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# Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial

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**Abstract** Indomethacin (INDO) and, more recently, ibuprofen (IBU) have been used to treat haemodynamically significant patent ductus arteriosus (PDA) in preterm infants. Both are cyclo-oxygenase blockers, but seem to have a different influence on regional circulation. In a prospective, randomised, controlled study, we compared INDO and IBU with regard to efficacy and safety for the early non-invasive treatment of PDA. Doppler echocardiography was used to study 232 preterm infants (gestational age 23–34 weeks) with respiratory distress syndrome of whom 175 had persistent, haemodynamically significant PDA at 48–72 h of life. They were randomised to receive three intravenous doses of either INDO (0.2 mg/kg, at 12 h intervals) or IBU (a first 10 mg/kg dose followed by two doses of 5 mg/kg at 24 h intervals), recording rate of ductal closure, need for additional treatment, side-effects and clinical course. The efficacy of the pharmacological treatment was similar in the two groups (56/81, 69% INDO; 69/94, 73% IBU). Patients treated with INDO showed a significant increase in serum creatinine ($89 \pm 24$ versus $82 \pm 20$ mmol/l, $P = 0.03$) and a near-significant tendency for a lower fractional excretion of sodium ($3 \pm 3$ versus $4 \pm 2\%$, $P = 0.08$); moreover, 12/81 (15%) INDO patients versus 1/94 (1%) IBU patients became oliguric ($< 1$ ml/kg per h) during treatment ($P = 0.017$). *Conclusion*: our findings confirm that, by comparison with indomethacin, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome. In particular, no increased incidence of intracranial haemorrhage was observed after ibuprofen treatment.

**Keywords** Doppler echocardiography · Ibuprofen · Indomethacin · Patent ductus arteriosus · Respiratory distress syndrome

**Abbreviations** *BPD* bronchopulmonary dysplasia · *CBF* cerebral blood flow · *IBU* ibuprofen · *ICH* intracranial haemorrhage · *INDO* indomethacin · *PDA* patent ductus arteriosus · *PVL* periventricular leukomalacia · *RDS* respiratory distress syndrome

## Introduction

Persistent patent ductus arteriosus (PDA) is a common complication in premature infants ventilated for respiratory distress syndrome (RDS), affecting more than 40% of very low birth weight infants [11, 12]. This significant failure to constrict after birth is due to lower intrinsic tone, less ductal muscle and fewer subendothelial cushions, which would normally allow for ductal obliteration, together with the higher sensitivity of the immature PDA to the vasodilating effects of prostaglandins and nitric oxide and haemodynamic derangement due to RDS and surfactant therapy [5, 11]. The clinical consequences of persistent PDA are related to the degree of left-to-right shunting through the ductus and diastolic steal, leading to a redistribution of blood flow to the organs with localised vasoconstriction, reduced perfusion to the brain, gut and kidney, and increased pulmonary blood flow [8, 11]. Action to close the PDA with left-to-right shunting has been shown to reduce pulmonary, cerebral, haemodynamic, renal and gastrointestinal morbidity [5, 10, 14].

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Inhibiting prostaglandin synthesis with non-selective blockers of both cyclo-oxygenases 1 and 2 seems effective for the non-surgical closure of patent ductus and, since 1976, indomethacin (INDO) has been widely used with a reported efficacy of 70%–80% [9, 12]. Its use raises some concern, however, regarding cerebral, gastrointestinal and renal perfusion [2, 4, 6, 21, 22], since INDO causes a decline in cerebral blood flow (CBF) velocity, reduces mitochondrial oxygenation and disrupts cerebrovascular control [7]. Moreover, side-effects such as necrotising enterocolitis or isolated bowel perforation, oliguria and transient renal failure may be encountered [10]. These INDO-related complications have tempered enthusiasm for its use, inducing many researchers to seek new, safer pharmacological strategies for PDA closure.

According to earlier reports, another cyclo-oxygenase inhibitor, ibuprofen (IBU), has also proved effective, with fewer cerebral, renal and mesenteric effects [15, 17, 18, 19, 20]. This non-steroidal anti-inflammatory drug may also enhance CBF autoregulation, extending the blood pressure range where the CBF is not altered, and has been shown to protect neurological function following oxidative stress in animal models; its effects on CBF in humans has already been evaluated [18]. Given the evidence of minimal adverse effects on major organs, IBU may became the treatment of choice for preterm infants with PDA [23, 24, 25].

