ARTICLE

Randomized Pilot Study Comparing Oral Ibuprofen With Intravenous Ibuprofen in Very Low Birth Weight Infants With Patent Ductus Arteriosus

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What's Known on This Subject

Intravenous ibuprofen closes PDA in approximately two thirds of cases with some adverse effects.

What This Study Adds

(1) Oral ibuprofen probably has a better efficacy and fewer adverse effects in closure of PDA. (2) Closure of PDA may be obtained with an incomplete course of ibuprofen either orally or intravenously.

ABSTRACT

BACKGROUND. We conducted a prospective, randomized, single-masked pilot study with the principal aim of comparing efficacy and tolerance between oral and intravenous ibuprofen in early closure of patent ductus arteriosus in very low birth weight infants. The possibility of ductal closure with only 1 or 2 doses of treatment was a secondary objective.

MATERIAL AND METHODS. Sixty-four very low birth weight patients with echocardiographically confirmed patent ductus arteriosus and respiratory distress were studied. The patients were randomly assigned to receive either oral (group O, $n = 32$) or intravenous (group I, $n = 32$) ibuprofen starting on the third day of life. After the first dose of treatment in both groups, echocardiographic evaluation was performed to determine the need for a second or third dose. The rate of ductal closure, adverse effects, complications, and the patient's clinical course were recorded.

RESULTS. In each group, 24 (75%) patients were born after 28 weeks' gestation. The rate of ductal closure tended to increase in group O (84.3% vs 62.5%). Closure of the ductus was obtained after 1 or 2 doses of treatment in 19 (70.3%) of 27 patients in group O and 14 (70%) of 20 patients in group I. The adverse effects were increased in group I (31.2% vs 9.3%). There were no significant differences with respect to complications during the stay. Adverse effects were significantly fewer when closure was achieved after an incomplete course of treatment (23.1% vs 76.9%).

CONCLUSIONS. In very low birth weight infants, the rate of early ductal closure with oral ibuprofen is at least as good as with the intravenous route. Ductal closure may be obtained with an incomplete course of ibuprofen. Oral ibuprofen is associated with fewer adverse effects. However, a larger sample is needed for more definitive conclusions. *Pediatrics* 2008;122:e1256–e1261

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Key Words
ibuprofen, ductus arteriosus, premature infant

Abbreviations
PDA—patent ductus arteriosus
VLBW—very low birth weight
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
CLD—chronic lung disease
GEB—gastrointestinal bleeding
PVL—periventricular leukomalacia

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THE INCIDENCE OF patent ductus arteriosus (PDA) in very low birth weight (VLBW) infants is ~30%.[1] It is inversely related to gestational age. More than two thirds of infants delivered before 28 weeks' gestation receive either pharmacological or surgical closure of the PDA.[2] In premature infants, PDA is associated with increased risks of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), chronic lung disease (CLD), and death.[3,4] Therefore, closure of a hemodynamically significant PDA is indicated. Intravenous indomethacin and intravenous ibuprofen are the 2 widely prostaglandin synthesis inhibitors used for this indication.

In a previously published article, we stated that 1, 2, or 3 doses of oral ibuprofen were likely to close efficaciously PDA with a good tolerance.[5] However, this trial was unmasked, and there were no comparative groups. We performed a prospective, randomized, single-masked study aiming principally to compare efficacy and tolerance between oral ibuprofen and intravenous ibuprofen in early closure of PDA in VLBW infants. The possibility of ductal closure with only 1 or 2 doses of treatment was a secondary objective.

MATERIALS AND METHODS

Patients

The study was conducted in the NICU of the Neonatal and Maternity Center of Tunis (Tunisia) over a period of 1 year (January 2007 to December 2007) after approval by the ethical committee of the center. The patients were enrolled after written informed consent was obtained from their parents. The criteria for enrollment were as follows: gestational age $<$ 32 weeks; birth weight $<$ 1500 g; postnatal age between 48 and 96 hours; respiratory distress requiring $>$25% oxygen supplementation; and echocardiographic evidence of significant left-to-right shunting across PDA. Exclusion criteria were: right-to-left shunting; major congenital anomalies; IVH grade 3–4; tendency to bleed (defined by the presence of blood in endotracheal aspirate, gastric aspirate, stools or urines, and/or by oozing from puncture sites); serum creatinine level of $>$16 mg/dL; serum urea nitrogen level of $>$9 mg/dL; and a platelet count of $<$60 000/μL. The presence of a single exclusion criterion was enough to exclude the patient from the study.

