age, and birth weight.

RESULTS

We identified 324 infants of whom 172 (53%) had a clinically significant PDA (Fig 1); 160 (93%) of these infants were treated with at least 1 course of ibuprofen. This cohort of infants had a mean \pm SD birth weight of 757 ± 127 g, and mean gestation of 25.6 ± 1.4 weeks; 147 (92%) completed a com-

**FIGURE 1**

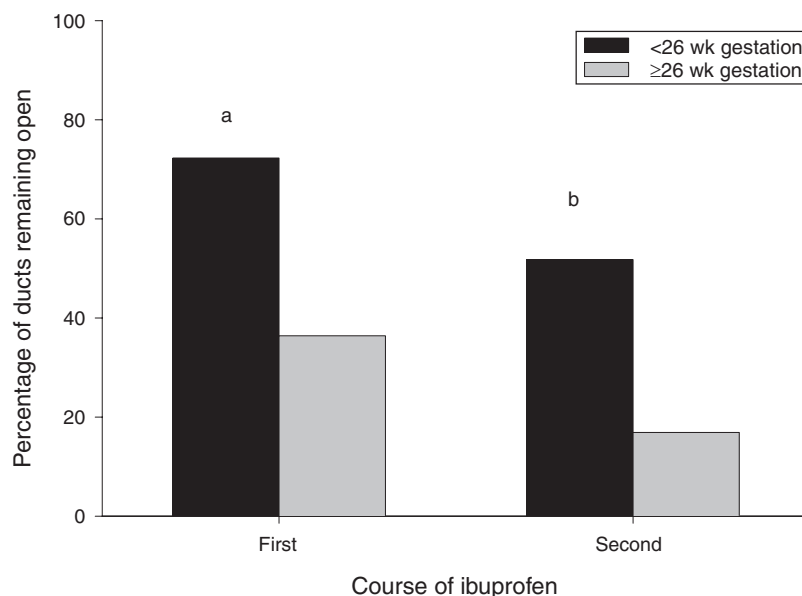
Flowchart showing the outcomes of infants weighing <1000 g with symptomatic PDA.

plete initial treatment course of ibuprofen (3 doses). No infants developed pulmonary hypertension during their treatment course. Baseline clinical data of the study infants are presented in Table 1.

The overall closure rate after a single course of ibuprofen was 45.0%. Infants whose PDA failed to close were significantly lighter (mean \pm SD birth weight: 731 \pm 128 g versus 789 \pm 120 g; $P = .004$) and less mature (mean \pm SD gestation: 25.4 \pm 1.4 vs 26.0 \pm 1.4 weeks; $P = .002$). Closure rates were significantly lower in infants born at <26 weeks' completed gestation ($P < .001$), and in those weighing <750 g at birth ($P < .001$) (Fig 2; Table 2). Gestational age corre-

FIGURE 2

The percentage of ducts remaining open is significantly greater in infants of <26 weeks' gestation than in infants of ≥ 26 weeks' gestation after both the first and second courses of ibuprofen. ^a $P < .001$; ^b $P = .025$.



lated significantly with successful treatment after both a first ($r = 0.21$; $P = .003$) and a second course of ibuprofen ($r = 0.32$; $P = .002$). On logistic regression analysis only gestational age was associated with successful PDA closure with treatment (odds ratio [OR]: 1.65 [95% confidence interval (CI): 1.19–2.29] $P = .003$).

Thirty-nine (24.3%) infants were below the 10th birth weight centile for gestation. Birth centile did not correlate with treatment success (first course: $r = 0.01$, $P = .46$; second course: $r = 0.12$, $P = .14$). We found no significant

association between age at time of commencing primary course of ibuprofen and closure rate.

Eighty of the study infants received a second course of ibuprofen, after which 40% of the remaining PDAs successfully closed. There were no significant differences in closure rates between the first and second courses (Table 2, Fig 2). Three infants received a third course of ibuprofen, and 1 of these infants went on to undergo a surgical PDA ligation.

In this study, 50 (31.3%) of the extremely low birth weight (ELBW) infants treated with ibuprofen had PDAs that failed to close and required surgical ligation. Ligation rates were significantly higher in infants of <26 weeks' gestation and those weighing <750 g at birth (Table 2).