The main aim of this study was to ascertain whether IBU is as effective as INDO in inducing PDA closure and whether it has less pronounced effects on renal and cerebral function in preterm infants with RDS.

## Subjects and methods

### Subjects

The study was conducted at two Neonatal Intensive Care Units of the University of Padova and the Ca' Foncello Hospital, Treviso, Italy, between January 1998 and December 2000. Neonates admitted to both units were eligible for the trial if the following criteria were met: gestational age $\leq 34$ weeks, postnatal age 48–72 h; RDS treated with mechanical ventilation (conventional or high-frequency oscillatory ventilation), echocardiographic evidence of PDA. Our institutions adopt a screening protocol for the early diagnosis and treatment of "silent" PDA in preterm infants with RDS on the 2nd day of life. The term "silent" describes a PDA with echocardiographic and Doppler evidence of left-to-right shunting, without the classical clinical signs. Exclusion criteria were: major congenital anomalies, persistent pulmonary hypertension, recent bleeding (less than 48 h previously), a platelet count of 50,000/mm$^3$ or less, urine output below 1 ml/kg per h during the previous 12 h, serum creatinine concentrations greater than 140 mmol/l and serum urea nitrogen in excess of 14 mmol/l. The study was approved by the local Ethics Committee and written parental consent was obtained.

### Study design

A complete echocardiographic and Doppler evaluation (HDI 3000 CV, ATL, USA or Vingmed Sound, System 5, Norway, with a 7.5 MHz transducer) was performed in all infants eligible for the study by physicians unaware of the infant's treatment group. The purpose was to evaluate the patency of the ductus arteriosus and shunting at the baseline and after each dose of the drug. The diagnosis of PDA was based on the typical flow pattern obtained by colour Doppler echocardiography. Shunting was defined as haemodynamically significant if a disturbed diastolic flow was easily detectable in the main pulmonary artery with a diastolic backflow in the aorta immediately below the ductus arteriosus and a forward flow above the ductal insertion. We echocardiographically studied the first 50 patients in both groups after each dose of the drug to ascertain the rate of PDA closure. All patients underwent echocardiographic and Doppler evaluation after the last dose of the assigned treatment and subsequently after a second non-randomised rescue treatment, if necessary, or whenever there was a clinical suspicion that the ductus had reopened after closure.

The infants enrolled at each unit were randomly assigned to either treatment group by means of cards in sealed envelopes. Each infant received three doses of either INDO (Liometacen, Chiesi Farmaceutici, Parma, Italy), 0.2 mg/kg at 12 h intervals or IBU (Arfen, Lisapharma, Erba, CO, Italy) in an initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48 h. The medication was infused continuously over a period of 15 min. The doses and intervals for IBU were in accordance with recommendations for its use in infants and neonates based on preliminary pharmacodynamic data [1].

When the ductus arteriosus was still patent after the randomly-assigned treatment in patients in either group receiving mechanical ventilation, another three doses of the same medication were given as a non-randomised rescue treatment. If this therapy also failed to induce ductal closure, the patient continued to receive mechanical ventilation and, if the ductus was judged to be haemodynamically significant or if further pharmacological treatment was contraindicated, surgical ligation of the ductus was performed.

### Concomitant treatment

Daily clinical care was provided by the attending neonatalogist who did not take part in the study. All infants were nursed in humidified incubators and, during the treatment period, all infants involved in the study were kept on a "none per os" regimen. Fluid intake was guided by body weight and serum sodium concentration to maintain serum sodium between 130 and 145 mEq/l, and a weight loss of 10% was allowed during the first post-natal days. The daily fluid intake began at 80 ml/kg and was increased by 20 ml/kg each day to a maximum of 150 ml/kg after the 1st week of life. Oliguria was defined as urine output of 1 ml/kg per h or less during a 24 h collection period. For the treatment of RDS, infants received respiratory support (conventional or high-frequency oscillatory ventilation, Babylog 8000 plus Dräger, Germany), oxygen supplementation and early rescue therapy with natural surfactant (Curosurf, Chiesi-Parma) in one or two doses of 100 mg/kg. Prophylactic antibiotics, ampicillin and gentamicin, were administered from admission to the neonatal intensive care unit and stopped after a mean of 6 days if bacterial cultures (blood, cerebrospinal fluid, tracheal aspirate and urine) remained negative.

