RESEARCH BRIEF

Ibuprofen Lysinate and Sodium Ibuprofen for Prophylaxis of Patent Ductus Arteriosus in Preterm Neonates

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This retrospective, study compared the efficacy and safety of Ibuprofen-Lysinate (Arfen, intramuscular formulation, Group I, *n*=156) used during 2000-2005 and Sodium-ibuprofen (Pedea, intravenous solution, Group II, *n*=60) used during 2006-2008, for the prophylaxis of Patent Ductus Arteriosus in inborn neonates with gestational age ≤28 weeks. Ductus closure rate after prophylaxis was significantly higher (73.1% *vs* 50%; *P*=0.002) and surgical ligation significantly lower (8.2% *vs* 23.3%**;** *P*=0.005) in Group I. A smaller number of neonates of Group I *vs* Group II showed oliguria and hemorrhagic disease.

Key words: *Ibuprofen, Patent ductus arteriosus, Preterm, Prophylaxis.*

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Different ibuprofen formulations have been used for both prevention and treatment of patent ductus arteriosus (PDA) in premature infants [1,2]. In this study, we compared effectiveness and safety of ibuprofen-lysinate (Ibu-Lys) and sodium-ibuprofen (Ibu-Na).

Methods

Data were retrospectively collected in our center between 2000 to 2008. Inborn neonates with gestational age (GA) ≤28 weeks received a standard 3-dose course of prophylactic ibuprofen (10-5-5 mg/kg at 24-hour intervals) starting within two hours of life. Two different compounds were intravenously used: Ibu-Lys (Arfen, intramuscular formulation, Lysafarma, Italy) during years 2000-2005 (Group I) and Ibu-Na (Pedea, ready-to-use intravenous solution, Orphan, France) during 2006-2008 (Group II). Exclusion criteria included antenatal indomethacin administration, GA<24 weeks, birthweight <450 grams, congenital heart defects, persistent pulmonary hypertension (PPHN), platelet count $<50\times10^9$/L, major congenital malformations, and premature rupture of membranes >4 weeks. Echocardiography was performed at birth (T0), at 72 hours of life (T72) to verify prophylaxis efficacy, and then as necessary. In case of still patent and hemodynamically significant ductus at T72, a course of ibuprofen (10-5-5 mg/kg/day) was administered and followed, in case of failure, by a course of IV indomethacin (0.2-0.2-0.2 mg/kg at 12-hour intervals). Indications for surgical ligation were unsuccessful medical treatment or contraindications to it (renal failure, thrombocytopenia, bleeding).

PDA was considered hemodynamically significant with at least two of the following criteria: left atrial/aortic root ratio >1.5, reverse end-diastolic flow in descending aorta, pulsatile transductal flow (Vmax) <1.8m/s, ductus diameter >1.5 mm. Fluid intake and surfactant administration were provided according to our standard protocols [3]. During prophylaxis period, urine output, serum creatinine, the occurrence of necrotising enterocolitis (NEC), spontaneous intestinal perforation (SIP), PPHN, pulmonary hemorrhage (PH), intraventricular hemorrhage (IVH) and hypocoagulability were encountered.

Statistical analysis was performed using the Stata Statistical Software: Release 10 (StataCorp LP, College Station, Tx). Univariate statistical analysis was performed using Student's *t* test for continuous variables, Wilcoxon rank-sum test (Mann Whitney U test) for non-parametric continuous variables and Fisher's exact test for categorical variables. Logistic regression analysis was built to verify the independence of treatment effect on

ductus closure. Prenatal/neonatal variables were included in the model if significant at a 0.10 level at univariate analysis. A $P<0.05$ was considered significant.