Study Design

The patients were randomly assigned to a treatment group by means of cards in sealed opaque envelopes. Each enrolled patient received a dose of 10 mg/kg of either oral (group O) or intravenous (group I) ibuprofen. After the first dose of treatment in both groups, echocardiographic evaluation was performed to determine the need for a second or a third dose. In each group, in case the ductus was still open after the third dose, intravenous ibuprofen (an initial dose of 10 mg/kg followed by 2 doses of 5 mg/kg each, after 24 and 48 hours) as a nonrandomized rescue treatment was given. If this therapy also failed to promote ductal closure and the patient continued to receive mechanical ventilation, surgical ligation of the ductus was performed. In each group, in case there was only minor ductal shunting after therapy and the patient did not require respiratory support, no additional treatment of the ductus was attempted. Oral ibuprofen (Ibuphil, Simed, Tunisia; a bottle of 125 mL containing 2.5 g of ibuprofen, 1 mL equals 20 mg of ibuprofen; pH: 5.8; osmolarity: 312 mosmol/L) was diluted in 3 mL of saline solution and then administered through a feeding tube, followed by flushing with distilled water. Intravenous ibuprofen (Pedea, Orphan Europe; a vial of 2 mL containing 10 mg of ibuprofen) was infused continuously over a period of 15 minutes. Tolerance was assessed daily during the week after the beginning of treatment by clinical examination (tendency to bleed, abdominal bloating, urine output), cranial ultrasound examination (IVH, change in grade), and laboratory tests (serum creatinine and serum urea nitrogen levels). Oliguria was defined as a urine output of 1 mL/kg per hour or less during a 24-hour collection period. Occurrence of any of the following conditions was enough to discontinue treatment: IVH grade 3–4, renal failure, NEC, and gastrointestinal bleeding (GEB).

Color Doppler Echography

In each enrolled patient, color Doppler echography (model SSA-350A, 7-MHz transducer [Toshiba, Tokyo, Japan]) of the heart, brain, and abdomen was performed before the entry in the study and after each dose of treatment by trained physicians. Physicians performing echocardiography and making the decision for second- and third-dose administration were unaware of assignment. The purpose was to confirm the presence of a left-to-right ductal shunting, to evaluate its degree, and to measure the internal diameter of the ductus. Shunting was graded as minor if a disturbed diastolic flow was scarcely detectable in the main pulmonary artery, and there was no diastolic backflow in the aorta immediately beneath the ductus arteriosus. It 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. It was graded as severe if a diastolic backflow was easily detectable in the pulmonary trunk and in the aorta with a left-atrium-to-aortic-root ratio of $>$1.6, and if diastolic backflow was detectable in the medium cerebral artery or in the superior mesenteric artery or in the renal arteries.[6] If shunting was graded as moderate or severe, PDA was considered hemodynamically significant. Cranial ultrasound examination was performed, first before entering the study, then repeated after each dose, 1 week after the last dose and before discharge. The study patients were assessed for IVH and for periventricular leukomalacia (PVL) which were graded, respectively according to classifications of Papille and of de Vries, with higher grades indicating greater severity.[7,8]