### Clinical course

Clinical and laboratory data were reported prospectively on data sheets designed for this study. We reported the following clinical data: gestational age, birth weight, sex, antenatal steroids defined as two doses of betamethasone at least 24 h before delivery, premature rupture of membranes, maternal gestosis, caesarian section, Apgar score at 1 and 5 min, need for positive pressure ventilation in delivery room, Clinical Risk Index of Babies score, type of ventilation during PDA treatment, radiological grade of RDS, fractional inspired oxygen ($FiO_2$%), mean airway pressure (MAP) and oxygenation index (OI = $MAP \times FiO_2 \times 100/PaO_2$) at 2 and 12 h of life, then every 24 h until day 5, fluid intake (ml/kg of actual

daily weight), urine output and daily body weight. Renal function was evaluated by daily assessment of urine output and weight gain, as well as serum creatinine concentration, serum urea nitrogen, and fractional excretion of sodium before and after treatment.

Cranial ultrasound scans were performed in all infants before and after the first course of treatment, and at 7, 14 and 28 post-natal days. If clinically relevant, additional ultrasound scans were also performed. Infants were scanned for intracranial haemorrhage (ICH), graded according to the Papile standard classification system, i.e. grade 1 = subependymal haemorrhage, grade 2 = intraventricular haemorrhage without ventricular dilatation, grade 3 = intraventricular haemorrhage with ventricular dilatation, grade 4 = intraventricular haemorrhage with intraparenchymal extension [16]. Head sonograms were also assessed for parenchymal echodensities, representing ischaemic events. Echodense abnormalities that later showed cystic changes were classified as periventricular leukomalacia (PVL).

Respiratory outcome was defined on the basis of the number of days on mechanical ventilation and additional oxygen, the number of patients still on additional oxygen at 36 weeks post-conceptional age with radiographic findings typical of bronchopulmonary dysplasia (BPD), and the need for oxygen therapy at home. Any evidence of necrotising enterocolitis, ascertained by clinical and radiological evaluation or isolated bowel perforation, was also recorded, together with the time it took to regain birth weight and the time to full enteral feeding. Sepsis (defined by positive blood culture) was also recorded, as was the time to discharge and the number of deaths.

### Statistical analysis

As our primary aim was to detect clinical differences of at least 20% in the efficacy of IBU compared with INDO, assuming a closure rate of 80%, with a $P$ value of 0.05 and a power of 95%, we had to enroll at least 80 patients in each group. Data on continuous variables were compared by the Student's $t$-test for unpaired data and by one-way analysis of variance (ANOVA). Categorical variables were analysed by the chi-squared and Fisher's exact tests. All statistical analyses were done with the SAS statistical package for Windows, V 6.12.

## Results

### Demographic data

The study considered 232 eligible patients who underwent echocardiographic and Doppler ultrasound evaluation between 48 and 72 h of life of whom 49 were excluded because their ductus had already closed, five because of bleeding or coagulopathy, and three due to severe right-to-left shunting through the ductus caused by severe pulmonary hypertension. Thus, 175 patients were randomised for treatment, 81 of them assigned to receive INDO and 94 IBU at a mean (SD) age of 65 (12) and 60 (16) h of life respectively ($P = 0.14$). The characteristics of the newborns before treatment are shown in Table 1.

### Efficacy of treatment

The rate of ductus closure after the first and second doses in 54 INDO and 53 IBU patients is shown in Table 2. Global closure rates after three standard doses were 69% for INDO versus 73% for IBU. Reopening of the ductus after the first course of treatment was observed in two IBU cases, which received a second successful course of treatment. A total of 25 patients in each group received a further three rescue doses of the same medication, achieving closure in 11 cases (44%) on INDO and 12 (48%) in the IBU group. At the end of the pharmacological treatments, the PDA closing efficacy was 82% for INDO and 86% for IBU. Finally, 15% on INDO and 12% on IBU underwent surgical ligation at a mean (SD) post-natal age of 13.4 (6.4) days. Minimal ductal shunting after medical therapy was observed in two patients who did not require respiratory support and no further treatment was attempted. The ductus closed spontaneously in these cases.

Pharmacological closure was less likely to occur in the lowest gestational age group ($P = 0.001$), but there was no difference in the efficacy of the two drugs or the need for surgical ligation (Table 3). Prenatal steroids correlated with a better pharmacological response: 27 infants (75%) in the INDO group and 41 (82%) in the IBU group who had received two doses of prenatal steroids at least 24 h before delivery achieved PDA closure with pharmacological treatment as opposed to 29 (64%) and 28 (64%) respectively who had not ($P = 0.03$).