Biochemical and hematologic laboratory data sets were available for 100 of the 160 infants. Platelet counts did not vary over the treatment course. Platelet transfusions were given to 5 infants; excluding posttransfusion values from the analysis did not change

TABLE 1 Population Characteristics

Birth weight, mean \pm SD, g	757 \pm 127
Completed gestation, mean \pm SD, wk	25.6 \pm 1.42
Male ($N = 160$), n (%)	75 (46.9)
Growth restricted (<10th centile), n (%) ^a	39 (24.3)
Age at first treatment, median (IQR), d	6 (4–9)
Age at second treatment, median (IQR), d	15 (12–20)
Use of antenatal steroids ($N = 149$), n (%) ^b	136 (91.3)
Surfactant administration ($N = 152$), n (%) ^c	146 (96.1)
Oxygen dependence at 36 wk ($N = 125$), n (%) ^d	75 (60)

IQR indicates interquartile range.

^a British 1990 growth reference for weight, Child Growth Foundation.³⁷

^b Data not recorded for 11 infants.

^c Data not recorded for 8 infants.

^d Data not available for 35 infants because of death and transfer to other units.

TABLE 2 Effects of Different Population Characteristics on Rates of Closure With Ibuprofen and PDA-Ligation Rates in Infants Weighing <1000 g for the First and Second Courses of Ibuprofen

	Closure Rate, %	OR	95% CI	P
First course				
Total (N = 160)	45			
<26 wk (n = 83) vs ≥26 wk (n = 77)	27.7 vs 63.6	0.22	0.11–0.43	<.001
<750 g (n = 73) vs ≥750 g (n = 87)	30.1 vs 57.5	0.32	0.17–0.62	<.001
Second course				
Total (N = 80)	40.5			
<26 wk (n = 55) vs ≥26 wk (n = 25)	30.9 vs 60	0.30	0.11–0.80	.026
<750 g (n = 46) vs ≥750 g (n = 34)	30.4 vs 52.9	0.39	0.16–0.98	.064
PDA-ligation rate				
<26 wk (n = 38) vs ≥26 wk (n = 12)	45.8 vs 15.58	4.57	2.16–9.7	<.001
<750 g (n = 32) vs ≥750 g (n = 18)	43.8 vs 20.7	2.99	1.49–5.99	.003

the results. Serum sodium and creatinine levels remained stable, whereas serum urea levels decreased significantly over the time period studied. There were no differences in platelet count and serum sodium and urea levels between the infants treated with ibuprofen and the comparison group. Creatinine levels decreased significantly in the comparison group in contrast to the static levels in the ibuprofen group (Fig 3).

DISCUSSION

The aim of this study was to document the PDA closure rates after first and second courses of ibuprofen in ELBW infants. Our cohort consisted of 160 infants weighing <1000 g with a clinically symptomatic PDA. The overall incidence of symptomatic PDA in ELBW infants born throughout the study period was 53%. This rate is comparable with that from a group of infants

weighing <1 kg of whom 55% received medical treatment for a PDA.¹ The overall closure rate we report after an initial course of ibuprofen is 45%, considerably lower than the reported levels in the literature of between 57% and 89%.^{5,6,12,16,17} These differences in closure rate are likely to be attributable to the immaturity of the population we studied in comparison to published studies where infants born at gestations of up to 34 weeks were included. A small study examining the effect of nonsteroidal antiinflammatory drugs (NSAIDs) on cerebral blood flow reported closure rates of up to 57% with ibuprofen use in premature infants with a median gestation of 26 weeks; this rate of closure is comparable to that seen in our group of infants of ≥26 weeks' gestation.¹⁶ Our figures are comparable to reported closure rates with indomethacin treatment reported in similar populations of premature infants.^{9,18} These studies considered all ELBW infants as a single group, whereas, to our knowledge, we are the first to correlate lower gestational age at birth with reduced ductal closure rates after NSAID use.