Concomitant Treatment

For all patients enrolled in the study, fluid intake was begun at 70 mL/kg per day with increases by increments of 10 mL/kg each day to a maximum of 120 mL/kg per day by the end of the study. Dopamine infusion at the dose of 3 μg/kg per minute was started once urine output deer $\leq$1 mL/kg per hour. Intravenous furosemide at a loading dose of 2 mg/kg was prescribed in case of radiologic evidence of pulmonary edema. Ventilatory support was imposed by the severity of the respiratory distress and included nasal continuous positive airway pressure, intermittent positive pressure ventilation, and high-frequency oscillatory ventilation. Nasal continuous positive airway pressure was used as the first step. Intermittent positive pressure ventilation was indicated once arterial to alveolar ratio for oxygen pressure was $<$0.15, arterial partial pressure of carbon dioxide was $>$65 mm Hg, or in case of recurrent apnea. High-frequency oscillatory ventilation was indicated as a last resort when arterial to alveolar ratio was $<$0.10 or when alveolar pathology required ventilator peak inspiratory pressure of $>$24 cm H_2O. Inhaled nitric oxide was used to treat persistent pulmonary hypertension. Surfactant (Curosurf, Chiesi, Italy; a vial of 1.5 mL containing 120 mg) was administered intratracheally at the dosage of 100 to 200 mg/kg prophylactically (infants at $<$27 weeks' gestation) and as a very early rescue (infants $>$27 weeks' gestation) when arterial to alveolar ratio was

<0.25. Prophylactic antibiotics (cefotaxime, ampicillin, and amikacin) were started on admission and discontinued 2 days later if infectious tests were negative.

Early Outcome

Because it is difficult to relate some multifactorial complications to ibuprofen treatment, we considered 1 week after the administration of the last dose as a limit for the implication of ibuprofen in some complications. During this week, all patients enrolled in the study were prospectively assessed for ductal closure, number of doses required, mode and duration of ventilation, surfactant treatment, renal failure, IVH, NEC, and GEB. NEC was graded according to Bell's classification.[9]

Late Outcome

After the week of treatment, the patients were assessed for IVH, NEC, CLD, PVL, nosocomial sepsis, duration of hospital stay, time to regain birth weight, time to full enteral feeding, and death. CLD was defined according to the new Bancalari's classification, which differentiated 3 groups of preterm infants on the basis of treatment with supplemental oxygen at 28 days and 36 weeks.[10]

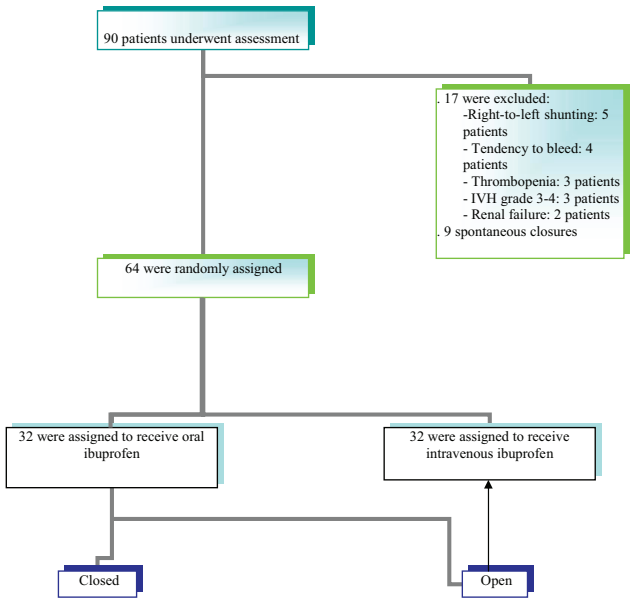

FIGURE 1
Enrollment.

Statistical Analysis

We calculated that a study group of 62 patients would be necessary for the study to be able to detect a difference of at least 25 percentage points in the closure rate between the oral ibuprofen and intravenous ibuprofen groups, assuming a closure rate of 65% with intravenous ibuprofen, with a P value of .05 and a power of 80%. Continuous data are presented as mean ± SD. Comparisons between groups were performed by using independent-samples t test for parametric continuous variables, Wilcoxon rank-sum test for nonparametric continuous variables, and Fisher's exact and χ^2 tests for categorical variables.

RESULTS

The number of patients who were eligible for the study, who were excluded and who were randomly assigned to receive oral ibuprofen or intravenous ibuprofen, are shown in Fig 1. There were no significant differences between the 2 groups in baseline clinical characteristics (Table 1). In each group, 75% of the patients were born after 28 weeks' gestation.

