

1-10-2018

# What is the Most Efficacious Pharmacological Therapy for Patent Ductus Arteriosus Closure in Premature Infants?

N Bussman

*The Rotunda Hospital, Dublin*

Afif F. El-Khuffash

*Royal College of Surgeons in Ireland, [afifelkhuffash@rcsi.ie](mailto:afifelkhuffash@rcsi.ie)*

---

## Citation

Bussman N, El-Khuffash AF. What is the Most Efficacious Pharmacological Therapy for Patent Ductus Arteriosus Closure in Premature Infants? *Irish Medical Journal*, 2018;111(9):817.

This Article is brought to you for free and open access by the Department of Paediatrics at [e-publications@RCSI](mailto:e-publications@RCSI). It has been accepted for inclusion in Department of Paediatrics Articles by an authorized administrator of [e-publications@RCSI](mailto:e-publications@RCSI). For more information, please contact [epubs@rcsi.ie](mailto:epubs@rcsi.ie).

---

— Use Licence —



This work is licensed under a [Creative Commons Attribution-Noncommercial-Share Alike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

---

# What is the Most Efficacious Pharmacological Therapy for Patent Ductus Arteriosus Closure in Premature Infants?

**N. Bussmann<sup>1,2</sup>, A. EL-Khuffash<sup>1,3</sup>**

1. Department of Neonatology, The Rotunda Hospital, Dublin, Ireland.
2. National Children's Research Centre, Our Lady's Children's Hospital Crumlin, Dublin, Ireland.
3. School of Medicine (Department of Pediatrics), Royal College of Surgeons in Ireland, Dublin, Ireland.

Dear Editor,

We read with great interest the systematic review and meta-analysis by Mitra et-al published recently in JAMA. (1) This metanalysis attempts to identify the pharmacological intervention which results in the best closure rates of a patent ductus arteriosus (PDA) in infants less than 37 weeks gestation. The group carried out a detailed review of 67 randomised controlled trials (RCTs), published between 1980 and 2017, including 4802 patients examining fourteen variations of indomethacin, ibuprofen, or acetaminophen (paracetamol) as treatment modalities for a PDA. The following primary outcomes were assessed: PDA closure within one week of administration of the first dose, need for repeat pharmacotherapy or surgical ligation. Adverse outcomes were defined as necrotising enterocolitis, neurological events, bronchopulmonary dysplasia, oliguria and neonatal mortality. This paper has an important message incorporating new information that is not in keeping with current clinical practice: a high oral dose of ibuprofen was associated with a greater rate of closure of a PDA at one week when compared to standard dose intravenous (IV) ibuprofen, IV indomethacin and oral acetaminophen. There were no differences between the no treatment/placebo group or treatment groups in mortality, necrotising enterocolitis or intraventricular haemorrhage.

PDA treatment remains a controversial topic. The indication for, the optimal timing of, and modality of treatment are topics of constant debate. One of the major challenges of metanalyses such as this one is the large degree of heterogeneity in the gestational age of included infants, the timing of intervention, the variation in the definition of a haemodynamically significant PDA, and the high rate of open label PDA treatment in both the intervention and placebo arms of the included RCTs. In addition, there are several other factors that can determine ductal patency, and the PDA's response to therapeutic interventions. Many of those confounders may not be captured in those RCTs thereby limiting the interpretability of the results. For example, the concomitant use of frusemide can limit drug efficacy in preterm infants by stimulating renal synthesis of Prostaglandin

E2, an important determinant of ductal patency. (2) In addition, recent evidence suggests that specific genetic pathways play a key role in the modulation of ductal patency, and its response to medication. (3)

The gestational age of the infant and the timing of treatment administration, drug metabolism and renal excretion are likely to play important roles in determining pharmacokinetics of the administered medication and therefore, its efficacy. Those parameters can potentially vary widely in the premature infant population. (4) Ibuprofen is metabolised into two inactive metabolites by cytochromes CYP2C8 and CYP2C9. CYP2C9 levels are low at birth and increase during the first few weeks of life. The levels of metabolite formation vary, and thus the rate of clearance and half-life of ibuprofen, depending on the infant's maturational age. Regression analysis of seven studies indicated that when the Ibuprofen area under the curve between 0 and 24 hours of administration (AUC<sub>0-24</sub>) was over 600mg.h/l, the probability for PDA closure increased significantly ( $p = 0.0054$ ). However, as post-natal age advances the dose of Ibuprofen needs to be increased in order to maintain an Ibuprofen AUC<sub>0-24</sub> level of > 600mg.h/l. Suggestions are made for dosage increments based on post-menstrual age as follows: <70 hours, 10-5-5 mg/kg/day; 70-108 hours, 14-7-7 mg/kg/day; 108-180 hours, 18-9-9 mg/kg/day.

