Oral Ibuprofen Prophylaxis for Symptomatic Patent Ductus Arteriosus of Prematurity

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Background: *The oral suspension form of ibuprofen has been shown to have the same efficacy and safety as indomethacin in the treatment of symptomatic PDA, however its role is still questionable in the prophylaxis of symptomatic PDA.*
Objectives: *1. To assess the efficacy and safety of the drug in the prevention of symptomatic PDA in premature infants. 2. To study its pharmacokinetics-pharmacodynamics relationship.*
Material and Method: *A randomized, single-blinded, controlled study was performed on premature neonates with a gestational age between 28-32 weeks, birthweight ≤ 1500 grams at the neonatal unit, Queen Sirikit National Institute of Child Health from July 2003 to April 2004. Three doses of ibuprofen suspension or placebo were given 24 hours apart. Clinical evaluation was performed daily until the 28th day of life. Echocardiogram was performed prior to the drug administration, on the 3rd and 7th day of life.*
Results: *There were 22 and 20 cases in the ibuprofen and control group respectively. The epidemiologic data between the groups before enrollment showed no significant differences. Prevalence of symptomatic PDA was lower in the ibuprofen than in the control group without any significant side effects (0/22 vs 5/20, p = 0.015 on day 3 and 0/22 vs 6/20, p = 0.006 on day 7). Comparing with the pharmacokinetic study in older children and adult, the present study revealed nearly the same C_{max} but longer T_{max} and $T_{1/2}$ in premature neonates.*
Conclusion: *Oral ibuprofen suspension could reduce the prevalence of symptomatic PDA without any significant side effects.*

Keywords: *Oral ibuprofen, Patent ductus arteriosus, Preterm*

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The ductus arteriosus (DA) is a normal structure connecting the pulmonary artery to the descending aorta during fetal life. In full-term newborns, the DA closes within 24 to 48 hours after delivery. However, in preterm newborns, the DA frequently fails to close. As many as 70 percent of preterm infants delivered before 28 weeks of gestation require either medical or surgical closure of a patent ductus arteriosus (PDA). The clinical consequences of a PDA are related to the degree of left-to-right shunting through the DA. In response to a large left-to-right shunt, blood-flow distribution is altered, producing feeding intolerance, necrotizing enterocolitis, and decreased glomerular filtration rate. PDA also exposes the pulmonary microvasculature to systemic blood pressure and increased pulmonary blood flow, resulting in increased interstitial and alveolar edema and loss of pulmonary compliance. The increased fraction of inspired oxygen and mean airway pressure that are required to overcome these changes

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in compliance increases the incidence of chronic lung disease in preterm infants[1].

Indomethacin has been widely used in the prophylaxis and treatment of PDA[2-4] but with many adverse effects, ie. renal dysfunction, NEC, gastrointestinal hemorrhage, periventricular leukomalacia (PVL) and IVH[5-8]. Ibuprofen, another cyclo-oxygenase inhibitor has been reported by many authorities to have the same efficacy in PDA closure as indomethacin with fewer vasoconstrictive effects[9-11]. Although ibuprofen has many benefits over indomethacin, pulmonary adverse effects have been reported[12]. All of these studies were conducted with intravenous form (ibuprofen lysine) that is not widely available in many countries including Thailand. The oral suspension form of ibuprofen has been shown to have the same efficacy and safety in the treatment of symptomatic PDA[13,14]. If it could be shown to be as efficacious and as safe as the intravenous route, then oral ibuprofen would afford several important advantages: 1) intravenous ibuprofen is not available in Thailand and many other countries, 2) the required oral dose is of minimal volume (0.25-0.5 mL for infants who weigh 500-1000 g), 3) oral administration is very simple, and 4) the oral form of the drug is less expensive than the intravenous one. The present study was designed to determine whether oral ibuprofen treatment is efficacious and safe in the prophylaxis of symptomatic PDA in prematurity.

Objectives

1. To assess the efficacy of oral ibuprofen suspension in the prevention of symptomatic PDA in premature infants.

2. To evaluate the safety of ibuprofen on major organs.

3. To study the ibuprofen pharmacokinetics in order to correlate appropriate concentration that is probably required for maintenance of ductal closure (pharmacokinetics-pharmacodynamics relationship).

Material and Method

The present study was approved by the ethics committee of the Ministry of Public Health.