Closure rates of 44% are reported after a second course of treatment with indomethacin in infants of <28 weeks' gestation.⁹ However, there are no previously published data on the efficacy of a second course of ibuprofen treatment. In our population, we found that the rate of closure of a PDA after a second course of treatment was similar to the first (40.0% vs 45.0%). This was true both above and below 26 weeks' gestation (Table 2). Recent published data have associated PDA ligation with adverse outcomes, including chronic lung disease (CLD), neurosensory impairment, and retinopathy of prematurity.^{19,20} Our data, which demonstrate similar closure rates after the first and second courses, suggest that in extremely premature infants who fail

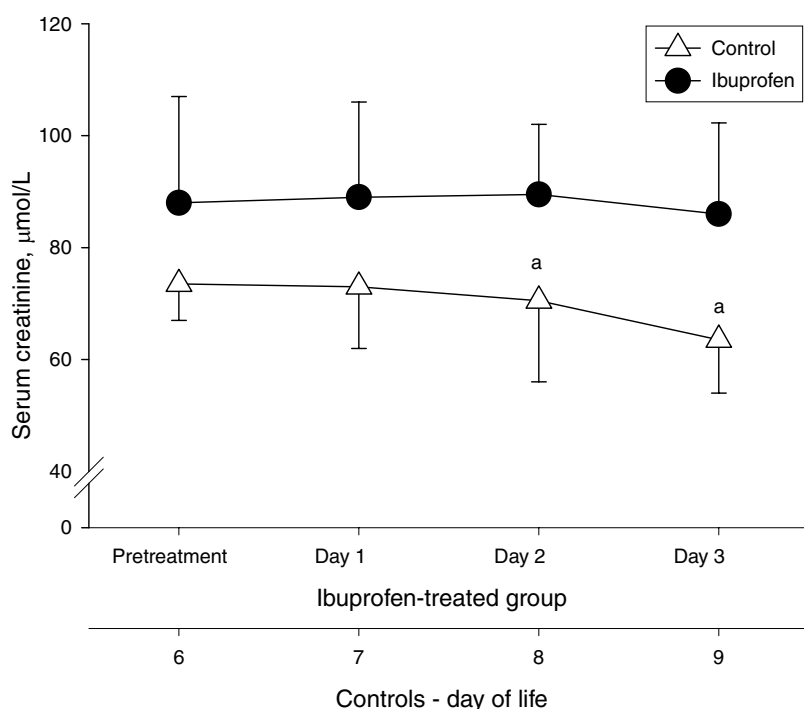


FIGURE 3 Median (\pm quartile) serum creatinine levels after ibuprofen treatment plotted against controls of a similar gestation and age. ^a There is a significant decrease in creatinine levels in controls compared with baseline ($P < .05$). Ibuprofen-treated creatinine levels do vary from baseline.

to respond to a primary course of ibuprofen, a second course should be considered before consideration of surgical ligation.

Spontaneous closure of the DA has been reported to occur in up to 40% of ELBW infants weighing <1000 g. However, because we did not perform an echocardiogram on all infants, we are unable to comment on this in our 152 asymptomatic infants. The treated group, however, was clinically symptomatic and commenced treatment at day 6 of life, a time by which "spontaneous closure" is reported to have occurred.¹ Factors influencing persistent ductal patency include extreme immaturity, ELBW, and significant respiratory distress, all of which presented in our cohort of infants. A clear association between PDA and low gestation is reported in the literature. The relationship, however, between gestation and the efficacy of indomethacin treatment is contradictory.^{1,3,7,9} In 1 cohort of ELBW infants, no significant relationship was described between rate of PDA closure and gestation,¹ whereas in a study of infants of <28 weeks' gestation, an association was described between closure rate and gestation with an initial but not a second course of indomethacin.⁹ We describe a consistent relationship between efficacy of ibuprofen for PDA closure and gestation both for initial and repeated courses. Our lack of association between age at treatment and closure rate reflects findings in another group of ELBW infants.¹ In contrast to other published data,¹ we found no association between PDA closure and growth restriction or antenatal steroid administration; however, >90% of our infants had been exposed to antenatal steroids.

