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REVIEW

Clinical pharmacology of ibuprofen in preterm infants: A meta-analysis of published data

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OBJECTIVES: Ibuprofen is a non-selective anti-inflammatory cyclooxygenase inhibitor drug of the propionic acid class of non-steroidal agents, available without prescription in the USA. In preterm infants, ibuprofen is used to close the Patent Ductus Arteriosus and it was found to be more effective than indomethacin. This meta-analysis determined whether differences exist in the closure rate of Patent Ductus Arteriosus following the oral vs. intravenous ibuprofen administration to preterm infants; it examines metabolism, pharmacokinetics and adverse renal effects of ibuprofen.

METHOD: The bibliographic search was performed using PubMed and EMBASE databases as search engines. In addition, the books ''Neofax: a Manual of Drugs Used in the Neonatal Care'' by Young and Mangum and the ''Neonatal Formulary'' were consulted.

RESULTS: Patent Ductus Arteriosus closure was 89% with oral ibuprofen (9 reports) vs. 75% with intravenous ibuprofen (13 reports); p = 0.011. The half-life ($t_{1/2}$) of ibuprofen is 43.1 and 26.8 hours in infants on the 3rd and 5th day of life, respectively. In adults, the half-life of ibuprofen is 2 hours. The rapid shortening of ibuprofen $t_{1/2}$ is due to the rapid increase of cytochromes CYP2C9 and CYP2C8 activities, which metabolize ibuprofen and which surge in the liver during the first weeks of life. Ibuprofen reduces the renal glomerular filtration and the sodium tubular transport rates.

CONCLUSION: Oral ibuprofen is more effective than intravenous ibuprofen to close patent ductus arteriosus. Ibuprofen has fewer renal adverse effects than intravenous ibuprofen and has the most favourable risk/benefit ratio.

KEYWORDS: adverse-effects; ibuprofen; metabolism; neonate; pharmacokinetics.

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INTRODUCTION

After birth, the patent ductus arteriosus (PDA) closes spontaneously within 2 to 4 days in full-term infants.[1] In contrast, in 80% of the infants weighing <1,000 g, the ductus remains open.[1] The incidence of PDA increases with prematurity and is inverse related to the gestational age.[2] The major factor determining the closure of PDA is the tension of oxygen which increases significantly after birth causing contraction of ductal smooth muscle and closure of PDA.[3] Prostaglandins play a role in maintaining the patency of the ductus arteriosus during fetal life and have an opposite effect to that of oxygen.[4] Ibuprofen is a potent inhibitor of prostaglandin E2 synthesis and is employed to stimulate the closure of PDA.[5]

The pharmacological basis of the PDA closure is the inhibition of prostaglandin synthesis by non-selective cyclo-oxygenase (nsCOX) inhibitors leading to ductal constriction.[6] Indomethacin was the first nsCOX inhibitor employed to close the PDA.[6] It has been used for many years and is still used today. Ibuprofen is likewise a nsCOX inhibitor, which is better tolerated than indomethacin.[7-16]

In Europe, 16 neonatal intensive care units administer ibuprofen intravenously while 13 administer ibuprofen orally[17] to treat PDA. Three recent articles[18-20] have shown that %PDA closure was significantly higher after oral than after intravenous ibuprofen administration. This prompted us to review the literature on the closure of PDA to ascertain whether differences exist in the two administration regimens of ibuprofen as regards the closure rate of PDA and possibly the adverse renal effects.

The literature on the metabolism, pharmacokinetics, and renal adverse effects of ibuprofen in preterm infants published in the last twenty years is spread out. The objective of the present study is to review and produce a meta-analysis of the clinical pharmacology of ibuprofen in preterm infants. In particular, the following subjects are considered: (a) to define the %PDA closure following oral or intravenous administration of ibuprofen, to review (b) the metabolism and (c) the pharmacokinetics of ibuprofen in preterm infants. Another subject of this study is (d) the assessment of the renal adverse

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effects of ibuprofen in preterm infants and finally, (e) to ascertain whether the renal adverse effects are affected by the administration routes of ibuprofen.

