Diuresis as the clinical marker of efficacy of ibuprofen in pharmacological closure of patent ductus arteriosus in preterm infants

WERONIKA ŁAGAN, KATARZYNA NIEDRYGAS, ANNA ZELWIAŃSKA, JOANNA SAWICKA

Abstract
Until recently, indomethacin was the first-choice drug in the treatment of patent ductus arteriosus in preterm infants, despite the observation of frequent side effects. Since recently, an alternative for indomethacin is available – ibuprofen, a drug of similar efficacy yet higher safety profile. In kidneys, two isoforms of cyclooxygenase are present; their products: PGE2, PGI2 and TXA2 regulate the blood flow, glomerular filtration and tubular transport of sodium and potassium. Inhibition of cyclooxygenase decreases the production of prostanooids, which results in vasocostriction, not only of ductus arteriosus, but also other vessels e.g. renal vessels, which can result in the decrease of diuresis. The aim of this study was retrospective assessment of diuresis in newborns diagnosed with haemodynamically relevant ductus arteriosus and treated with ibuprofen after the 3, and before the 7 day of life. The changes in hourly diuresis would serve as a marker of clinical efficacy of pharmacological closure of patent ductus arteriosus in preterm newborns. 39 newborns were qualified for the study (18 boys, 21 girls), with mean birth weight of 960 g (SD: 312 g) and mean gestational age of 27 weeks (SD: 3 weeks). The efficacy of pharmacological PDA closure was confirmed by means of echocardiography in 23 patients (59%) (IBU+), and in 16 patients surgical ligation of the PDA was necessary (41%) (IBU–). The study resulted in no statistically relevant difference in diuresis between group IBU+ and IBU–, hence the alterations in the volume of hourly diuresis cannot be considered as a prognostic factor which allow prediction the efficacy of pharmacological treatment.

Key words: patent ductus arteriosus, prematurity, diuresis, ibuprofen

Introduction
Ductus arteriosus (arterial duct) is the vessel connecting the trunk of pulmonary artery and descending aorta. In utero, its patency is vital for proper fetal circulation. The closing of ductus arteriosus is frequently impaired in preterm newborns with low birth weight. Persistent, haemodynamically relevant ductus arteriosus typically increases the risk of various complications, such as necrotizing enterocolitis, periventricular leukomalacia or bronchopulmonary dysplasia.

Accounting that clinical symptoms of PDA are highly untypical and occurring late, the first-choice diagnostic test in neonates is echocardiography, which is performed between 2 and 3 day of life.

The echocardiographic criteria for the diagnosis of a patent and haemodynamically relevant ductus arteriosus (Skinder) include:
1) Any left-right flow through the ductus arteriosus in neonates with 3 or 4 grade RDS.
2) Ductus diameter > 1.5 mm.
3) The LA/Ao (left atrium to aorta diameter) index > 1.4: 1.
4) Diastolic reflux flow in descending aorta.
5) Enlargement of left atrium and left ventricle (which results in the interatrial septum protruding to the right).

Treatment comprises either pharmacological methods: indomethacin or ibuprofen or surgical ligation. The use of cyclooxygenase (COX) inhibitors implies the risk of numerous adverse effects, such as the possibility of intra-ventricular hemorrhage, necrotizing enterocolitis with intestinal perforation, thrombocytopenia, hyponatremia increased creatinine level and decrease in glomerular filtration leading to oliguria.

Ibuprofen is used in the first week of life, so that the effectiveness of the COX inhibitor treatment is the most substantial. It is usually administered after the third day of life, after echocardiographic confirmation of haemodynamically relevant patent ductus arteriosus.

The individual sensitivity of constitutive cyclooxygenase, liable to genetic expression and blockage both in PDA endothelium and blood vessels of the kidney can be used to predict the effectiveness of ibuprofen treatment.
Objectives of the study

The aim of the study is to assess the possibility of employing daily diuresis as the clinical marker of effectiveness of ibuprofen in the treatment of haemodynamically relevant PDA in neonates with very low birth weight.