All premature neonates with a gestational age between 28-32 weeks, birthweight less than or equal to 1500 grams who were admitted to the neonatal unit, Queen Sirikit National Institute of Child Health from July 2003 to April 2004 were recruited in the present study. They were all evaluated by a single neonatologist and patients with the following criteria were excluded from the present study.

1. Maternal prenatal infection
2. Maternal drug abuse
3. Maternal non-steroidal anti-inflammatory drug use
4. Hydrops fetalis
5. Unstable clinical conditions
6. Congenital heart disease (other than PDA)
7. Other major congenital anomalies
8. Persistent pulmonary hypertension
9. Serum creatinine equal to or greater than 1.5 mg/dL
10. Platelet count equal to or less than 75,000 cells/ L
11. Abnormal coagulogram

An informed consent was obtained from the parents before recruitment. Patients were then evaluated by a single pediatric cardiologist who was blind to the treatment being given. Color Doppler echocardiography (GE VingMed Color Display Monitor, System 5, Transducer FPA 7.5 MHZ; GE Ultrasound) was performed on all infants within 24 hours of life.

Patients were randomly assigned into the present study and control group by block randomization. Sample size was calculated with confidence interval 0.05, and power 0.8, including an approximate 20% drop out rate. There were 22 patients in ibuprofen group a 20 cases in control group.A total of 42 subjects were recruited.

The patients in the study group were given 3 doses of ibuprofen suspension (Junifen, Boots Company, Thailand) at a dosage of 10mg/Kg via the orogastric tube, followed by 0.5 mL of distilled water. The first dose was given within the first 24 hours of life. The second and third doses were given at 24 and 48 hours after the first dose respectively. If the patient vomited within 45 minutes after the first dose, the time for the drug administration were delayed until the patient could be safely fed. Patients with any significant adverse drug reactions that required treatment were excluded from the study. Blood samples (0.2 mL each) were drawn from an umbilical catheter by the two-syringe method to analyse plasma drug concentration by High Performance Liquid Chromatography (HPLC) method. The time schedule for blood sampling was before the first dose, then at 2 hours, 4 hours, 8 hours, 10 hours, 12 hours, 14 hours, 18 hours after the first dose, 30 minutes before the second dose, 8 hours after the second dose, 30 minutes before the third dose and 8 hours after the third dose.

The patients in the control group were given 3 doses of orange starch suspension as placebo that

looked like ibuprofen with the same method and time schedule. The orange, starch suspension was prepared by the same pharmacist through out the entire study.

The medical personnel who took care of the patients were blind to the group assignment. All medical and nursing care was performed without any interference from the study team.

Clinical evaluation was performed daily by the same neonatologist until the 28th day of life. Echocardiogram was performed on the first day prior to the drug administration, then on the 3rd and 7th day of life.

Symptomatic PDA was defined as echocardiographic evidence of hemodynamically significant PDA (left atrium/aortic root diameter ratio > 1.4 or ductal size > 1.5 mm) together with any of the clinical findings: bounding pulses, pulse pressure > 35 mmHg, hyperactive precordium, tachycardia (heart rate > 170 beats/minute) and cardiomegaly in the chest X-ray. If present, symptomatic PDA was treated without any interference from the study team. Complete blood count, BUN, creatinine, electrolyte and coagulogram were performed 24 hours after the full course of drug administration.

Continuous data, such as weight, gestational age, various treatment modalities, IVH, and age at start of treatment, are presented as mean $\pm$ standard deviation. The mean differences were tested with independent t-test. Categorial variables such as sex, antenatal steroid therapy, number of PDA cases, etc were analyzed with the percentage in each variable and the mean difference in each variable were compared by chi-square or Fisher's exact test. Survival rate at day 28 and changes in serum creatinine concentrations were compared using t-test.

Results

There were one hundred and thirteen patients admitted during this 10-month-period. Only 42 cases were recruited in the present study since 71 cases (62.83%) were excluded due to their unstable clinical conditions. These 42 cases were randomized to the ibuprofen (n = 22) and control group (n = 20). There were no significant differences in sex, gestational age, birth weight, Apgar scores at 1 and 5 minutes, antenatal steroid, age of drug administration, and the presence of PDA by echocardiogram between the groups before enrollment. The epidemiologic data are shown in the Table 1. The daily fluid intake in the first 7 days of life did not differ significantly between the groups.

Prevention of symptomatic PDA

From the clinical and echocardiogram evaluation, the authors classified the patients into three groups, no PDA, asymptomatic PDA and symptomatic PDA.

