NSAIDs act by inhibiting the cyclo‐oxygenase (COX) enzyme, thereby leading to down regulation of PGE₂, a potent relaxant of the PDA. However, use of indomethacin in preterm infants has been associated with transient or permanent derangement of renal function, NEC, gastrointestinal haemorrhage or perforation, alteration of platelet function, and impairment of cerebral blood flow/cerebral blood flow velocity. Therefore, variations in indomethacin therapy have been attempted to mitigate the said adverse effects while maximising therapeutic benefit. These include using continuous infusion of indomethacin rather than intermittent bolus doses, which may reduce its adverse effects on cerebral oxygenation, and use of a prolonged course of indomethacin, which may provide increased therapeutic benefit compared to a short course of indomethacin.

**Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of Cochrane Systematic Reviews**

ll available prostaglandin inhibitor drugs appear to be more effective in PDA closure when compared to placebo or no treatment (high‐certainty evidence for indomethacin; moderate‐certainty evidence for ibuprofen; low‐certainty evidence for early administration of acetaminophen). Oral ibuprofen appears to be more effective in PDA closure compared to ibuprofen (moderate‐certainty evidence); and high‐dose ibuprofen appears to be more effective in PDA closure compared to standard‐dose ibuprofen (moderate‐certainty evidence). There was no evidence of any difference in PDA closure effectiveness between the three available prostaglandin inhibitor drugs (low‐ to moderate‐certainty evidence). There is no evidence on the effect of treatment of symptomatic PDA on the composite outcome of death or moderate/severe neurodevelopmental disability.

From a safety perspective, compared to indomethacin administration, NEC appears to be lower with ibuprofen (any route; moderate‐certainty evidence), exclusive oral administration of ibuprofen (low‐certainty evidence), and with acetaminophen (low‐certainty evidence). On the contrary, NEC appears to be more common with a prolonged course of indomethacin versus a shorter course. Oliguria is also higher with use of indomethacin versus ibuprofen (moderate‐certainty evidence), the use of ibuprofen versus either placebo or acetaminophen, and with early pharmacological treatment of PDA, initiated within the first seven days of life versus later treatment.

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| Vantagens | Desvantagens |
| Fármacos usados (p.e ibuprofeno) são facilmente acessíveis e o seu custo não muito elevado | Potenciais efeitos adversos graves |
| Mais eficaz que o placebo | Não muito eficaz |
| Não invasiva (permite poupar intervenção cirúrgica complexa em grupo de risco) | Dosagem ainda não bem definida |
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In conclusion, in extreme preterm infants with a large PDA, there was no evidence that early treatment with ibuprofen was associated with an improvement in the composite outcome of death or moderate or severe BPD compared to placebo at 36 weeks post-menstrual age.

In this study, we described the enantiomer‐specific PK and found that S‐ibuprofen clearance shows important maturation, especially with PNA, resulting in an up to 3‐fold increase in CLS during a 3‐day treatment regimen. This rapid increase in clearance needs to be incorporated in dosing guidelines by adjusting the dose for every day after birth to achieve equal ibuprofen exposure, also during a 3‐day treatment regimen. To obtain similar exposure in AGA preterm neonates, the loading dose should be increased by 2 mg/kg for every postnatal day of treatment initiation, starting with 10 mg/kg. A maintenance of 50% of the loading dose plus 1 mg/kg increase with every postnatal day will result in minimal differences in exposure between different PNAs. Studying enantiomer‐specific PK of ibuprofen did not provide us with new insights, and in future studies measuring total ibuprofen suffices.