

Do we know how to treat PDA with paracetamol?

Current evidence on the pharmacokinetics and pharmacodynamics of paracetamol for hsPDA closure in extreme preterm infants

Paracetamol is increasingly used for the treatment of a haemodynamically significant patent ductus arteriosus (hsPDA) and is touted as a better alternative to ibuprofen, the current drug of choice in the UK. This review examines the evidence from randomised controlled trials (RCT) comparing paracetamol with ibuprofen, in terms of dose and pharmacokinetic and pharmacodynamic profiles. It appears that there is a lot to ascertain before paracetamol can be confidently used over ibuprofen for management of hsPDA in preterm infants.

Anupam Gupta

Consultant Neonatologist¹
anupam.gupta@mft.nhs.uk

Arin Mukherjee

Consultant Neonatologist¹ and Honorary Senior Lecturer²
arindam.mukherjee@mft.nhs.uk

¹Department of Neonatology, St Mary's Hospital, Manchester University NHS Foundation Trust

²University of Manchester

Keywords

paracetamol; therapeutic drug level; patent ductus arteriosus; preterm infant

Key points

Gupta A., Mukherjee A. Do we know how to treat PDA with paracetamol? Current evidence on the pharmacokinetics and pharmacodynamics of paracetamol for hsPDA closure in extreme preterm infants. *Infant* 2021; 17(5): 186-93.

1. Lower cumulative doses of IV paracetamol may be equally efficacious to higher daily cumulative doses while assuring a better safety profile.
2. Our review casts doubt on the therapeutic drug concentration of paracetamol as a marker of its safety or efficacy.
3. Well-designed multicentre RCTs allowing exploration of predictive kinetic behaviour of paracetamol are needed to establish its safety and efficacy over NSAIDs.

Background

Prolonged exposure to a hsPDA in extremely premature infants (<28 weeks' gestation) can lead to significant mortality and morbidity. Ibuprofen remains the first-line treatment but paracetamol is emerging as a strong alternative.

The spontaneous closure rate of PDA is inversely proportional to gestation at birth. Infants born at <28 weeks' gestation have the lowest chance of spontaneous closure of the PDA. The literature observes spontaneous PDA closure rates in only 34% of infants <28 weeks' gestation.¹ It is known that prolonged exposure to hsPDA for greater than 7-13 days, increases the incidence of bronchopulmonary dysplasia (BPD) or death.² It is well established that the effects of non-steroidal anti-inflammatory drugs (NSAID, eg ibuprofen or indomethacin), in ductal constriction, decreases considerably beyond two weeks of age.²⁻⁴ It is postulated that non-prostaglandin pathway mechanisms are involved in keeping ductal patency beyond this age.⁴ Most published trials showed the benefits of potential treatment when initiated within the first two weeks of life.²⁻⁵

Intravenous (IV) ibuprofen is the only licenced medication for management of PDA in the UK.⁶ Although there is an increased awareness of the benefits of paracetamol in PDA treatment, the exact mechanism by which paracetamol closes a

PDA is not fully understood. It appears that paracetamol inhibits prostaglandin synthetase activity by acting at the peroxidase segment of the enzyme, as opposed to the cyclooxygenase segment.¹

A recent national survey⁷ of UK neonatal intensive care units (NICU) carried out by the authors observed that 82% of NICUs in the UK use paracetamol to treat PDA. While the majority of units (65%) used it as a second-line treatment for PDA, 10% used it as a first-line treatment in preference to ibuprofen.

Available evidence from the literature suggests that the dose of paracetamol used to treat PDA varies between 30mg/kg/day and 60mg/kg/day, as does the duration – from three days to seven days. A recent systematic review⁸ of paracetamol recognised it as a promising alternative to ibuprofen, but was unable to provide practice recommendations due to the heterogeneity in the methodology and designs of the available clinical trials.

Aims and objectives

The objective of this review was to examine evidence on the dose, pharmacokinetic and pharmacodynamic profile of paracetamol and establish its current position regarding use for management of hsPDA in preterm infants.

We carried out this targeted literature review to improve understanding of the current evidence on the pharmacokinetic (with particular focus on therapeutic drug

levels) and pharmacodynamic (efficacy, safety profile and drug regimens) properties of paracetamol in PDA management. It is envisaged that this will help neonatologists in their understanding of the clinical use of paracetamol and identify gaps in knowledge to encourage better designed clinical trials for the future.

Methodology

A thorough literature search of online databases was performed. The articles classed as RCTs on use of paracetamol for management of PDA were evaluated. We searched the online databases Medline, Embase and Cochrane using the keywords patent ductus arteriosus AND paracetamol. We then reviewed the results for articles on case reports, observational studies and RCTs. The exercise returned 46 articles on paracetamol for PDA management, which were mostly case series and case reviews. Twenty RCTs were identified; eight of these RCTs used an IV preparation of paracetamol and 12 RCTs used oral paracetamol. These RCTs were evaluated in our review.