In the ibuprofen group (n = 22) there were 15 infants with asymptomatic PDA on day 0 and only one case with asymptomatic PDA (4.55%) on day 3. By the 7th day, PDA was not detected in any infant from this group.

In the control group (n=20), there were 14 asymptomatic PDA on day 0 and two cases with symptomatic PDA before day 3; their PDA's were treated by intravenous indomethacin (0.2 mg/kg/dose for 3 doses) on day 2 and day 3 respectively. On day 3, there were three more cases with symptomatic PDA and two cases of asymptomatic PDA. All three cases with symptomatic PDA were treated successfully, two with indomethacin and the third with oral ibuprofen (10 mg/kg/dose for 3 doses). On day 7, there was one more case with symptomatic PDA.

Cases of asymptomatic and cumulative symptomatic PDA are summarized in Table 2.

Table 1. Epidemiologic data of both groups

Clinical characteristics	Ibuprofen group (n = 22)	Control group (n = 20)	p-value
Sex (M:F) (%)	14:8 (1.8:1)	13:7 (1.8:1)	0.927
Gestational age (week)	30.64$\pm$1.76	30.20$\pm$2.14	0.473
Birth weight (gram)	1,279.64$\pm$80.33	1,214.50$\pm$217.52	0.295
Apgar score			
1 min	6.38$\pm$2.52	7.10$\pm$1.71	0.291
5 min	7.90$\pm$2.17	8.15$\pm$1.53	0.679
Antenatal steroid (%)	13/22 (59.09)	10/20 (50.00)	0.554
Age of drug administration (hour)	23.93$\pm$0.46	22.88$\pm$10.13	0.732
PDA before enrollment	14 (70.00%)	15 (68.18%)	0.899

Table 2. Asymptomatic and cumulative symptomatic PDA

		Study group (n = 22)	Control group (n = 20)	p-value
Day 0	Asymptomatic	15	14	0.899
	Symptomatic	0	0	0.827
Day 3	Asymptomatic	1	2	0.493
	Symptomatic	0	5	0.015*
Day 7	Asymptomatic	0	0	0.827
	Symptomatic	0	6	0.006*

The safety of ibuprofen

There were no statistical differences in the prevalence of PPHN, prevalence of bronchopulmonary dysplasia (BPD), days on mechanical ventilation, days of oxygen therapy, abdominal distention, feeding difficulty, NEC, IVH, retinopathy of prematurity (ROP), length of hospital stay and survival rate between the present study and the control group. Although the cases in the study group were started on feeds later than those in the control group, the days to full feeding were not different between the groups. There were no statistical differences in the laboratory results including BUN, Cr, coagulogram (international normalized ratio, partial thromboplastin time, prothrombin time, thrombin time) and platelet count before and 24 hours after the complete course of drug administration.

Upper gastrointestinal bleeding occurred in the study group more frequently than in the control group but the difference was not statistically significant. The number of cases that needed intervention was not different between the groups as well. (Table 3)

One of the patients in the study group died from Staphylococcus coagulase negative septicemia on day 16 and one from the control group died from clinical sepsis at day 11.

Ibuprofen pharmacokinetics

There were many variations in the pattern of drug kinetics. With the use of Win Nonlin program for the calculation, the authors could fit only drug data of 17 cases. The mean, standard deviation (SD) and median of these data are shown in Table 4.

With the right skewness of the data distribution, the authors used the median for the interpretation. Cases with ductal closure had the median C_{max} level of 31.73 mcg/mL after the first dose. The only case with residual PDA on the 3rd day had very low T_{max} (2 hours) very low $T_{1/2}$ (6.99 hours) and very rapid drug elimination (Ke 0.0999/hour).

Discussion

The presented data showed a significantly higher percentage of ductal closure both on day 3 and day 7 in the study than in the control group with minimal adverse effects. These data corresponds with previous studies of the intravenous[9,15] and oral form of ibuprofen which suggested ibuprofen as an alternative for PDA treatment with equal efficacy and low side effects[16-19].

The high prevalence of upper gastrointestinal bleeding and longer time to start feeding in the present study warns physicians that the drug is not without risk as has already been stated by others[20].

Although there was a report of PPHN associated with ibuprofen administration[21], there were no cases of PPHN in the present study. However, the patients in the present study were more mature and the drug was administered later compared to that study.