Efficacy of Treatment

The rate of closure of PDA was marginally favorable in group O (84.3% vs 62.5%, P = .04; 95% confidence interval: 0.99–1.84). Surgical ligation of the PDA was performed in 1 (3.1%) patient in group O and in 4 (12.5%) patients in group I (P = .25). There was no reopening of the ductus after closure was achieved. In 3 (9.3%) patients in group O and in 4 (12.5%) patients in group I, a minor ductal shunting persisted after therapy. In all these patients, the ductus closed spontaneously. Furosemide was prescribed in 4 patients in each group.

The number of doses needed in both groups did not differ (1.9 ± 0.2). Closure of the ductus was obtained after 1 dose of treatment in 11 and 8 patients, after 2 doses in 8 and 6 patients, and after 3 doses in 8 and 6 patients of groups O and I, respectively. On the other hand, there were no differences between failure of therapy groups (Table 2). In each group, when the therapy failed, the ductus shunting was severe.

Early Outcome

During the week after treatment, oliguria developed in no patient in group O and in 3 patients in group I (P = .23). An increase in serum creatinine level >16 mg/dL was observed in 3 patients in group I and in no patient in group O (P = .23). The change in creatinine concentrations in group O versus group I was 5.7 ± 1.2 mg/dLversus 10.9 ± 1.2 mg/dL (P < .01). Dopamine infusion was prescribed in 1 patient in group O and in 3 patients in group I. There were no differences between groups in the incidence of IVH 1–2 (n = 3 vs 3), IVH 3–4 (n = 1 vs 1), NEC (n = 2 vs 1), and bowel perforation (Ø vs Ø).

Late Outcome

Survival at 1 month was similar in the 2 groups (71.9% vs 75%; P = 1). When we consider all the duration of hospital stay, there were no significant differences between the treatment groups in, CLD (2 vs 3), NEC (4 vs 3), IVH (13 vs 12; P = .78), PVL (2 vs 2), sepsis (10 vs 9), and duration of intubation (5.7 ± 1.1 vs 5.1 ± 1.2 days). Mean duration of hospital stay was 37.5 ± 6.3 days in group O versus 39.5 ± 5.5 days in group I.

DISCUSSION

On the basis of our data, it seems that the rate of early ductal closure in VLBW infants is at least as effective

TABLE 1 **Baseline Characteristics of the Study Patients**

Characteristic	Group O ($N = 32$)	Group I ($N = 32$)	P
Gestational age, mean ± SD (range), wk	29.3 ± 1.2 (25–31.5)	28.3 ± 1.1 (25–31.5)	NS
<28	8	8	NS
28,1–30	13	12	NS
30,1–32	11	12	NS
Birth weight, mean ± SD (range), g	1227.2 ± 188 (600–1470)	1197.72 ± 158 (630–1420)	NS
<750 g, *n*	4	5	NS
751–1000 g, *n*	10	11	NS
1001–1500 g, *n*	18	16	NS
Gender			
Male, *n*	16	15	NS
Female, *n*	16	17	NS
Delivery by cesarean section, *n* (%)	22 (68.7)	20 (62.5)	NS
Maternal preeclampsia, *n* (%)	18 (56.2)	20 (62.5)	NS
Antenatal indomethacin , *n* (%)	0 (0.0)	0 (0.0)	NS
Antenatal glucocorticoids , *n* (%)	24 (75)	25 (78.1)	NS
Perinatal asphyxia, *n* (%)	3 (9.3)	2 (6.2)	NS
Early-onset infection, *n* (%)	2 (6.2)	3 (9.3)	NS
Surfactant treatment, *n* (%)	25 (78.1)	26 (81.2)	NS
NCPAP, *n* (%)	19 (59.3)	18 (56.2)	NS
IPPV, *n* (%)	9 (28.1)	10 (31.2)	NS
Airway pressure, mean ± SD (range), cm H_2O	7.1 ± 1.2 (6–9)	7.3 ± 1.3 (6–9)	NS
HFOV,*n* (%)	4 (12.5)	4 (12.5)	NS
Airway pressure, mean ± SD (range), cm H_2O	13.1 ± 1.8 (10–16)	12.8 ± 1.6 (10–17)	NS
Inspired oxygen fraction, mean ± SD (range), %	49.7 ± 13 (25–100)	47.7 ± 15 (25–100)	NS
IVH, *n* (%)	10 (31.2)	12 (37.5)	NS
Grade 1	6	7	
Grade 2	4	5	
Mean ductal diameter, mm	2.6	2.5	NS
Mean maximal shunt velocity, m/s	1.7 ± 0.4	1.8 ± 0.6	NS
Mean left-atrium-to-aortic-root ratio	1.6 ± 0.3	1.8 ± 0.4	NS
Degree of ductal shunting			
Moderate	10	11	NS
Severe	22	21	NS