### Safety of treatment

The renal profile before and after pharmacological treatment of PDA is shown in Table 4. During treatment, diuresis was lower in the INDO group and the number of patients with oliguria was much higher, i.e. 15% versus 1% with IBU ($P = 0.017$), whereas fluid intake was similar in the two groups (data not shown). We also found significantly higher post-treatment serum creatinine levels in INDO versus IBU patients ($P = 0.03$). These effects were transient and disappeared within 24 h. However, after a second course of treatment, the mean (SD) urine output did not differ significantly between INDO and IBU groups, 3.8 (1.2) versus 3.5 (2.6) ml/kg per h, nor did the mean (SD) serum creatinine concentration or serum urea nitrogen, 80 (13) versus 78 (12) and 5 (6) versus 4(5).

After the first treatment, ICH changed in three patients in each group to grade 3, and one patient in the IBU group to grade 4. No further increase in ICH was observed after six doses of the drug. No altered coagulation or platelet counts were noted during treatment (data not shown).

Regarding respiratory outcome, the number of days on the ventilator and oxygen therapy was similar in the two groups, as was the incidence of BPD.

Necrotising enterocolitis and localised bowel perforation affected the same number of patients in both groups and developed at a mean (SD) post-natal age of 14 (9) days. The time to reach full enteral feeding and regain birth weight was also the same. No significant differences were noted in terms of sepsis or other infectious complications. Seven patients died in the INDO

**Table 1.** Baseline characteristics of the study groups. Values are given as mean ± SD or number (%). *P* values were not significant

| | INDO ($n=81$) | IBU ($n=94$) |
|---|---|---|
| Birth weight (g) | 1214 ± 427 | 1126 ± 412 |
| Gestational age (weeks) | 29 ± 3 | 28 ± 2 |
| Small for gestational age | 15 (18) | 22 (23) |
| Male | 43 (53) | 52 (55) |
| Antenatal glucocorticoids | 44 (54) | 50 (53) |
| Premature rupture of membrane | 15 (18) | 10 (11) |
| Maternal gestosis | 21 (26) | 33 (35) |
| Caesarean section | 60 (74) | 69 (73) |
| Apgar score at 1 min | 5 ± 2 | 5 ± 2 |
| Apgar score at 5 min | 7 ± 2 | 7 ± 2 |
| Positive-pressure ventilation in delivery room | 63 (78) | 74 (79) |
| Clinical risk index of babies | 4 ± 4 | 5 ± 4 |
| High-frequency oscillatory ventilation | 12 (15) | 23 (24) |
| Surfactant therapy | 62 (76) | 79 (84) |
| Percentage inspired oxygen at 48 h | 34 ± 14 | 34 ± 13 |
| Percentage inspired oxygen at 72 h | 31 ± 13 | 31 ± 10 |
| Mean airway pressure at 48 h | 7 ± 2 | 8 ± 3 |
| Mean airway pressure at 72 h | 8 ± 2 | 8 ± 3 |
| Oxygenation index at 48 h | 5 ± 2 | 6 ± 5 |
| Oxygenation index at 72 h | 5 ± 4 | 5 ± 5 |
| Need for sedation | 30 (37) | 41 (44) |
| Need for vasoactive drugs | 32 (40) | 42 (45) |

**Table 2.** Efficacy of treatment. Values given as number (%). *P* values not significant

| | INDO ($n=81$) | IBU ($n=94$) |
|---|---|---|
| PDA closed after 1 dose[a] | 3/54 (5) | 4/53 (7) |
| PDA closed after 2 doses[a] | 6/54 (11) | 13/53 (24) |
| PDA closed after 3 doses[b] | 56/81 (69) | 69/94 (73) |
| PDA closed after 6 doses[b] | 11/81 (14) | 12/94 (13) |
| Total PDA closed[b] | 67/81 (82) | 81/94 (86) |
| Ductal ligation[b] | 12/81 (15) | 11/94 (12) |

[a]Percentage calculated on number of patients who underwent echocardiography after each dose of drug
[b]Percentage calculated on total number of patients in each treatment group

**Table 3.** PDA closure according to gestational age. Values expressed as number/total (%)

| | Total ($n=175$) | INDO ($n=81$) | IBU ($n=94$) |
|---|---|---|---|
| PDA closed after 3 doses | | | |
| < 28 weeks gestation | 50/83 (60)* | 19/33(57)* | 31/50 (62)* |
| ≥28 weeks gestation | 75/92 (81)* | 37/48 (77)* | 38/44 (86)* |
| PDA closed after 6 doses | | | |
| < 28 weeks gestation | 9/32 (28)* | 3/13 (23)* | 6/19 (31)* |
| ≥28 weeks gestation | 15/19 (79)* | 7/11 (64)* | 8/8 (100)* |
| Ductal ligation | | | |
| < 28 weeks gestation | 19/83 (23)* | 8/33 (24)* | 11/50 (12)* |
| ≥28 weeks gestation | 4/92 (4)* | 4/48 (8)* | 0/44 (0)* |