BIBLIOGRAPHIC SEARCH

The bibliographic search was performed electronically using PubMed and EMBASE databases as search engines. The following key words were used: ''ibuprofen neonate'', ''patent ductus arteriosus and ibuprofen'', ''pharmacokinetics ibuprofen neonate'', ''ibuprofen metabolism'', ''ibuprofen metabolism neonate'', ''CYP2C9 ibuprofen neonate'', ''CYP2C8 ibuprofen neonate'' and ''adverse renal effects ibuprofen neonate''. In addition, the books ''Neofax: a Manual of Drugs Used in the Neonatal Care'' by Young and Mangum published in 2010[21] and the ''Neonatal Formulary'' published in 2011[22] were consulted.

RESULTS

Dose of ibuprofen for preterm infants

Neonatal Formulary[22] states that ibuprofen is an effective alternative to indomethacin in the management of PDA. Young and Mangum[21] suggest administering ibuprofen intravenously, by syringe pump over 15 min, at the dose of 10 mg/kg, followed by 5 mg/kg after 24 and 48 hours. The Neonatal Formulary[22] states that some studies suggest that oral treatment is just as effective. A second course of treatment may be effective when the first course is not.

Closing of PDA in preterm infants

Table 1 summarizes reported data on %PDA closure. Thirteen studies on PDA closure obtained by the intravenous administration of ibuprofen and nine studies on the PDA closure obtained by the oral administration of ibuprofen have been reported. The %PDA closure (mean ± SD) was 89.4 ± 6.7% (oral ibuprofen) and 74.9 ± 14.3% (intravenous ibuprofen; p = 0.0108). The coefficients of variation were 7.1% (oral ibuprofen) and 19.1% (intravenous ibuprofen). The gestational age and the body weight of the infants enrolled in the study are shown in Table 1. Ibuprofen (10 mg/kg), followed by 5 mg/kg, after 24 and 48 hours, was administered to all infants.

Comparison of %PDA closure between oral and intravenous administration of ibuprofen to preterm infants

Three recent articles[18-20]compared the rate of PDA closure following oral or intravenous administration of ibuprofen. In Cherif et al.,[18] 32 patients received ibuprofen orally while 32 other infants received ibuprofen intravenously. The %PDA closure was 84.3% (for oral ibuprofen) versus 62.5% (for intravenous ibuprofen — $p<0.05$). Surgical ligation of the PDA was performed in 1 (3.1%) patient included in the oral ibuprofen group and in 4 (12.5%) patients in the intravenous ibuprofen group (p = 0.25). During the first week after treatment, creatinine concentrations were 5.7 ± 1.2 mg/dL (for oral ibuprofen) and 10.9 ± 1.2 mg/dL (for intravenous ibuprofen — $p<0.01$). An increase in serum creatinine level >16 mg/dL was observed in none of the patients in the ''oral group'', but in 3 patients in the ''intravenous group'' ($p<0.01$). The duration of the hospital stay was 37.5 ± 6.3 and 39.5 ± 5.5 days (non significant) for the oral and intravenous ibuprofen groups, respectively. The adverse effects were 9.3% in the oral group and 31.2% in the intravenous group (p = 0.02). The authors did not explain how they estimated the percent of the adverse effects. Survival at 1 month was similar in the two groups (71.9% versus 75%, non significant).

In Gokmen et al.,[19] oral and intravenous ibuprofen was administered to 52 and 50 infants, respectively. The %PDA closure was 84.6% (oral ibuprofen) and 62.0% (intravenous ibuprofen; p = 0.011). Six patients (11.5%) in the oral ibuprofen group required a second course of drug therapy, compared to 19 infants (38%, p = 0.012) in the intravenous ibuprofen group. The duration of mechanical ventilation

Table 1 - Demographic data of the preterm infants and percentage of the patent ductus arteriosus (PDA) closure