The reduced PDA closure rates in infants of <26 weeks' gestation likely reflect the developmental regulation of the DA. Permanent DA closure occurs

after remodeling, resulting in obliteration of the ductal lumen. In term infants, DA constriction produces wall hypoxia leading to remodeling and permanent closure. The differences in the anatomic structure of the preterm DA requires luminal blood flow to be eliminated before wall hypoxia develops and closure with remodeling occurs.^{7,9,21} There is enhanced ductal sensitivity to circulating dilator prostaglandins at low gestational ages,^{21–23} and in animal models local production of endogenous vasodilators has been shown to further contribute to ongoing patency in the preterm ductus.⁴ The DA in the extremely preterm infant is thus physiologically and anatomically programmed to remain patent.

In comparison to indomethacin, ibuprofen has a superior adverse effect profile, with reduced incidence of both oliguria and raised creatinine levels.^{12,24–26} Our findings that creatinine levels did not rise with ibuprofen treatment are consistent with other published evidence on the use of ibuprofen in preterm infants.²⁶ There is evidence that ibuprofen does delay renal maturation as measured by both creatinine clearance and amikacin clearance in neonates administered ibuprofen within the first 5 days of life,^{13,27,28} and the delay in the physiologic decrease in creatinine levels seen in our ibuprofen-treated group supports these findings.

Urea levels fell in both the ibuprofen and the comparison group, whereas sodium levels remained stable, suggesting that fluid retention did not cause the decrease in urea in the ibuprofen group.

Some authors have expressed concern about an increase in the incidence of CLD after ibuprofen treatment.²⁹ This association with CLD has also been demonstrated with indomethacin.³⁰ Despite high rates of antenatal steroid administration, the incidence of oxy-

gen dependence at 36 weeks' corrected gestation in our study group was 60%. This rate, however, is in keeping with rates reported for infants weighing <1250 g at birth in 2 recent large, multicenter, controlled trials.^{30,31} The incidence of CLD in our population of infants treated with ibuprofen is therefore comparable with that in similar populations in other centers.

This study was an uncontrolled observational study performed over 7 years and suffers from the uncertainty inherent in this methodology. We have attempted to ensure that the data are as robust as possible within these limitations. Our data are limited by the fact that PDA closure was not confirmed by an echocardiogram at the end of treatment; therefore, we cannot exclude the possibility that ongoing ductal flow was present in some infants who were asymptomatic and deemed to have "successful treatment." Over the time period of the study, treatment protocols did not change, and the proportion of infants treated did not vary by year. All data were collected prospectively as part of a routine neonatal data set that was regularly validated by the clinical team. We believe these data are reliable and the numbers sufficient to draw clinically useful conclusions.

The optimal management of a PDA in the most immature infants remains controversial. There are no published randomized, controlled trials comparing long-term outcome after treatment with NSAIDs to placebo in this population, although some outcome data exist in larger infants.^{32–35} In view of the relatively low PDA closure rates we report in infants of <26 weeks' gestation, alternative therapeutic options need to be investigated. An extended ibuprofen course to maintain ductal constriction for a longer period could potentially increase the probability of luminal obliteration and successful

closure.²⁵ In addition, it has been speculated that increasing the dose of ibuprofen may increase closure rates;²⁴ however, in view of the relative immaturity of the prostaglandin pathways in the preterm DA, this approach may not be effective and could result in increased toxicity. Recent data on increasing the dose of indomethacin have not demonstrated increased closure rates but have been associated with an increase in retinopathy of prematurity.³⁶ Future strategies for the treatment of PDA in extremely preterm infants will require thorough investi-

gation in the setting of randomized, controlled trials before implementation into routine clinical practice.

CONCLUSIONS

This study documents PDA closure rates from the largest cohort of infants weighing <1000 g who were treated with ibuprofen and provides the only data on treatment outcome after a second course of ibuprofen. Closure rates in infants between 26 and 29 weeks' gestation were good, with 83% responding to either 1 or 2 courses. However, rates were lower in less mature infants, with a significant

relationship demonstrated between increasing gestational age and successful PDA closure with ibuprofen treatment. Ibuprofen delayed the postnatal decrease in creatinine but had no other effect on biochemistry or hematology.

In this population of ELBW infants, 40% of infants who failed initial treatment with ibuprofen had their PDA close after a second course. These data support the consideration of a second course of ibuprofen in even the most immature infant, before proceeding to surgical ligation.

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A Second Course of Ibuprofen Is Effective in the Closure of a Clinically Significant PDA in ELBW Infants

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