NS indicates not significant; NCPAP, nasal continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; HFOV, high-frequency oscillatory ventilation.

with oral ibuprofen in comparison to the intravenous route. This is the first randomized study, to our knowledge, comparing oral ibuprofen and intravenous ibuprofen in closure of PDA. The rate of closure in the group assigned to intravenous ibuprofen was similar to rates previously reported.[6,11] Some trials on the use of oral ibuprofen for closure of PDA have been recently published.[5,12–18] All studies had small sample sizes. Aly,[14] in a randomized pilot study, reported that PDA was closed in 7 of 9 premature infants (≤35 weeks) given oral ibuprofen and in 10 of 12 premature infants given intravenous indomethacin ($P = .75$). Fakhraee,[16] in a randomized study, reported that PDA was closed in all of 18 premature infants (≤34 weeks) given oral ibuprofen and in 15 of 18 premature infants given oral indomethacin ($P > .05$). Efficacy of oral ibuprofen compared with intrave-

TABLE 2 **Comparison Between Failures of Therapy Groups**

Variable	Group O, PDA not Closed ($N = 5$), *n* (%)	Group I, PDA not Closed ($N = 12$), *n* (%)	P	Relative Risk (95% CI)
Antenatal glucocorticoids	4 (80)	10 (83.3)	.59	0.96 (0.58–1.59)
Gestational age				
<28 wk	4 (80)	6 (50)	.54	1.60 (0.78–3.27)
28–30 wk	1 (20)	3 (25)	.68	0.80 (0.11–5.96)
30–32 wk	0 (0)	3 (25)	.59	
Birth weight				
<750 g	3 (60)	5 (41.6)	.87	1.44 (0.54–3.84)
751–1000 g	1 (20)	4 (33.3)	.97	0.60 (0.09–4.12)
1001–1500 g	1 (20)	3 (25)	.68	0.80 (0.11–5.96)
HFOV, %	3 (60)	4 (33.3)	.69	1.80 (0.62–5.27)
Sepsis, %	3 (60)	7 (58.3)	.63	1.03 (0.43–2.43)

CI indicates confidence interval; HFOV, high-frequency oscillatory ventilation.

nous indomethacin, was reported by Supapannachart et al[13] and Chotigeat et al,[15] as well. In nonrandomized open trials, Heyman et al, [17] Cherif et al,[5] and Hariprasad et al[17] reported a ductal closure with oral ibuprofen respectively in 21 (95.4%) of 22 patients, 38 (95%) of 40 patients, and in 11 (84.6%) of 13 patients. The authors concluded that oral ibuprofen might constitute a feasible alternative in the treatment of PDA.

There are not enough studies on pharmacokinetics of oral ibuprofen in premature infants. Raju et al[19] reported, in a pilot study including a small number of premature infants, that ibuprofen was absorbed rapidly after oral administration, and peak concentrations in plasma were observed after 1 to 2 hours. Sharma et al[20] reported a wide interindividual variability for plasma concentrations, elimination half-life, and area under the plasma concentration-time curve. In our study, ibuprofen plasma levels were not measured. The slower absorption of oral ibuprofen, compared with the intravenous route, and the longer half-life probably prolonged the time of contact with the ductus leading to a higher responsiveness.