Methodology

The study comprises retrospective analysis of the changes in hourly diuresis in patients hospitalized in the Neonatal Pathology and Intensive Care Ward of the Clinic for Children’s Diseases of the Polish-American Institute of Pediatrics, Jagiellonian University Medical College between 2005-2008.

The inclusion criteria for the study comprised:
1) gestational age below 34 weeks,
2) very low birth weight (VLBW),
3) echocardiographically confirmed, haemodynamically relevant PDA (LA/Ao > 1.4, PDA diameter > 1.5 mm, steal in descending aorta, or any left-right flow in a preterm neonate with respiratory distress syndrome > 3 grade,
4) discontinuation of ibuprofen treatment after first week of life.

The exclusion criteria comprised:
1) ductus-dependent congenital heart defect,
2) intracranial and/or digestive tract hemorrhage,
3) necrotizing enterocolitis,
4) anuria.

The patients who fulfilled the criteria, were analyzed in terms of: hourly diuresis, body weight (g), daily fluid intake (ml/kg), ventilation parameters (MAP, FiO₂), blood pressure and echocardiographic parameters.

The Analysis of Variance was employed to analyze quality variables, whereas quantity variables were analyzed with the use of Accurate Fisher Test. The level of statistical relevance was \( p < 0.05 \).

Results

39 newborns were included in the study (18 boys, 21 girls). Mean body weight was 960 g (SD ± 312 g). Fifteen of the neonates weighed below 801 g, nine 801-1000 g, fifteen above 1000 g. Mean gestational age was 27 weeks (SD ± 3 weeks). The effectiveness of pharmacological PDA closure was confirmed echocardiographically in 23 patients (59%), [IBU(+) group], whereas 16 patients required surgical ligation of the PDA (41%), [IBU(–) group].

No significant difference was found in hourly diuresis volume before and in subsequent days of ibuprofen treatment in the group where pharmacological closure of PDA was obtained (\( p = 0.22-0.52 \)) (Tab. 1).

Neither was the hourly diuresis volume different between the groups IBU(+) and IBU(–), before and in subsequent days of ibuprofen treatment.

<table>
<thead>
<tr>
<th>Ibuprofen intake</th>
<th>Pharmacological closure</th>
<th>Surgical ligation</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>48h before</td>
<td>5.59</td>
<td>1.22</td>
<td>5.03</td>
</tr>
<tr>
<td>24h before</td>
<td>3.99</td>
<td>1.13</td>
<td>4.31</td>
</tr>
<tr>
<td>Day of administration</td>
<td>3.67</td>
<td>1.16</td>
<td>4.17</td>
</tr>
<tr>
<td>24h after</td>
<td>3.27</td>
<td>1.07</td>
<td>3.64</td>
</tr>
<tr>
<td>48 after</td>
<td>3.64</td>
<td>1.49</td>
<td>3.97</td>
</tr>
</tbody>
</table>

Fig. 1. Quantitative changes in hourly diuresis volume in IBU (+) and IBU (–) groups in 48 and 24 hours before ibuprofen treatment and in subsequent days of treatment.

The IBU (+) group did not significantly differ from the IBU (–) group in terms of mortality – five children died within the group with successful pharmacological closure, while four children died in the group where surgical intervention was necessary.

The lack of correlation between ibuprofen effectiveness and gestational age might stem from the small numerical strength of the studied group.