RESULTS

Overall, 216 neonates received IV ibuprofen prophylaxis: 156 Ibu-Lys (Group I) and 60 Ibu-Na (Group II). Maternal/neonatal characteristics were similar between the groups, except for a higher rate of IUGR, twins, lower birthweight and need for surfactant therapy in Group II (***Table* I**). Ductus closure rate after prophylaxis was significantly higher (73.1% *vs* 50%; *P*=0.002) and surgical ligation significantly lower (8.2% *vs* 23.3%; *P*=0.005) in Group I. Logistic regression analysis showed that Ibu-Na was significantly associated with higher unsuccessful prophylaxis rate, independently on gender, IUGR, and twins. Surfactant therapy and lower birthweight were also significantly and independently associated with higher prophylaxis failure rate (***Table* II**). A smaller number of neonates of Group I *versus* Group II showed oliguria (20/156 *vs* 14/60*; P*=0.064) and hemorrhagic diseases, such as severe IVH (7/156 *vs* 7/60; *P*=0.067) and PH (4/156 *vs* 6/60, *P*=0.029), despite more neonates with hypocoagulability in Group I (29/156 *vs* 3/60; *P*=0.011). No differences were found between the groups in PPHN (7/156 *vs* 4/60; *P*=0.503), NEC (2/156 *vs* 1/60; *P*=0.187) and SIP (1/156 vs 0/60; *P*=1.000). Nevertheless, considering the first week of life, a lower number of SIP was observed in Group I (1/156 *vs* 4/60; *P*=0.021).

DISCUSSION

Our study highlights higher efficacy and safety of Ibu-Lys compared to Ibu-Na for PDA prophylaxis. Only three variables (birthweight, surfactant treat-ment, Ibu-Na) were significantly and independently associated with higher unsuccessful prophylaxis rate. It is known that birthweight and RDS affect ibuprofen efficacy [4], while difference in effectiveness related to type of compound has never been reported.

The recent Cochrane review on the topic [1], including six trials, analyzed the prophylaxis efficacy regardless the kind of formulation, although four studies used IV Ibu-Lys (Arfen), one IV ibuprofen-THAM (Orphan-Europe, France) and one oral ibuprofen suspension (Junifen, Boots Company, Thailand). The highest rate of prophylaxis failure (27.7%) was with ibuprofen-THAM [5], and the lowest (9.1%) using Ibu-Lys [6].

Ibuprofen is a weak acid, used as salt with different bases: sodium hydroxide, tris (hydro-xymethyl)

TABLE I BASELINE CLINICAL CHARACTERISTICS OF THE STUDY GROUPS

	Group I (Ibu-Lys) (N = 156)	*Group II (Ibu-Na) (N = 60)*
Mothers		
Preeclampsia, *n* (%)	29 (18.6)	5 (8.3)
HELLP syndrome , *n* (%)	4 (2.6)	1 (1.7)
Gestational HT, *n* (%)	19 (12.2)	47 (11.7)
Gestational DM, *n* (%)	9 (5.8)	2 (3.3)
pPROM, *n* (%)	50 (32.1)	16 (26.7)
Chorionamniotitis, *n* (%)	18 (11.5)	6 (10.0)
IUGR, *n* (%)†	16 (10.3)	16 (26.7)
Antenatal steroids, n (%)	140 (89.7)	56 (93.3)
Complete course, *n* (%)	93 (59.6)	32 (53.3)
Cesarean Section, *n* (%)	123 (78.8)	48 (80.0)
Infants		
Gestational age, wks*	26.9 ± 1.3	26.7 ± 1.1
Birthweight, g*†	872 ± 244	793 ± 221
Male, *n* (%)†	78 (50.0)	39 (65.0)
SGA, *n* (%)	30 (19.2)	16 (26.7)
Twin, *n* (%)†	36 (23.1)	23 (38.3)
Apgar score* at 5 min	7.3 ± 1.2	7.4 ± 1.1
Intubation, *n* (%)	98 (63.6)	40 (66.7)
Surfactant therapy, *n* (%)†	103 (66.0)	51 (85.0)
Multiple doses, *n* (%)	31 (19.9)	17 (28.3)
Age at first dose (h), *n* (%)	4.7 ± 3.0	5.0 ± 6.2
Fluid intake (mL/kg)*		
Day 1	70.2 ± 11.8	67.1 ± 9.9
Day 4	129.8 ± 20.2	123.8 ± 16.3
Sepsis, *n* (%)	11 (7.1)	3 (5.0)