GA (Weeks)	BW (g)	Number of cases	Dose of ibuprofen (mg)	Route of administration	%PDA closed	Reference
22.4-31.0	565-1460	34	10-5-5	Intravenous	100	7
28.1 ± 1.1	934 ± 288	23	10-5-5	Intravenous	87.0	43
28.1 ± 1.7	1048 ± 315	205	10-5-5	Intravenous	84.0	34
25.6 ± 1.4	757 ± 127	160	10-10	Intravenous	85.0	64
27.0 ± 2.9	853 ± 383	22	10-5-5	Intravenous	72.7	42
26[a]	857[a]	22	10-5-5	Intravenous	72.7	65
26.6[a]	994[a]	30	10-5-5	Intravenous	94.0	66
26 ± 1.7	835 ± 215	35	10-5-5	Intravenous	63.0*	67
26.0 ± 1.7	838 ± 215	20	10-5-5	Intravenous	77.0	68
27.7 ± 3.2	1086 ± 572	23	10-5-5	Intravenous	52.6	69
28.3 ± 1.1	1197 ± 158	32	10-5-5	Intravenous	62.5	41
28.7 ± 2.1	na	50	10-5-5	Intravenous	62.0	19
26.3 ± 1.3	872 ± 123	34	10-5-5	Intravenous	61.7	70
27.5 ± 1.75	979 ± 266	22	10-5-5	Oral	95.5	46
na	na	13	10-5-5	Oral	84.6	47
31.2 ± 2.5	1521 ± 398	12	10-5-5	Oral	83.3	48
29.4 ± 1.0	1237 ± 198	40	10-5-5	Oral	95.0	41
27.8 ± 2.4	1052 ± 443	13	10	Oral	100	55
<32 weeks	500-1500	33	10-5-5	Oral	93.9	45
29.3 ± 1.2	1227 ± 188	32	10-5-5	Oral	84.3	18
28.5 ± 1.9	na	52	10-5-5	Oral	84.6	19
26.4 ± 1.1	892 ± 117	36	10-5-5	Oral	83.3	70

Gestational age and body weight are the mean ± SD unless otherwise stated; GA = gestational age; BW=body weight; [a]mean, SD is not available; na = not available; *first course of ibuprofen. Barzilay et al. (55) administered only 10 mg/kg ibuprofen.

support was longer in the intravenous group (p = 0.02). Intermittent positive pressure ventilation occurred in none of the oral ibuprofen group and in two infants of the intravenous group (p = 0.02). None of the patients had oliguria. The serum creatinine levels did not differ significantly between the two groups (p = 0.28). The plasma sodium level was decreased significantly in both groups. Only one patient in each group had surgical ligation.

In Erdeve et al.,[20] oral and intravenous ibuprofen was administered to 36 and 34 infants, respectively. After the first course of treatment, the %PDA closure was 83.3 (for oral) and 61.7% (for intravenous ibuprofen — p = 0.04). Six patients (16.7%) in the oral ibuprofen group compared to 13 infants (38.2%) in the intravenous ibuprofen group (p = 0.012) required a second course of drug therapy. The need for steroid use to treat chronic lung disease was required by 8 infants of the ''oral group'' and by 17 infants of the ''intravenous group'' (p = 0.01). During the first course, there were decreases in the bilirubin level (5.2 ± 2.7 versus 4.4 ± 1.7 mg/dL — p = 0.03) in the oral versus intravenous ibuprofen. None of the patients had oliguria. Renal function test results did not differ significantly between the groups.

Rectal administration of ibuprofen to infants of different ages and to adult subjects

The pharmacokinetics of ibuprofen were measured following rectal administration of 20 mg/kg to 5 infants aged 1 to 7 weeks (group 1), to 8 infants aged 8-25 weeks (group 2), to 7 infants aged 26-52 weeks (group 3) and to 7 adults 20-40 year old (group 4).[23] The $t_{1/2}$ (hours) was 4.6 ± 5.1, 1.9 ± 0.5, 2.1 ± 0.7 and 2.2 ± 0.4 in the groups 1, 2, 3 and 4, respectively. Half-life reached the adult value in infants 8 to 25 week old, or after 2 to 6 months of life. Ibuprofen was detectable in blood within 20 min and plasma concentrations >10 mg/l were seen from 40 min to 8 hours.

Metabolism of ibuprofen in adult subjects and fetuses

In adults, ibuprofen is metabolized into two inactive metabolites: 2-[4-(2-hydroxy-2-methyl propyl) phenyl] propionic acid and 2-[3-(2-carboxypropyl) phenyl] propionic acid.[24] CYP2C9 is the major cytochrome mediating the 2- and 3-hydroxylations of ibuprofen[25] and CYP2C8 contributes to the metabolism of ibuprofen.[25,26] A considerable inter-individual variability in the activities of CYP2C9 and CYP2C8 has been reported in adults.[25,26] The relative expression of CYP2C9 and CYP2C8 contribute to the variability in the clearance and $t_{1/2}$ of ibuprofen. The activity of CYP2C9 is low at birth[25] and surges during the first week of life.[26] In fetuses, the low amounts of RNA are constituted by equal amounts of CYP2C8, CYP2C9 and CYP2C18 RNA, and after birth the rise of total 2C RNA is essentially caused by an increase in CYP2C9 RNA, which represents a 10-fold increase as compared with other subfamilies.[25] These important maturational effects could explain the significant increase in ibuprofen clearance with postnatal age.[27]

