

Ibuprofen and paracetamol for patent ductus arteriosus

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The last ten years, the next ten years in Neonatology

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Abstract

We aimed to assess the state of the art of pharmacological treatment of patency of ductus arteriosus (PDA) with ibuprofen and paracetamol in preterm infants. We pointed out that ibuprofen is the first choice drug for PDA treatment and indomethacin should be abandoned for its frequent adverse effects. However, also the pharmacological prevention of PDA should be abandoned because many preterm infants have spontaneous closure of PDA and ibuprofen may have dangerous adverse effects. Oral paracetamol has been found in two randomized controlled studies to have the same effectiveness of ibuprofen in closing PDA but without toxicity. If these data will be confirmed the management of PDA in preterm infants should be re-evaluated.

Keywords

Ductus arteriosus, ibuprofen, paracetamol, preterm infant.

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Introduction

The patency of ductus arteriosus (PDA) is a frequent complication in preterm infants suffering from respiratory distress syndrome (RDS), and 60% to 70% of preterm infants of < 28 weeks' gestation receive medical or surgical therapy for a PDA [1]. Neonates with a left-to-right shunt through the ductus complicating their RDS have higher respiratory failure, lower survival rate, and increased risk of intracranial haemorrhage (ICH), bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC) [2]. Therefore, closure of PDA is indicated before a significant left-to-right shunting occurs.

Ibuprofen for patent ductus arteriosus

Patent ductus arteriosus can be treated effectively with intravenous indomethacin and ibuprofen that are non-selective cyclooxygenase inhibitors and decreases prostaglandin synthesis leading to permanent ductal closure in 60% to 80% of infants [3-5]. However, preterm infants treated with ibuprofen experience lower serum creatinine values, higher urine output, and less undesirable decreased organ blood flow and vasoconstrictive adverse effects than indomethacin-treated patients [4]. Therefore, a recent overview concluded that "ibuprofen currently appears to be the drug of choice" [4], and consequently the use of indomethacin for closing PDA in preterm infants should be abandoned.

It has been debated the opportunity of preventing PDA through its pharmacological prophylaxis, but Ohlsson and Shah in a recent meta-analysis demonstrated that, although ibuprofen prophylaxis decreases the occurrence of PDA and the need of its rescue treatment or surgical closure, it does not confer any short term benefits and exposes many patients, in whom PDA would have been spontaneously close, to the possible renal and gastrointestinal adverse effects of ibuprofen [5]. In fact, it has been reported that a high percentage (24-58%) of preterm infants shows spontaneous closure of the ductus arteriosus despite their extreme immaturity [5, 6].

On the other hand, a high percentage (22-30%) of preterm infants born at the lower gestational ages fails to respond to a single course of indomethacin or ibuprofen, and requires further doses of drug and/or surgical ligation of PDA [5, 6]. Thus, it has been suggested that the actual dose regimens of these drugs could be inadequate because of large interindividual

pharmacokinetics and pharmacodynamic variations in premature infants during treatment for PDA [7]. Desfrere et al. demonstrated, in double blind randomized study in a cohort of infants of ≤ 29 weeks of gestational age, that the currently recommended dose regimen of ibuprofen (10-5-5 mg/kg/day) is associated with a low estimated probability (30.6%) of closing PDA while a high-dose regimen (20-10-10 mg/kg/day) might be associated with a greater, although unsatisfactory, probability (54.8%) of closing PDA, without relevant side effects [8]. Unfortunately, they were able to give this dose to a single patient and advocated further studies to assess the tolerability and safety of this dose regimen in a larger population [8]. Furthermore, Hirt et al. studied infants with gestational age from 25 to 34 weeks, and postnatal age ranging from 14 to 262 h (n = 66) and, based on pharmacokinetic findings, proposed to increase the dose regimen of ibuprofen during the postnatal period from 10-5-5 mg/kg/day in preterm infants < 70 h of age to 14-7-7 mg/kg/day in infants 70-108 h of age and 18-9-9 mg/kg/day in infants 108-180 h of age [9]. Thus, they suggested to increase the dose during the postnatal period, although all their patients received the standard regimen, and they concluded that their assumptions about the proper ibuprofen regimen need to be tested prospectively.

Therefore, we performed a multicenter randomized controlled study to compare the effectiveness of the current ibuprofen regimen (10-5-5 mg/kg/day) to that of a high-dose regimen (20-10-10 mg/kg/day) in closing PDA in a cohort of infants (n = 70) with gestational age < 29 weeks and a hemodynamically significant PDA diagnosed at 12-24 hours of life [10]. We found that 37% of infants treated with the standard dose regimen had persistent PDA after the first ibuprofen course in comparison with 14% of infants treated with the high-dose regimen (p = 0.03) [10]. No differences in the occurrence of adverse effects were observed between the two groups. We concluded that the high-dose ibuprofen regimen is more effective than the standard dose regimen in closing PDA in preterm infants without increasing the adverse effect rate [10]. These findings seem to confirm the assumption of Hirt et al. [9] that it is unlikely that a high-dose of ibuprofen would lead to an increase in toxicity as they did not find any relationship between the ibuprofen area under curve (AUC) increase and serum creatinine in their study on optimizing the ibuprofen dose. Nevertheless, the possible nephrotoxic effect of ibuprofen remains

controversial and it may not be considered exempt from causing adverse renal effects [11].