Results

The dose, duration, route of administration of paracetamol for treatment of PDA remains variable across RCTs. A loading dose followed by a lower daily cumulative dose of IV paracetamol appears to have a better safety profile, while retaining similar efficacy in comparison to higher daily cumulative doses. Heterogeneity of the clinical trials and their trial designs preclude the use of therapeutic drug monitoring as a marker of safety and effectiveness for paracetamol treatment across all gestations of prematurity. The outcome and safety profile of paracetamol in the longer term remains unascertained.

Pharmacokinetics

While the half-life of paracetamol in adults is suggested to be 5.6 hours, pharmacokinetic studies in preterm and term newborn infants found these to be 4.6 hours and 2.9 hours respectively.⁹ In adults, paracetamol metabolism takes place in the liver by following pathways leading to non-toxic metabolites that are eventually eliminated by the kidneys:¹⁰

- glucuronidation (45-55%)
- sulphation (sulphate conjugation) (20-30%)
- N-hydroxylation and dehydration, then glutathione conjugation (<15%).

However, in extremely preterm infants the main mode of metabolism is sulphation¹¹ and the glucuronidation metabolism of paracetamol increases with advancing gestational age.¹² As the extent of glucuronidation and sulphation is dependent on the gestation and maturity of infants, a uniform standard serum level across all gestations becomes hypothetical. Hence, serum paracetamol levels remain an unpredictable marker to guide direct treatment.¹³ In addition, appropriate clinical trial designs and assays incorporating robust evaluation of gestation-specific serial serum concentrations, to determine optimal dose response threshold and toxicity, are yet to happen in extreme preterm infants.^{3,14}

Allegaert et al¹¹ carried out one of the most comprehensive works in producing pharmacokinetic evidence on IV paracetamol use in neonates. The authors demonstrated that an increased volume of distribution supports the use of a loading dose in neonates. They also reported that size (described by patient weight) is the major co-variate contributing to paracetamol clearance variance in neonates as paracetamol clearance (mg/kg/hour) increases marginally throughout the neonatal life. The authors suggested a loading dose of 20mg/kg followed by 10mg/kg every six hours within the age range evaluated (32-44 weeks' post-menstrual age) to achieve the desired mean concentration of the drug.

In vivo, the serum concentration of a drug at any given time is in a state of continuous dynamic equilibrium with its absorption, distribution, storage in tissues, liberation and elimination. Hence, any evaluation of the serum therapeutic concentration requires comprehensive pharmacokinetic compartment modelling. Compartment models in pharmacokinetic studies simulate these dynamic interplays of drug absorption, distribution and elimination. A single compartment linear disposition pharmacokinetic model (zero-order input, first-order elimination) is supposedly the least accurate evaluation, as it assumes a homogenous distribution of the drug in the body. The pharmacokinetic evaluation by Allegaert et al is based on a two-compartment model, which is better than a single compartment model.

In addition, the presence of factors such as renal disease, liver impairment and hyperbilirubinaemia, can all affect paracetamol metabolism and clearance.

Any infant on enzyme-inducing anti-epileptic drugs (eg phenobarbitone, rifampicin, phenytoin) should be monitored closely with caution due to potential interaction with paracetamol.

To date, the majority of clinical trials on the use of paracetamol have relied on trial-and-error methods of drug dosage and serum levels rather than predicting the kinetic behaviour of paracetamol through comprehensive pharmacokinetic modelling.

In a very recent study by Cakir et al, the authors compared continuous infusion vs standard intermittent bolus infusion of paracetamol to treat PDA.¹⁵ In spite of obvious theoretical advantages of continuous infusion in achieving consistent therapeutic serum concentrations, the study did not find any merit in the use of paracetamol infusion in comparison to intermittent bolus doses for the pharmacological treatment of PDA. Lower rates of PDA-related morbidity (BPD, necrotising enterocolitis, NEC, and need for ligation) were noted with intermittent dosing.

Pharmacodynamics

Unlike NSAIDs, which have a vasoconstrictive mechanism of action, paracetamol exerts a vasodilatory effect.¹³ This observation may explain the fewer side effects encountered with paracetamol use. Vasoconstriction is thought to be the primary causative factor for renal impairment, cerebral ischaemia and NEC seen with some NSAIDs.