** Values expressed as mean ± SD; HELLP indicates hemolysis, elevated liver enzyme level and low platelet count; pPROM, preterm premature rupture of membranes; IUGR, intra uterine growth restriction; SGA, small for gestational age; DM: diabetes mellitus; HT: hypertension; †P<0.05.*

TABLE II DUCTUS PATENCY MODELS (ADJUSTED FOR THE STATISTICALLY SIGNIFICANT VARIABLES)

	OR	*95% CI*
Birthweight*	0.82	0.71-0.94
IUGR	0.73	0.29-1.82
Male	0.99	0.53-1.85
Twin	0.76	0.38-1.51
Surfactant therapy	3.47	1.54-7.85
Ibu-Na	2.28	1.16-4.49

** OR increase per 100 g. IUGR: intra uterine growth restriction.*

aminomethane (THAM), amines such as Lysine. During neonatal period, Ibu-Lys IM formulations (Arfen, Imbun) were off-label intravenously utilized [4,6-9] because no neonatal IV compounds existed. The IV ibuprofen formulation specifically manufactured for neonatal period (Pedea) was approved in 2004 and adopted by us from 2006. The only study on bioequivalence of two Ibuprofen formulations intravenously adminis-tered was performed in healthy male adults with a single 5 mg/kg dose: Ibu-Lys (Imbun) was bioequivalent to Ibu-Na (Pedea) [10].

Since we found higher efficacy of Ibu-Lys *versus* Ibu-Na, presumably biochemical properties of Ibu-Lys influence its effectiveness. Ibu-Lys higher lipophilicity determines higher transmembrane passage and tissue concentrations, and less drug removal, probably influencing its bioavailability and plasma concentration-time curve areas under the curve (AUC). A study showed that higher AUC values are associated with higher ductus closure rate; neonates with closed ductus versus neonates with persisting PDA had significantly higher values of either AUC after the first dose of ibuprofen or cumulated AUC after the three doses [11], prolonging the contact-time between drug and ductus wall [12].

We are aware that our study was retrospective, at different time-points, and with different samples-size, although the main treatment protocols (ibuprofen, fluids and surfactant administration) remained unchanged [3]. Further prospective randomized trials need to confirm our data. Since a new IV Ibu-Lys (Neoprofen) was recently commercialized for neonatal use [13], a prospective head-on comparison with Ibu-Na (Pedea) should be performed to define the optimal regimen.

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REFERENCES

1. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2006;1:CD004213.
2. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database of Syst Rev. 2010;4:CD003481.
3. Bersani I, De Carolis MP, Lacerenza S, De Rosa G, Fusco FP, Cota F, *et al.* Is the prophylaxis of patent ductus arteriosus useful in extremely premature infants? Turk J Pediatr. [in press].
4. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwé W, Jespers A, *et al.* Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:1945-9.
5. Gournay V, Roze JC, Kuster A, Daoud P, Cambonie G, Hascoet JM, *et al*. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:1939-44.
6. Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, *et al*. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: A multicenter, randomized study. Pediatrics. 2005;115:1529-35.
7. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. JAMA. 1996;275:539-44.
8. Dani C, Bertini G, Reali MF, Murru P, Fabris C, Vangi V, *et al.* Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta Pediatrica. 2000;89:1369-74.
9. De Carolis MP, Romagnoli C, Polimeni V, Piersigilli F, Zecca E, Papacci P, *et al.* Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. Eur J Ped. 2000;159:364-8.
10. Chassard D, Geneteau A, Gualano V, Brault M. Bioequivalence study of two ibuprofen formulations administered intravenously in healthy male volunteers. Clin Drug Investig. 2004;24:739-47.
11. Hirt D, Van Overmeire B, Treluyer JM, Langhendries JP, Marguglio A, Eisinger MJ, *et al.* An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study. Br J Clin Pharmacol. 2008;65:629-36.
12. Cherif A, Khrouf N, Jabnoun S, Mokrani C, Amara MB, Guellouze N, *et al.* Randomized pilot study comparing oral ibuprofen with intravenous ibuprofen in very low birth weight infants with patent ductus arteriosus. Pediatrics. 2008;122:e1256-61.
13. Poon G. Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus. Proc (Bayl Univ Med Cent) 2007:20;85-5.