At clinically appropriate ibuprofen concentrations the free fraction of bilirubin was increased by a factor of 4 thus ibuprofen may increase the risk of bilirubin encephalopathy when used in sick, premature infants[22]. Although the authors did not completely evaluate this complication in this study, there were no overt cases of suspected bilirubin encephalopathy.

The pharmacokinetic parameters of oral ibuprofen among the preterm infants with PDA showed a large interindividual variability[23,24].

The authors could not fit drug data of five subjects to Win Nonlin program because there were many variations in the pattern of drug kinetics and only the data of 17 cases were selected by the program for calculation.

The present study revealed higher C_{max}, T_{max}, and $T_{1/2}$ than data in a previous study[24]. The daily differences in physiologic factors or different method of HPLC used may have affected these pharmacokinetic data. The present study suggests that the drug

Table 3. Clinical and laboratory monitoring of the drug safety

Outcomes	Ibuprofen group (n = 22)	Control group (n = 20)	p-value
Respiratory tract			
-PPHN	0	0	
-BPD	7/21 (33.3%)	2/20 (10.0%)	0.130
-Days of mechanical ventilation (mean ± SD)	11.66±12.49	7.59±14.36	0.332
-Days of oxygen therapy (mean ± SD)	15.27±15.96	9.98±9.83	0.199
GI tract			
-Abdominal distention	10/22 (45.5%)	6/20 (30.0%)	0.303
-Feeding difficulty	12/21 (57.1%)	8/20 (40.0%)	0.272
-NEC	8/21 (38.1%)	6/20 (30.0%)	0.585
-Days of start feeding (mean ± SD)	6.23±4.72	3.70±1.69	0.029*
-Days to full feeding (mean ± SD)	29.71±17.90	26.94±23.29	0.677
-Upper GI bleeding	12/22 (54.5%)	6/20 (30%)	0.196
-Bleeding needed Rx	5/22 (22.7%)	4/20 (20%)	0.872
IVH	2/21 (9.5%)	4/19 (21.1%)	0.398
ROP	3/21 (14.3%)	2/19 (10.5%)	1.000
Days of hospital stay (mean ± SD)	61.90±28.97	53.65±25.42	0.339
Survival rate at day 7	22/22 (100%)	20/20 (100%)	1.000
Survival rate at day 28	19/21 (90.5%)	19/20 (95.0%)	1.000
Serum BUN (mean ± SD)			
Day 1	12.22±4.35	13.35±4.15	0.334
Day 3	15.14±6.50	17.84±13.65	0.422
Serum Cr (mean ± SD)			
Day 1	0.82±0.18	0.91±0.22	0.211
Day 3	0.87±0.17	0.86± 0.22	0.883
Prolonged coagulogram			
Day3	4/22 (13.6%)	2/20 (15%)	0.573
Platelet count (mean ± SD)			
Day 1	224,545.45±64,680.70	219,400±50,988.50	0.778
Day 3	185,590.91±55,825.12	184,368±84,343.40	0.957

Table 4. The mean, SD and median of pharmacokinetic data

	Mean	SD	Median
Apparent volume of distribution (Vd/F) in l/Kg	0.3125	0.1146	0.3175
Absorption rate constant(Ka) in hr^{-1}	0.6562	1.1646	0.2035
Elimination rate constant(Ke) in hr^{-1}	0.0342	0.0348	0.0244
Area under the curve(AUC) in l/hr	464,514.18	1,903,449.42	1,808.20
Time to maximum concentration (T_{max}) in hours	17.16	28.32	10.89
Maximum concentration(C_{max}) in mcg/ml	31.78	8.67	31.73

level necessary for PDA closure could be lower than previously reported[15,25].

Heyman E, et al. reported that 63.4% of their premature babies had their ducts closed with only a single dose of oral ibuprofen[17]. It is possible that the slower rate of oral ibuprofen absorption and the longer time to reach C_{max} in premature babies could sustain ibuprofen level long enough to exert its pharmacological effect at the ductal site. Twenty-two cases in the ibuprofen group of the present study had ductal closure within 3 days of complete drug administration. The drug level of the only case of asymptomatic PDA on day 3 reached maximum concentration within 2 hours, and the elimination process was very fast. The pharmacokinetic data of the present case was nearly equal to those in older children and adults. This patient had the highest gestational age and birthweight was rather high when compared with other subjects in the study group. This may reflect that the drug biodisposition process was so mature that the drug level was not sustained long enough for exerting its action. Data from the other cases with their ductal closure suggested that the sustained average ibuprofen level of about 30 mcg/mL might be enough for ductal closure. More studies are needed to confirm this.