Pharmacokinetics of ibuprofen in preterm infants

Little is known about the pharmacokinetics of ibuprofen in neonates. Some articles lack the main pharmacokinetic parameters. The kinetic parameters of ibuprofen were measured in 13 preterm infants on the 3rd and 5th day of life.[28] Their gestational age was 28.9 ± 1.9 weeks and their birth weight was 1250 ± 460 g. These infants were suffering from a respiratory distress syndrome and a hemodynamically important PDA. Standard doses of ibuprofen were administered on days 3, 4 and 5. A remarkable interindividual variability was observed in ibuprofen pharmacokinetic parameters. The volume of distribution (Vd) of the central compartment and AUC0-24 decreased significantly from day 3 to day 5 of life. The closure of PDA was associated with a decreased Vd from 0.247 l/kg to 0.147 l/kg (p = 0.03). Cmax, Vd, $t_{1/2}$, and clearance were not significantly different from the days 3 and 5 of life. $t_{1/2}$ of ibuprofen shortness from 43.1 ± 26.1 hours on the 3rd day of life to 26.8 ± 23.3 hours on the 5th day of life.[29] These estimates are not significantly different because of the high standard deviation. The $t_{1/2}$ is 1.9 ± 0.5 hours in infants 8 to 25 week old.[23] This rapid shortening of $t_{1/2}$ during neonatal maturation is due to the rapid increase of CYP2C9 and CYP2C8 hepatic activities.

Table 2 summarizes the pharmacokinetic parameters of ibuprofen obtained in 7 studies. Some articles lack the main pharmacokinetic parameters. The $t_{1/2}$ values are available in 6 out of 7 studies and ranged from 15.7 ± 3.8[29] to 43.1 ± 26.1[28] hours — thus it varied 2.8-fold. There are only 3 estimates of clearance (ml/min/mg) which ranged from 2.06 ± 0.33[30] to 9.49 ± 6.82;[28] thus it varied over 4-fold. Vd ranged 0.062 ± 0.004[30] to 0.36[27] L/kg, thus, it varied over 5.8-fold. The area under the curve (AUC) reported by Aranda et al.[30] is several times greater than the other AUC estimates. AUC (μg.h/kg) ranged from 299 ± 69[23] and 524 ± 156;[28] therefore, it varied 1.7-fold, a modest variation.

The PDA closure rate is 50% when AUC0-24 of ibuprofen is <600 mg.h/l, and 91% when ibuprofen AUC0-24 >600 mg.h/l — p = 0.006.[27] Regression analysis revealed that ibuprofen AUC0-24 value >600 mg.h/l increases the

Table 2 - Demographic data of the neonates and pharmacokinetic parameters of ibuprofen administered to preterm infants.

GA (weeks)	BW(g)	Dose(mg/kg)	n	Cmax (μg/ml)	$t_{1/2}$ (hours)	Cl (ml/h/kg)	Vd (l/kg)	AUC (μg.h/ml)	Reference
26.8 ± 0.59*	945 ± 59.9*	10IV	21	181 ± 11.1[d]	30.5 ± 4.2*	2.06 ± 0.33*	0.062.1 ± 0.004*	7698 ± 1096**	30
28.6 ± 1.9	1250 ± 460	10,5,5[b]IV	13	43.5 ± 11.2	43.1 ± 26.1	9.49 ± 6.82	0.24 ± 0.08	524 ± 156	28
30.4 ± 0.33	1262 ± 55	10PO	20	18.3[c]	15.7 ± 3.8	na	na	403 ± 80	29
27.8 ± 2.4	1052 ± 443	10PO	33	30.7[c]	na	na	na	618[c]	55
na	4400 ± 600[a]	19.0 ± 1.6[a](Rectally)	5	na	4.6 ± 5.1[a]	na	na	299 ± 69[a]	23
26.6[c]	855[c]	10,5,5[b]IV	62	na	25.5[c]	na	0.18[c] (l)	Na	32
25 to 34	na	10,5,5[b]IV		38.4[c]	42.2	9.13[c]	0.36[c] (l)	Na	27

The figures are the mean ± SD unless otherwise stated; n = number of infants; *mean ± SEM; **the unity is not stated; na = not available; IV = intravenous administration; PO = oral administration; a = the postnatal age was 1 to 7 weeks; b = the dose was 10 mg/kg followed by 5 mg/kg after 24 and 48 hours; c = mean, SD is not available; d = plasma concentration 1 h after intravenous administration of 10 mg/kg ibuprofen to 21 preterm infants within the first 3 hours after birth.