Closure of the ductus, in our study, was obtained after 1 or 2 doses of treatment, in 70% of both groups. The regimen commonly used is 10 + 5 + 5 mg/kg of ibuprofen every 24 hours. This regimen was based on the finding of Aranda and Varvarigou.[21,22] The small number of patients (10 in the study of Aranda and 11 in the study of Varvarigou) and the wide interindividual variability of ibuprofen plasma concentrations make these findings debatable. Although, this regimen was confirmed by the double-blind dose finding study of Desfrere et al,[23] it is not excluded that, if closure can be obtained with only 1 or 2 doses, the tolerability and safety of the treatment will probably be better. Indeed, in our study, the adverse effects were significantly fewer when the closure was achieved after an incomplete course of treatment. In each group, when the closure of the ductus was obtained with an incomplete course, the ductal shunting was moderate, suggesting that ibuprofen regimen could be reviewed according to degree of ductal shunting. In their article, Aranda et al[21] reported that it was unclear whether high maintained plasma concentrations of ibuprofen were necessary for ductal closure. In our previous open trial,[5] closure of the ductus with incomplete course of oral ibuprofen was obtained in 34 (89.4%) of 38 patients. Similarly, in the open trial of Heyman et al,[17] closure of the ductus with incomplete course of oral ibuprofen was obtained in 20 (95.2%) of 21 patients. A randomized, controlled regimen-finding study should be performed.

The adverse effects, in our study, were fewer in group O (9.3% vs 31.2%). Although the calculated *P* value was significant (.02), the 95% confidence interval for the relative risk (1.01–11.00) does not support a significant difference. The adverse effects in group I were similar to those previously reported.[6,11] Although renal failure was reported with intravenous ibuprofen at rates ranging from 6.8% to 57%,[6,11,22,24–28] it was reported by no study using oral ibuprofen.[5,12–18] However, Tiker and Yildirim[29] reported an anecdotal observation on transitional renal impairment in a 880 g, 29 weeks old infant given simultaneously a complete course of oral ibuprofen and aminoglycoside. Neither blood ibuprofen level nor aminoglycoside blood level was measured. In our study, renal failure was observed in 3 (9.3%) patients in group I versus none (0%) in group O. Rates of NEC reported with intravenous ibuprofen varied from 4.5% to 17%.[6,11,22,24–28] In a pool of 151 patients treated with oral ibuprofen, NEC was reported in12 (7.9%) cases.[5,12–18] Tatli[30] reported 2 cases of spontaneous intestinal perforation after oral ibuprofen treatment for PDA in 2 VLBW infants, but did not precise the osmolality and pH of the suspension used. It seems that intravenous ibuprofen was simply used orally, which is so different from a suspension intended for oral route. Recent concerns raised over oral ibuprofen because of its high osmolality.[31] In our study, NEC was observed in 1 (3.1%) patient in group I versus 2 (6.2%) patients in group O ($P = 1$). The osmolality of the ibuprofen suspension was 312 mosmol/L, and the pH was 5.8, both of which are not associated with gastrointestinal irritation. None of our patients had bowel perforation. In published, randomized, clinical trials, no case of GEB was reported with intravenous ibuprofen. In a pool of 151 patients treated with oral ibuprofen, GEB was reported in 19 cases (12.6%). In our study, GEB developed in 1 patient in group O and in no patient in group I. The rate of IVH reported with intravenous ibuprofen in our study was similar to those reported previously.[6,11,22,24–28]

Finally, there are several limitations to our study. The study was not powered to detect differences in complications. Larger sample size could also detect significance between groups in efficacy. The study would have been strengthened by measuring the blood levels of ibuprofen in both groups. Despite these limitations, study adds valuable information on the feasibility of using oral ibuprofen for PDA closure in premature infants.

CONCLUSIONS

Our data indicate that, for VLBW infants, the rate of early ductal closure was comparable and the adverse effects were fewer with oral ibuprofen in comparison to the intravenous route, but the differences were not statistically significant. A larger sample study is certainly needed for more definitive conclusion. On the other hand, our data suggest that ductal closure may be obtained with incomplete course of ibuprofen. A regimen-finding, well-designed study should be performed to confirm this trend.

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