Similarly, there is considerable variability in the pharmacokinetic parameters of indomethacin in preterm infants. Indomethacin is mainly metabolised by O-demethylation and N-deacylation; both drug and metabolites are conjugated with glucuronic acid in the liver. Renal excretion of the unchanged drug plays a very small role in overall drug clearance. The major metabolite of indomethacin is demethyl-indomethacin, with two other minor metabolites: deacylated indomethacin and p-chlorobenzoic acid. Studies examining the AUC<sub>0-24</sub> of administered indomethacin (mainly after one dose of administration) demonstrate that blood concentration can vary by up to 5-fold, highlighting the heterogeneity of clearance patterns amongst infants. (5) Paracetamol undergoes hepatic elimination. Glucuronidation and sulfation results in non-toxic products that are efficiently excreted in the urine. Oxidation by cytochrome P450 results in potentially toxic reactive species that are detoxified by conjugation with glutathione. Recent evidence demonstrates that liver and renal function, postnatal age and the weight of the infant play key roles in regulating paracetamol drug levels. (6)

This metanalysis (like many other previous reports) found no difference in the rates of important short and long-term outcomes between treated and untreated infants. (7-13) All the studies to date are marred by a distinct failure to physiologically categorise PDA severity and the likely shunt volume, and relate those measures to the development of important clinical outcomes. Inclusion criteria are usually based on arbitrary cut offs of PDA size or less specific clinical criteria. Both the magnitude of the shunt and its impact on the pulmonary and systemic circulations may explain the association between a PDA and morbidities. In addition, all of the trials to date have a high rate of open label treatment in the control arms. Consequently, the effects of a persistent long standing haemodynamically important PDA on infant's morbidity and mortality has never been systematically investigated.

This information highlights the need for an individualised dosing regimen for infants taking into consideration the gestation, the timing of treatment and likely clearance of the administered drug. It would be more appropriate to use a targeted pharmacotherapeutic approach by assessing the likely clearance of the given medication to estimate the appropriate AUC<sub>0-24</sub> required for efficacious ductal closure. A more comprehensive appraisal of PDA severity using echocardiography may improve our understanding of haemodynamic significance and enable more accurate targeted treatment of those infants.

**Correspondence:**

Afif EL-Khuffash

Department of Neonatology,

Rotunda Hospital,

Dublin,

Ireland.

Email: afif\_faisal@hotmail.com

1. S Mitra IF, ME Tamayo, L Mbuagbaw, T Vanniyasingam, AA Veroniki, AM Zea, Y Zhang, B Sadeghirad, L Thabane. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants. A Systematic Review and Meta-analysis. JAMA. 2018;319(12):1221-38.

2. Green TP, Thompson TR, Johnson DE, Lock JE. Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. N Engl J Med. 1983;308(13):743-8.

3. Hajj H, Dagle JM. Genetics of patent ductus arteriosus susceptibility and treatment. Semin Perinatol. 2012;36(2):98-104.

4. Pacifici GM. Clinical pharmacology of ibuprofen in preterm infants: A meta-analysis of published data. Medical Express. 2014;1(2).

5. Pacifici GM. Clinical pharmacology of indomethacin in preterm infants: implications in patent ductus arteriosus closure. Paediatr Drugs. 2013;15(5):363-76.

6. Cook SF, Stockmann C, Samiee-Zafarghandy S, King AD, Deutsch N, Williams EF, Wilkins DG, Sherwin CM, van den Anker JN.

Neonatal Maturation of Paracetamol (Acetaminophen) Glucuronidation, Sulfation, and Oxidation Based on a Parent-Metabolite Population Pharmacokinetic Model. Clin Pharmacokinet. 2016;55(11):1395-411.

7. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003(2):CD003745.

8. El-Khuffash AF, Slevin M, McNamara PJ, Molloy EJ. Troponin T, N-terminal pro natriuretic peptide and a patent ductus arteriosus scoring system predict death before discharge or neurodevelopmental outcome at 2 years in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2011;96(2):F133-F7.

9. Cunha GS, Mezzacappa-Filho F, Ribeiro JD. Risk factors for bronchopulmonary dysplasia in very low birth weight newborns treated with mechanical ventilation in the first week of life. J Trop Pediatr. 2005;51(6):334-40.

10. Shortland DB, Gibson NA, Levene MI, Archer LN, Evans DH, Shaw DE. Patent ductus arteriosus and cerebral circulation in preterm infants. Dev Med Child Neurol. 1990;32(5):386-93.

11. Van OB. Patent ductus arteriosus: how aggressive should we be? Neonatology. 2007;91(4):318.

12. Brooks JM, Travadi JN, Patole SK, Doherty DA, Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. Arch Dis Child Fetal Neonatal Ed. 2005;90(3):F235-F9.

13. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ. Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed. 2008;93(6):F407-F12.