*$P < 0.05$ when comparing results for < 28 weeks gestation with results for ≥28 weeks gestation

**Table 4.** Renal outcome. Values expressed as mean (SD) or number (%)

| | INDO ($n=81$) | IBU ($n=94$) |
|---|---|---|
| Serum creatinine pre-treatment (μmol/l) | 82 ± 16 | 81 ± 20 |
| Serum urea nitrogen pre-treatment (mmol/l) | 7 ± 11 | 7 ± 9 |
| Fractional sodium excretion pre-treatment (%) | 6 ± 3 | 5 ± 4 |
| Serum potassium pre-treatment (mEq/l) | 4.3 ± 0.6 | 4.5 ± 0.7 |
| Serum creatinine post-treatment (μmol/l) | 89 ± 24* | 81 ± 20* |
| Serum urea nitrogen post-treatment (mmol/l) | 8 ± 8 | 7 ± 8 |
| Fractional sodium excretion post-treatment (%) | 3 ± 2 | 4 ± 3 |
| Serum potassium post-treatment (mEq/l) | 4.1 ± 0.6 | 4.1 ± 0.6 |
| Oliguria ( ≤ 1 ml/kg per h) | 12 (15)* | 1 (1)* |
| Fluid retention ( > 5% actual body weight) | 12 (15) | 5 (5) |
| Diuresis pre-treatment (ml/kg per h) | 3.6 ± 1.8 | 3.8 ± 1.7 |
| Diuresis during treatment (ml/kg per h) | 2.8 ± 1.2* | 3.5 ± 1.2* |
| Diuresis post-treatment (ml/kg per h) | 3.7 ± 1.5 | 3.8 ± 1.4 |

*$P < 0.05$

group (four of respiratory problems, two of sepsis and one of intestinal perforation) and 11 in the IBU group (three of ICH, four of respiratory problems and five of sepsis) (Table 5).

## Discussion

This is the second large randomised trial comparing INDO with IBU for treating PDA in preterm infants with RDS to confirm that IBU is just as effective as INDO in closing PDA when given at 48–72 h of life. By comparison with the previous report [24], we observed much the same efficacy of INDO and IBU after a first course (69% and 73% versus 66% and 70% in [24]), but after a second course, pharmacological PDA closure was better in our trial (82% and 86% versus 70% and 74% in [24]). We found no significant difference in closing rate with the two drugs after the first and second doses, as reported elsewhere [3]. This may be due to the lower infusion rate used in our study. Moreover, the second course of treatment improved results without increasing the side-effects of either drug. Unfortunately, we do not have data on PDA closure after any fourth and fifth doses, and this may be a good point to address in future studies.

The efficacy of both cyclo-oxygenase blockers in closing PDA is related to gestational age. As reported in earlier studies, infants of lower gestational age (< 28 weeks) are significantly less responsive to pharmacological treatment (60% versus 81%) and undergo surgical ligation more frequently: 23% versus 4% in our series [10, 11].

Due to their negative effect on prostaglandin production, antenatal steroids are known to increase the response of the ductus to the constricting effect of oxygen and to decrease its sensitivity to the dilating

**Table 5.** Outcome. Values expressed as mean (SD) or number (%). *P* values not significant

| | INDO ($n=81$) | IBU ($n=94$) |
|---|---|---|
| Days of ventilation | 14 ± 16 | 12 ± 12 |
| Days of oxygen | 31 ± 38 | 35 ± 40 |
| Oxygen therapy at home | 8 (11) | 10 (12) |
| BPD at 36 weeks | 13 (16) | 23 (24) |
| ICH progression to grade 3 | 3 (2) | 3 (2) |
| ICH progression to grade 4 | 0 | 1 (1) |
| ICH grade 3–4 | 7 (8) | 10 (10) |
| Post-haemorrhagic hydrocephalus | 6 (7) | 6 (6) |
| PVL | 6 (7) | 11 (12) |
| Necrotising enterocolitis/localised bowel perforation | 2 (3)/2 (3) | 2(2)/2 (2) |
| Time to full enteral feeding (days) | 21 ± 13 | 22 ± 12 |
| Time to regain birth weight (days) | 16 ± 7 | 18 ± 7 |
| Time to 2000 g (days) | 57 ± 30 | 59 ± 23 |
| Sepsis | 3 (4) | 5 (5) |
| Death | 7 (8) | 11 (11) |
| Days at discharge | 73 ± 37 | 65 ± 34 |