Table 3 - Adverse effects due to the oral or intravenous administration of ibuprofen to preterm infants

Parameter	Oral ibuprofen*		Intravenous ibuprofen*		Statistical significance	Reference
	Number of infants or valuation	Number of infants	Number of infants or valuation	Number of infants		
Serum creatinine	5.7 ± 1.2 (mg/dl)	32	10.9 ± 1.2 (mg/dl)	32	$p<0.01$	18
Adverse effects**	9.3%	32	31.2%	32	$p=0.02$	18
Second course of ibuprofen	612.0%	50	1938.0%	50	$p=0.012$	19
Second course of ibuprofen	616.7%	36	1338.2%	34	$p=0.012$	20
Bilirubin concentration	5.2 ± 2.7(mg/dl)	36	4.4 ± 1.7(mg/dl)	34	$p=0.03$	20
Need for steroid for chronic lung disease	822.2%	36	1750.0%	34	$p=0.01$	20

*Ibuprofen was administered at the dose of 10 mg/kg, followed by 5 mg/kg after 24 and 48 hours.**The authors did not explain how they calculated the %adverse effects.

probability for PDA closure (p = 0.0054). As postnatal age advances, it is necessary to increase the dose of ibuprofen to maintain an AUC value >600 mg.h/l. Infants younger than 70 hours should receive 10 mg/kg ibuprofen, infants aged between 70 and 108 hours should receive 14 mg/kg and infants aged between 108 and 180 hours should receive 18 mg/kg ibuprofen.[27] The ibuprofen administration scheme would be 10-5-5 mg/kg for infants younger than 70 hours, 14-7-7 mg/kg for neonates between 70 and 108 hours and 18-9-9 mg/kg for newborn infants between 108 and 180 hours.[27] The ibuprofen dose should be adjusted according to neonatal maturation.

After the oral administration of 10 mg/kg ibuprofen to preterm infants, this drug was detectable in plasma after 1 hour, demonstrating excellent drug absorption. Ibuprofen plasma concentration peaked at 30.7 μg/ml, after 8 hours, and it was 24.4 μg/ml, i.e. 78% of the peak value, 24 hours after the administration. The concentration of orally administered ibuprofen decays slowly.

Ibuprofen has a tetrahedral chiral carbon atom, the S-(+)-enantiomer possessing most of the beneficial activity.[31] The population pharmacokinetics of ibuprofen enantiomers was studied in 52 preterm infants.[32] At birth, ibuprofen $t_{1/2}$ and clearance were 34.3 hours and 3.5 ml/kg/h, respectively, for S-(+)-ibuprofen, and 8.3 hours and 25.5 ml/kg/h, respectively, for R-(-)-ibuprofen.[32] Values for $t_{1/2}$ and clearance were measured on days 0, 3 and 8 of life; these parameters remained unchanged for S-(+)-ibuprofen during this period. In contrast, $t_{1/2}$ was 8.3, 1.3 and 0.5 hours, respectively, and clearance was 25.5, 168 and 405 ml/kg/h, respectively, for R-(-)-ibuprofen.[32] When the loading dose of ibuprofen was 15 mg/kg, followed by 7.5 mg/kg after 24 and 48 hours, the individual Cmax of S-(+)-ibuprofen varied 4.5-fold whereas Cmax of R-(-)-ibuprofen varied 200-fold.

Binding of ibuprofen to plasma albumin of preterm infants and effect on bilirubin displacement from albumin

Ibuprofen binds to plasma protein at a percentage of 94.98.[30] A recent article[33] showed that 10 mg/kg ibuprofen, followed by 5 mg/kg after 24 and 48 hours, did not alter the unbound plasma bilirubin concentration in preterm infants.[33] Consistent results were reported by van Overmeire et al.[34] In vitro work revealed that ibuprofen displaced bilirubin from plasma albumin when its concentrations were higher than 100 μg/ml.[35] In plasma samples of jaundiced premature newborn infants, ibuprofen, at a concentration of 1.8 mM (371 μg/ml), increased unbound bilirubin concentration from 10.8 to 16.1 nM — $p<0.05$[36] and the displacement was competitive. The displacing effect of ibuprofen on plasma albumin seems to be of scarce clinical relevance.