There were no significant differences or changes in daily fluid intake, arterial blood pressure, ventilation parameters and echocardiographic parameters of PDA gravity observed.
Table 2. Effectiveness of pharmacological PDA closure depending on gestational age

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Pharmacological closure No (%)</th>
<th>Surgical ligation No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 26 weeks</td>
<td>8 (44.44)</td>
<td>10 (55.56)</td>
</tr>
<tr>
<td>27-28 weeks</td>
<td>6 (75)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>&gt; 28 weeks</td>
<td>9 (69.23)</td>
<td>4 (30.77)</td>
</tr>
</tbody>
</table>

$p = 0.1$

It has been remarked that ibuprofen efficacy in haemodynamically relevant PDA is greater in patients with birth weight > 800 g, which weighs in favour of more substantial sensitivity of the ductus arteriosus for the decline in prostaglandin concentration in this group of patients. It has also been observed that birth weight < 800 g is connected with statistically significant ($p = 0.03$) risk of failure of the pharmacological treatment of PDA (table 3, figure 2).

Table 3. Effectiveness of pharmacological PDA closure depending on the birth weight

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Pharmacological closure No (%)</th>
<th>Surgical ligation No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 800 g</td>
<td>5 (33.33)</td>
<td>10 (66.67)</td>
</tr>
<tr>
<td>801-1000 g</td>
<td>7 (77.78)</td>
<td>2 (22.22)</td>
</tr>
<tr>
<td>&gt; 1000 g</td>
<td>11 (73.33)</td>
<td>4 (26.67)</td>
</tr>
</tbody>
</table>

$p = 0.03$

Clearly though not statistically significant, differences in ibuprofen effectiveness between boys and the girls, require further verification in numerically stronger studies.

Discussion and conclusions

It has been traditionally accepted that in physiological conditions the COX-1 is the main source of prostaglandins and its blockage results in typical adverse effects of non-steroidal anti-inflammatory drugs (gastric ulcers or platelet dysfunction).

The COX-2 (synthesized in inflammatory reactions) inhibition is, in turn, responsible for the anti-inflammatory effect of NSAIDs.

It is worth to remember that there are two constitutive isoforms of COX in the kidney, and that PGE2, PGI2 and TXA2 which is produced by them regulate the blood flow, glomerular filtration and tubular transport of sodium and potassium.

The tissues of PDA contain the full set of enzymes that take part in PGE2 synthesis, which is constituted by three cyclooxygenase forms (COX-1, COX-2, COX-3), and two isoforms of PGE synthase (PGES cPGE, PGES mPGE).

Moreover, in the arterial duct take place genetic expression of NO synthase, synthesis of which is strictly bound with the blockage of both COX-1 and COX2. COX inhibition results in increased activation of NO synthase. This fact is possible where the failures of pharmacological treatment of PDA in neonates may stem from.

The efficacy of ibuprofen in treatment of haemodynamically significant PDA is greater in the group of patients with birth weight over 800 g, which stands for more substantial sensitivity of PDA for prostaglandin concentration decline in this group of patients.

Statistically significant lower efficacy of ibuprofen in newborns with birth weight below 800 g might stem from local genetic overexpression of COX in the endothelium of arterial duct, which is related to immaturity. In this group of patients, surgical ligation of the PDA should be considered as the first-choice treatment.

Lack of correlation of ibuprofen effectiveness and gestational age might stem from small numerical strength of the studied group.

More substantial effectiveness of ibuprofen in boys requires a study on a larger group of patients. The dif-
ference might indicate a significant role of a genetic factor in treatment of PDA in preterm newborns.

The thesis on the possibility of employing hourly diuresis as a marker of clinical efficacy of ibuprofen in closing significant PDAs has not been confirmed.

Despite the fact that impaired kidney function is widely observed in many studies in the course of COX inhibitors treatment, hereby no interrelation was confirmed between the degree of COX inhibition and the chance of PDA closure.

The changes in hourly diuresis volume in the subsequent days of ibuprofen treatment cannot constitute a prognostic factor for prediction of success in obtaining closure of PDA. There is no evidence confirming that individual sensitivity of COX, undergoing expression and blocked both in arterial duct epithelium and in the kidney vessels, can be employed to predict the effectiveness of ibuprofen treatment.

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