effects of prostaglandins [11]. Our results are consistent with this picture: we found that prenatal betamethasone significantly helped to close the ductus post-natally in both treatment groups (82% of IBU and 75% of INDO patients exposed prenatally to steroids responded to pharmacological PDA treatment versus 63% and 65% without prenatal steroids). Combining steroids with prostaglandin blockers might be useful for infants unresponsive to cyclo-oxygenase blockers alone.

INDO (the accepted pharmacological treatment for non-invasive PDA closure in preterm infants) reversibly blocks the cyclo-oxygenase pathway of prostaglandin synthesis [4] which is why it can be expected to have a variety of adverse effects, e.g. renal dysfunction, necrotising enterocolitis, enteric perforation, gastrointestinal and diffuse bleeding. The pathogenesis of this damage is a vasoconstriction and reduction of the renal and mesenteric blood flow. INDO also reduces CBF velocity and brain oxygenation and inhibits platelet aggregation [2, 4, 6, 7, 21, 22]. However, some experimental evidence suggests that the effect of INDO on these other organ systems may be due to a mechanism unrelated to prostaglandin inhibition that might account for some of the different effects of INDO and IBU on regional circulation [13, 20]. INDO affects renal function and urine production with a concomitant rise in serum urea nitrogen and creatinine levels and fall in glomerular filtration [2, 10, 14]. The demonstrated decrease in peak renal systolic blood flow velocity is maximal 10 min after INDO administration and recovers slowly, reaching basal values after 2 h [22]. In the previous large trial, urine output was significantly lower from day 3 to day 7 in the INDO group with an increase in serum creatinine concentration from day 4 to day 8 [24]. In our patients, oliguria became most evident after the second and third doses, but disappeared after 24 h of suspending treatment. Residual vasoconstriction from previous doses may have contributed to this effect because INDO has a longer half-life in infants of lower gestational age. Also, the reduction in renal blood flow induced by INDO could have a worse effect in neonates with a worse kidney function or hypovolaemia. Alternatively, other biochemical or hormone derangements may be responsible for the oliguria seen in our INDO-treated patients, or the lack of renal dysfunction after the second treatment course might be due to an improved renal function and volaemic balance.

Already in earlier studies, by comparison with INDO-treated patients, those treated with IBU had less frequently reduced diuresis and renal impairment, with a constant serum creatinine level after treatment and the same efficacy. This has been partly explained by the weaker cyclo-oxygenase 1 inhibiting effect of IBU [18, 19, 23, 24]. We also found a less severe renal function impairment in preterm infants treated with IBU, who developed oliguria less frequently and had no rise in serum creatinine after treatment.

Finally, INDO affects CBF in neonates. Edwards et al. [7] observed that INDO-treated preterm infants displayed a sharp reduction in CBF, oxygen delivery, blood volume and reactivity of blood volume to $CO_2$ changes, as measured by near-infrared spectroscopy. INDO is thought to act by increasing vasomotor tone. The effect is still significant 2 h after its administration. More recent studies have shown that pharmacological PDA closure with IBU (unlike INDO) does not significantly reduce cerebral perfusion [15, 18], but no increase in ICH or PVL has been demonstrated in INDO- or IBU-treated patients to date. We also found no difference in the incidence of haemorrhagic or ischaemic brain lesions: progression of ICH to grades 3 and 4 was seen in three patients (4%) on INDO and four (4%) on IBU, and the incidence of PVL did not differ significantly between the groups. Moreover, the incidence of major ICH was lower in the study groups than in the overall population of very low birth weight infants in our units. In preterm infants, IBU did not significantly reduce mesenteric blood flow velocity as compared to INDO [19], although this was not reflected in earlier full enteral feeding or faster weight gain and we observed the same incidence of necrotising enterocolitis and isolated bowel perforation in patients treated with both drugs. We encountered no other side-effects, e.g. increased bleeding tendency during venipuncture or endotracheal aspiration, gastrointestinal bleeding or haematuria.

We conclude that IBU is just as effective as INDO in closing PDA in infants with RDS, with fewer effects in terms of transient renal impairment. In particular, this study revealed no increase in ICH after treatment.

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