Adverse effects following the oral or intravenous administration of ibuprofen to preterm infants

Table 3 summarizes the adverse effects due to the administration of oral or intravenous ibuprofen to preterm infants. A second course of ibuprofen was required with higher frequency after intravenous ibuprofen in the studies by Gokmen et al.[19] and Ervede et al.[20] Cherif et al.[18] observed that the serum concentrations of creatinine were higher after intravenous ibuprofen administration. A lower percentage of adverse effects occurred after oral (9.6%) versus intravenous (31.2%; p = 0.02) administration of ibuprofen.[18] The authors did not explain how they assessed the percentage of the adverse effects. Ervede et al.[20] required higher need of steroids for the treatment of chronic lung disease in infants treated with intravenous ibuprofen. Bilirubin concentration decreased after intravenous ibuprofen administration.[20] This body of information is consistent with the view that the oral route is safer than the intravenous route for ibuprofen.

Renal adverse effects of ibuprofen in preterm infants

Acute kidney injury by ibuprofen in preterms is influenced by very low birth weight, dose regimens, genetic factors and concomitant use of drugs such as aminoglycosides.[37] The nephritic effects of NSAIDs are related to their mechanism of action, namely the blocking of prostaglandin synthesis through the inhibition of COX. Prostaglandin E2 is the main prostanoid synthesized along the nephron. The glomerular filtration rate in neonates is very low (2-4 ml/min or 20 ml/min/1.73 m2) and can only be maintained due to a delicate balance between vasodilatatory effects at the afferent and vasoconstrictor effects at the efferent glomerular arterioles.[38-40] The inhibition of prostaglandin E2 by ibuprofen is the major pathophysiologic effects of this drug on the kidney.[41]

Ibuprofen appears to be the therapeutic option of choice in the preterm infants with PDA because of its better renal tolerability compared to indomethacin.[12] Nevertheless, ibuprofen is not free from adverse renal effects. The urinary prostaglandin E2 concentration was measured in 20 preterm infants with a hemodynamically significant PDA at 48-72 hours and at 108-144 hours of life. The infants were

treated with a standard dose of ibuprofen. Twenty other preterm infants were the controls. Urinary prostaglandin E2 decreased significantly (66.9 ± 16.8 versus 27.1 ± 17.9 ng/l; $p < 0.001$) in the infants treated with ibuprofen and (71.7 ± 16.2 versus 53.2 ± 18.4 ng/l; $p < 0.001$) in the controls.[41] Urinary prostaglandin E2 was significantly lower ($p < 0.001$) in the ibuprofen group compared to the control group. After treatment with ibuprofen, GFR was significantly decreased for several days. The GFR was 12.8 ± 6.2 ml/min/1.73 m2 (ibuprofen) on the 7th day after ibuprofen treatment, while it was 18.1 ± 12.1 ml/min/1.73 m2 in controls ($p < 0.001$).[41]

Tubular function was also impaired during the first month of life after ibuprofen treatment. Ibuprofen caused a significant decrease in urinary sodium concentration: 78.0 ± 8.6 versus 57.0 ± 8.0 mmol/l — $p < 0.05$[42] and in the fractional excretion of sodium : 7.5 ± 1.3 versus 3.9 ± 0.6% — $p < 0.05$.[42] The reduction of urinary sodium concentration observed after the administration of ibuprofen is an adverse effect of this drug due to a decrease of the natriuretic effect of prostaglandins which reduce sodium reabsorption at the thick ascending limb of the loop of Henle.[42] Ibuprofen is toxic at the levels of glomerulus and tubule, but is less nephrotoxic than indomethacin.

The efficacy and tolerability of oral ibuprofen were compared with those of intravenous ibuprofen for early closure of PDA in very low-birthweight infants. Although renal failure, at rates ranging from 6.8% to 57%, has been reported with intravenous ibuprofen,[8-10,43,44] renal failure has not been reported in any study using oral ibuprofen given for a complete course.[46-52] Tiker and Yildirim[53] and Ervede et al.[54] reported anecdotal observations of transient renal impairment in very low-birthweight infants given a complete course of PDA after oral ibuprofen, and both reported that the cases recovered on follow-up.