It is interesting that in this study we observed that the ultimate outcome of PDA is not affected by the dose regimen of the first ibuprofen course provided that in case of persistent PDA a second course of ibuprofen is given at high-dose. However, further randomised controlled studies are warranted to confirm our findings in wide population and evaluate the efficacy of a second course of high dose ibuprofen if the first course fails to close the PDA [10].

Paracetamol for patent ductus arteriosus

The potential adverse effects of ibuprofen treatment and its possible failure in closing PDA makes welcome an alternative pharmacological treatment. In fact, the recent publication of case-series reporting on the effectiveness of paracetamol in closing PDA is very interesting.

Non-steroidal anti-inflammatory drugs are known to facilitate ductal closure by inhibiting synthesis of prostaglandins. Prostaglandin synthetase has cyclooxygenase and peroxidase components that operate at distinct, active sites with different catalytic activities [12]. Cyclooxygenase catalyzes the beginning of prostanoid synthesis from arachidonic acid, and indomethacin/ibuprofen compete with the arachidonic acid substrate for the active cyclooxygenase site. Differently, paracetamol seems to act at the peroxidase segment of the enzyme [12], which indicates that paracetamol-mediated inhibition is facilitated by a reduction in the concentration of local peroxide.

In 2011, Hammerman et al. reported the first case series of preterm infants ($n = 5$; gestational age: 26-32 wks; postnatal age: 3-35 days) in whom they observed that 60 mg/kg/day of oral paracetamol, in four divided doses, for a period of three days were effective in closing PDA without toxicity [13].

Subsequently, two randomized controlled studies investigated the effectiveness of oral paracetamol versus oral ibuprofen in the rescue treatment of PDA in preterm infants. Dang et al. studied 160 infants with gestational age ≤ 34 wks treated with 15 mg/kg every 6 h for 3 days of paracetamol or ibuprofen at standard dose. They found that the ductus was closed in 81.2% of infants in the paracetamol group compared with 78.8% of infants in the ibuprofen group ($p = 0.7$), and that the incidence of hyperbilirubinemia or gastrointestinal bleeding was significantly lower in the paracetamol

group [14]. Oncel et al. carried out a similar study in 90 preterm infants with gestational age ≤ 30 weeks: they found that, after the first course of treatment, the PDA closed in 77.5% of the patients assigned to the ibuprofen group versus 72.5% of those enrolled in the paracetamol group ($p = 0.6$) without different toxicity [15]. In a further prospective study, Oncel et al. studied the effect of intravenous paracetamol compared in 10 preterm infants with gestational age 24-29 wks who were treated with 15 mg/kg every 6 h for 3 days of paracetamol [15]. Intravenous paracetamol resulted in successful closure of hemodynamic significant PDA in all patients without evident adverse effects [15].

It is relevant to consider the possibility that paracetamol may be effective in the treatment of PDA refractory to ibuprofen. From this point of view, few data are available: Hammerman et al. successfully treated with paracetamol two patients with ibuprofen-resistant PDA at 3-18 days of life [13], while Oncel et al. successfully treated with paracetamol 5 preterm infants with ibuprofen-resistant PDA at 5-27 days of life [16]. The mechanism by which paracetamol can close ibuprofen refractory PDA might lie in the different site of action on prostaglandin synthetase of the two drugs [12], that hypothetically might have also a synergistic effect.

These data on the effectiveness of paracetamol for the treatment of PDA are very promising, because they suggest that if paracetamol will be confirmed to be effective in future randomized controlled trials, particularly as intravenous therapy, it may become the treatment of choice for the management of PDA mainly due to its better tolerability than ibuprofen, and an important alternative to surgical ligation in patients who are either ibuprofen resistant or for whom ibuprofen is contraindicated.

On the other hand, the combination of effectiveness and less toxicity of paracetamol compared to ibuprofen might change the risk:benefit ratio of PDA pharmacological therapy and, ultimately, affects the decision about which infants will benefit most from treatment of the PDA.

Conclusions

The pharmacological approach to PDA in preterm infants is one of the most common clinical problem neonatologists must deal with in neonatal intensive care units. Recently, it has been demonstrated that the pharmacological prophylaxis of PDA is no more recommended and that ibuprofen is the first choice

drug for its rescue treatment. However, emerging evidences suggest that paracetamol might have the same effectiveness of ibuprofen with minimal or absent toxicity. If these findings will be confirmed the management of PDA in preterm infants should be re-evaluated.

Declaration of interest

The Author declares that there is no conflict of interest. The Author confirms that there is no any professional affiliation, financial agreement or other involvement with any company whose product figures prominently in the submitted manuscript

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