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## EDITORIAL

### Oral ibuprofen and the patent ductus arteriosus: a new approach to an old problem<sup>☆,☆☆</sup>

### Ibuprofeno via oral e a persistência do canal arterial: uma nova abordagem para um problema antigo

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Patent ductus arteriosus (PDA) is present in up to 75% of infants born before 28 weeks gestation, and issues concerning PDA remain a popular topic in neonatology. The large range of articles addressing the assessment and treatment of PDA demonstrates the continuing uncertainty regarding the best way to manage an infant with this complication of prematurity. PDA is associated with many of the adverse outcomes of prematurity; however, there are conflicting results on the benefits of PDA closure from the many randomised and observational studies targeting PDA treatment. Consequently, there are ongoing questions as to when to treat, what to treat, and how to treat. Complicating factors, such as efficacy, dosage issues, risk of side effects, and the large variation in cost of potential treatments are becoming increasingly important, as neonatologists try to optimize available therapies. Neonatology has a track record of introducing medications before the pharmacokinetics in our population are properly understood. Enteral or intravenous indomethacin was the mainstay of PDA treatment for many years, ever since its use was first described in 1976.<sup>1,2</sup> More recently, ibuprofen, initially as an intravenous infusion, has been utilized and found to be of similar efficacy as intravenous indomethacin.<sup>3</sup> There are, however, indications that the appropriate dose to maintain therapeutic ibuprofen levels is not being achieved with intravenous dosing, resulting in

increased treatment failure rates.<sup>4</sup> Oral medication, which is simple to administer and effective, with minimal side effects, would be likely to change the balance in favour of treatment in many preterm infants.

In this issue of the Journal, Yang et al.<sup>5</sup> describe their experience with the use of oral ibuprofen *versus* intravenous indomethacin in a group of extremely low birth weight infants. In this retrospective cohort study, oral ibuprofen syrup (10 mg/kg initial dose, followed by two doses of 5 mg/kg at 24-hour intervals) was found to be as efficacious as intravenous indomethacin. The closure rate on initial treatment was 81.8% for oral ibuprofen *versus* 88.5% for intravenous indomethacin ( $p = 0.40$ ). Importantly, there were no differences in side effects or complications between the two approaches. These were small infants, all under 1,000 g, and treated on average at 5 days of age.

Other studies have confirmed the high closure rates and favourable safety profile of oral ibuprofen. Most recently, Erdevé et al.<sup>6</sup> performed a randomised controlled trial of oral versus intravenous ibuprofen in 80 preterm infants, and found a higher initial closure rate with oral ibuprofen, though there was a higher re-opening rate in infants who received this treatment. Interestingly, there was also a reduction in the incidence of chronic lung disease in the orally treated group. Other studies have

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reported favourable outcomes for infants treated with oral ibuprofen compared with either intravenous indomethacin or intravenous ibuprofen.<sup>7-12</sup> One explanation for the improved efficacy of oral ibuprofen may lie within its pharmacokinetic profile. Oral ibuprofen administration results in more sustained therapeutic plasma levels. This was confirmed in a pharmacokinetic study by Barzilay et al.,<sup>13</sup> who observed a high area under the curve (AUC) due to prolonged drug levels following oral dosage. This concept is further supported by studies of continuous indomethacin infusion, which also show better ductal closure when therapeutic levels are constantly maintained.<sup>14</sup>

Neonatologists need a solution to the dilemma of which PDAs should be treated, and how to best achieve closure if indicated. Answers to the first question, are likely to come from more careful individual assessment of the physiological effects of the ductal shunt using techniques such as functional echocardiography,<sup>15</sup> rather than performing large trials of treatment in infants with variable underlying physiology. Regarding the best management, the availability of an inexpensive, safe, and more efficacious medical treatment for PDA would be of major benefit to neonatologists internationally, particularly to those working in developing countries, where the prohibitive costs of new, intravenous medications make oral treatment an appealing option. Another relevant issue is the uncertainty of the supply of intravenous medications for PDA treatment, which has plagued neonatology over the past few years, as rival companies compete to provide a monopoly treatment. All of these factors amount to a potentially great benefit of the use of oral ibuprofen in the management of PDA. The evidence for the use of oral ibuprofen for initial PDA treatment, even in the most immature infants, is mounting, and the paper by Yang et al.<sup>5</sup> adds further to this body of evidence.

## Conflicts of interest

The author has no conflicts of interest to declare.

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