DISCUSSION

The present study shows that the rates of PDA closure are 89.4% and 74.9% (p = 0.0108) after oral and intravenous administration of ibuprofen, respectively. The coefficients of variation are 7.1% for oral and 19.1% for intravenous ibuprofen.

Serum creatinine levels increase more extensively following intravenous than oral ibuprofen administration.[18] The need for steroid use to treat chronic lung disease was higher in the intravenous group.[20] Adverse effects occurred in 9.3% of cases, following oral ibuprofen versus 31.2% following intravenous ibuprofen administration.[18] The authors did not explain how they estimated the percent of the adverse effects. Infants treated with oral ibuprofen required a second course of drug therapy less frequently than infants treated with intravenous ibuprofen.[19] The duration of the mechanical ventilation support[19] was shorter, and the median duration of intermittent positive pressure ventilation was smaller, in the infants receiving oral versus intravenous ibuprofen.[19] This body of information is consistent with the view that oral ibuprofen administration has the most favourable risk/benefit ratio.

The area under the curve, AUC0-24 of ibuprofen >600 mg.h/l yields a PDA closure of up to 91%.[27] In order to achieve an ibuprofen AUC0-24 >600 mg.h/l, the ibuprofen administration regimen must be increased with postnatal maturation. The scheme suggested by Hirt et al.[27] should be 10-5-5 mg/kg for infants younger than 70 hours, 14-7-7 mg/kg for neonates between 70 and 108 hours and 18-9-9 for newborn infants between 108 and 180 hours.

Oral ibuprofen (10 mg/kg) peaked at 30.7 μg/ml 8 hours after the administration and 16 hours later, ibuprofen plasma concentrations were 80% of the peak value.[55] The slower absorption rate and the longer $t_{1/2}$ of oral versus intravenous ibuprofen prolong the time of contact with the ductus, leading to higher responsiveness.[55] Ibuprofen concentration decays slowly after oral administration.

Recent investigations showed that intravenous ibuprofen is an effective regimen of administration of this drug for the closure of PDA in preterm infants. Neumann et al.[71] found that oral ibuprofen appears to be as effective as intravenous ibuprofen for closing PDA in preterm infants. Aranda et al.[72] performed a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of intravenous ibuprofen for the early closure of PDA in 136 extremely low-birthweight infants. Sixty-eight infants were treated with 10 mg/kg of ibuprofen, followed by 5mg/kg after 24 and 48 hours. The other 68 infants received placebo. Patients' demographics were similar in the two groups of infants. The intent-to-treat analysis of the primary endpoint, namely subjects who died, were rescued, or dropped out of the study by day 14, was 21/68 (30.9%) with ibuprofen and 36/68 (52.9%) for placebo (p = 0.002). Intravenous ibuprofen was effective and safe in the early closure of PDA in preterm infants.

Indomethacin is used as standard therapy to close a patent ductus, but is associated with reduced blood flow to several organs.[73] Ibuprofen, may be as effective as indomethacin with fewer side effects.[73] In the review performed by Ohlsson et al.[73] 27 studies were included: ibuprofen was found to be as effective as indomethacin in closing a PDA, reducing NEC and transient renal insufficiency. Therefore, ibuprofen appears to be the drug of choice. Ohlsson et al.[73] concluded that oro-gastric administration of ibuprofen appears at least as effective as intravenous ibuprofen.

Metabolism is the main route of ibuprofen elimination in adults.[23] A remarkable level of interindividual variability of the ibuprofen kinetic parameters was found in preterm infants by all authors. Variation in the rate of ibuprofen metabolism should yield variation in pharmacokinetic parameters and in plasma levels of this drug. The $t_{1/2}$ of ibuprofen rapidly shortens with infant maturation and halves during the first week of life[27]. This is due to the fast increase of CYP2C9 and CYP2C8 activities that metabolize ibuprofen and surge in the liver during the first weeks of life.[26] The adult $t_{1/2}$ value is 2 hours[56] and this value is reached by infants at the age of 2 to 4 months.[23] Ibuprofen levels, in relation to treatment response, were not significantly different in the case of success or failure of PDA closure.[57,58] Durrmeyer et al.[59] observed that CYP2C polymorphism was not associated with PDA response to ibuprofen and this factor does not appear appropriate to optimize the ductal closure by modulating the ibuprofen dosing strategy. This suggests that ibuprofen concentration is not the only factor affecting the closing rate of PDA. Other factors, such as the genetic or environmental factors may influence the closure rate of PDA.