Conclusion

With completion of three doses administration, prophylactic ibuprofen suspension could reduce the prevalence of both asymptomatic and symptomatic PDA evaluated on day 3 and day 7. Ibuprofen suspension in this dosage did not have significant side effects, however, frequent gastrointestinal bleeding warrants careful observation during the administration. There were high interindividual variabilities of pharmacokinetic parameters in premature infants. The C_{max} value was nearly the same as that in older children or adults. Cases with ductal closure had C_{max} about 30 mcg/mL. The exact level that could close PDA was unknown but from this data, the authors can state that the level produced by suspension form with long elimination time may be adequate for PDA closure. The T_{max} and $T_{1/2}$ were longer than those studied in older children or adults. This prolonged T_{max} and $T_{1/2}$ may lead to an assumption that only a single dose of ibuprofen may be adequate for closing PDA.

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การให้ยาไอบูโพรเฟนกินเพื่อป้องกัน Symptomatic Patent Ductus Arteriosus ในทารกก่อนกำหนด

วราภรณ์ แสงทวีสิน, ชัยสิทธิ์ แสงทวีสิน, ชาญชัย รักษาสินบริสุทธิ์, กอบธัม สถิรกุล, วิบูลย์ กาญจนพัฒนกุล, มิรา โครานา, สุนทร ฮ้อเผ่าพันธ์

ความเป็นมา: *มีการศึกษาถึงการใช้ยาไอบูโพรเฟนกินเพื่อรักษาผู้ป่วยที่เป็น symptomatic PDA ในทารกก่อนกำหนด พบว่าได้ผลเช่นเดียวกับยาอินโดเมทธาซิน แต่การใช้ยาไอบูโพรเฟนกินเพื่อป้องกัน symptomatic PDA ยังมีการศึกษาน้อย*

วัตถุประสงค์: *1. เพื่อศึกษาประสิทธิภาพและความปลอดภัยของการใช้ยาไอบูโพรเฟนกินเพื่อป้องกัน symptomatic PDA ในทารกก่อนกำหนด 2. เพื่อศึกษาความสัมพันธ์ของเภสัชจลนศาสตร์และเภสัชพลศาสตร์ของยาไอบูโพรเฟนกินในการป้องกัน symptomatic PDA ในทารกก่อนกำหนด*

วัสดุและวิธีการ: *Randomized, single-blinded, controlled study ทารกก่อนกำหนดที่มีอายุครรภ์ 28-32 สัปดาห์ น้ำหนักแรกเกิด ≤ 1,500 กรัม ที่รับไว้ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินีในระหว่าง กรกฎาคม พ.ศ. 2546 - เมษายน พ.ศ. 2547 ทารกในกลุ่มศึกษาจะได้รับยาจริง กลุ่มควบคุมจะได้รับยาหลอก ทารกทุกรายจะได้รับยา 3 ครั้ง ห่างกันทุก 24 ชั่วโมง ประเมินอาการทางคลินิกทารกจนถึงอายุ 28 วัน การตรวจ Echocardiogram จะทำก่อนให้ยาและหลังคลอด วันที่3 และวันที่ 7*

ผลการศึกษา: *ทารกในกลุ่มศึกษามีจำนวน 22 ราย กลุ่มควบคุม มี 20 ราย ทารกทั้งสองกลุ่มไม่มีความแตกต่างในด้านข้อมูลระบาดวิทยา ทารกกลุ่มศึกษามีอุบัติการณ์ของ symptomatic PDA น้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (0/22 vs 5/20, p = 0.015 ในวันที่ 3 และ 0/22 vs 6/20, p = 0.006 on day 7) พบอาการไม่พึงประสงค์ในทารกสองกลุ่มไม่แตกต่างกัน การศึกษาทางเภสัชจลนศาสตร์พบว่ามีความแตกต่างระหว่างบุคคลอย่างมาก ค่า C_{max} ใกล้เคียงกับในผู้ใหญ่ แต่ค่า T_{max} and $T_{1/2}$ ในทารกก่อนกำหนดมีค่ามากกว่า*

สรุป: *การให้ยาไอบรูโพรเฟนกินสามารถลดอุบัติการณ์ของ symptomatic PDA โดยไม่เกิดภาวะแทรกซ้อนที่สำคัญ*