At birth, the $t_{1/2}$ of R-(-)-ibuprofen is shorter than that of S-(+)-ibuprofen. Kinetic parameters of R-(-)-ibuprofen rapidly modify during the first week of life, while those of S-(+)-ibuprofen remain essentially unchanged during this

period.[32] In infants, the Cmax of S-(+)-ibuprofen varied 4.5-fold, whereas that of R-(-)-ibuprofen varied 200-fold. R-(-)-ibuprofen and S-(+)-ibuprofen should be metabolized by different enzymes.

Concerns have been raised regarding the bilirubin-ibuprofen albumin interaction.[35,36] Therapeutic concentrations of ibuprofen do not affect the unbound bilirubin concentration in the plasma of preterm infants.[33,34] The effect of ibuprofen on the unbound bilirubin concentration seems of limited clinical relevance. However, ibuprofen should be used with caution in hyperbilirubinemic premature infants.

CONCLUSIONS

The PDA closure rate is higher following oral compared to intravenous administration of ibuprofen. The coefficients of variation of PDA closure rate were 7.4% and 19.1% after oral and intravenous treatment with ibuprofen, respectively. Oral ibuprofen has fewer adverse renal effects than intravenous ibuprofen and this suggests that oral ibuprofen has the most favourable risk/benefit ratio. The $t_{1/2}$ of ibuprofen halves in the first week of life and reaches the adult value after 2 to 4 months. The rapid shortening of $t_{1/2}$ is due to the rapid increase of CYP2C9 and CYP2C8 activities, which metabolize ibuprofen, and surge in the liver during the first weeks of life. Ibuprofen has a tetrahedral chiral carbon atom, the S-(+)-enantiomer possessing most of the beneficial activity. R-(-)-ibuprofen and S-(+)-ibuprofen have different metabolic properties and are metabolized by different enzymes. Therapeutic concentrations of ibuprofen do not displace bilirubin from plasma proteins, thus the effect of ibuprofen on the unbound bilirubin concentration has little clinical relevance.

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RESUMO

OBJETIVOS: O ibuprofeno é um inibidor não-seletivo da ciclooxigenase pertencente à classe de drogas anti-inflamatórias não-esteroidais do ácido propiónico; é fármaco disponível sem receita médica nos Estados Unidos. Em recém-nascidos, o ibuprofeno é usado para fechar o canal arterial patente e mostrou-se mais eficaz que a indometacina. Esta meta-análise determina se existem diferenças na taxa de fechamento de canal arterial patente após a administração oral versus intravenosa de ibuprofeno em prematuros; examina também o metabolismo, a farmacocinética e efeitos renais adversos do ibuprofeno.

MÉTODO: A pesquisa bibliográfica foi realizada utilizando as bases de dados PubMed e EMBASE. Além disso, os livros ''Neofax: a Manual of Drugs Used in the Neonatal Care'' by Young and Mangum and the ''Neonatal Formulary'' foram consultados.

RESULTADOS: A taxa de fechamento do canal arterial patente foi de 89% com o ibuprofeno oral (9 publicações) vs. 75% com ibuprofeno intravenoso (13 publicações), p = 0,011. A meia-vida ($t_{1/2}$) do ibuprofeno foi de 43,1 e 26,8 horas em crianças no tereiro e no quinto dia de vida, respectivamente. Em adultos, a meia-vida de ibuprofeno é de 2 horas. A rápida diminuição da meia-vida deve-se ao rápido aumento de atividade dos citocromos CYP2C9 e CYP2C8, que metabolizam o ibuprofeno; estes agentes apresentam grande elevação no fígado durante as primeiras semanas de vida. O ibuprofeno reduz a filtração glomerular renal e as taxas de transporte tubular de sódio.

CONCLUSÃO: O ibuprofeno oral é mais eficaz do que o ibuprofeno intravenoso para fechar o canal arterial persistente. A via oral produz menos efeitos adversos renais do que a intravenosa e apresenta uma relação risco/benefício mais favorável.

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