While vasodilation raises concerns of clinical hypotension following paracetamol administration, it has not been a major issue in the neonatal population.¹² It is postulated that the metabolite responsible for the vasodilatory effects is NAPQI (N-acetyl-p-benzoquinone imine). As less than 15% of paracetamol is metabolised via this route and NAPQI is detoxified rapidly by glutathione in the liver and excreted in the urine, under physiological conditions its impact is minimal and short-acting.¹³

Route of administration

A recent UK national survey noted that 73% of NICUs use only an IV preparation of paracetamol and 26% of units use either an IV or enteral preparation, depending on the fed status of their infants.⁷

It also appears that oral paracetamol has similar efficacy to oral ibuprofen.^{10,16} However, the oral route probably does not represent the optimal choice for extremely

low birth weight infants. Gut immaturity, poor enterohepatic circulation together with feed intolerance in these infants is likely to contribute to reduced efficacy and unpredictable paracetamol toxicity. A recent systematic literature review tentatively suggests that, while oral paracetamol appears to be effective in infants weighing 1,501g to 2,500g, more elaborate and comprehensive RCTs are needed to ascertain its effects in more premature infants.⁸

Dose

Following the first report in 2013 by Oncel et al,¹⁷ that an IV dose of paracetamol at 15mg/kg every six hours (daily cumulative dose of 60mg/kg/day) can be used in extremely premature infants successfully to close a PDA, many observational studies and some RCTs have used it with success. These trials neither clarified on the optimal dosage regimen nor did they come up with the timing of the initiation of therapy related to paracetamol use in neonatal age groups.¹⁸ There is no consensus on the dose, duration and the route of administration of paracetamol in hsPDA. Hence, irrespective of the route of administration, its off-label use is also affected by widely variable dosages and duration (between three and seven days).

Tekgunduz et al¹⁹ reported in a retrospective study that they encountered raised transaminase enzyme levels with IV administration of paracetamol at doses of 15mg/kg six hourly (cumulative dose 60mg/kg/day). The authors reduced the dose to 10mg/kg every eight hours and reported the closure rate of PDA with this lower dose at 83.3%.

Terrin et al²⁰ recommended a limitation of dosing to 45mg/kg/day to avoid potential toxicity and still had similar efficacy rates.

Enteral

We identified 12 RCTs on the use of oral paracetamol for PDA treatment (**TABLE 1**). Oral paracetamol appears to be well tolerated and there were no significant side effects in comparison to placebo. Efficacy was noted to be comparable to ibuprofen. The majority of the researchers used a dose of 15mg/kg every six hours for three days²¹⁻²⁸ giving a cumulative dose of 180mg/kg over the course of three; the others opted for a dose of 10mg/kg every six hours for three days.^{29,30} Kluckow et al³ and Dash et al³¹ went further to give the course for five

and seven days. A review of the studies can conclude that the dose and the duration of the oral treatment in the studies so far remains widely variable.

Of note, the median gestational age for RCTs using IV paracetamol was 27.6 weeks, whereas the median gestational age used in all studies for oral paracetamol was 31.1 weeks.

IV administration

There are eight RCTs that investigated the use of paracetamol for hsPDA closure (**TABLE 2**). El-Mashad, Dani and Meena et al³²⁻³⁴ used doses of 15mg/kg every six hours for three days, which translates into a cumulative dose of 180mg/kg for the full course of paracetamol. Harkin and Hochwald et al^{35,36} opted to use a loading dose of 20mg/kg followed by 7.5mg/kg every six hours for four days and 10mg/kg every six hours for three days, leading to similar cumulative doses of 130-133.5mg/kg.

Toxicity and side effect profile

As paracetamol can induce hepatocellular necrosis, perhaps the best early marker to determine hepatocellular injury is through estimation of liver transaminases (such as aspartate transaminase, AST, and alanine aminotransferase, ALT). Tekgunduz et al reported significant increase in transaminases above the pre-treatment levels (AST and ALT rose to 260 and 180U/L from pre-treatment levels of 43 and 11, respectively).¹⁹ This was observed at an IV paracetamol dose of 15mg/kg every six hours and reversed to normal levels over five days once treatment was discontinued. However, it appears that neonates tend to suffer less from the hepatotoxic effects of paracetamol than do older children.⁴¹

Overt liver failure is extremely rare too. We found only one case report of acute liver failure in a term neonate receiving oral paracetamol at 10mg/kg/dose every four hours for three days (daily dose 60mg/kg; cumulative dose 180mg/kg).⁴² The infant responded well to IV N-acetylcysteine. While this case report highlights the risk of severe hepatotoxicity in neonates after multiple doses of paracetamol for more than 2-3 days, such incidences have remained exceedingly rare.

Apart from this, we did not find any other case reports of term or preterm infants suffering from major side effects during treatment with paracetamol. The RCTs conducted to date depict an overall

very safe profile for paracetamol in PDA treatment. None of the 20 RCTs using either IV or oral paracetamol administered in a total of 886 preterm infants, reported any serious untoward incidents or reactions (**TABLES 1 and 2**).

Long-term safety profile

Bauer et al raised concerns about the possibility of adverse long-term neurological outcome in their ecological study by demonstrating an association between pre- and perinatal use of paracetamol and autistic spectrum disorders.⁴³ In 2017, a Swedish study by Bornehag et al reported a possible association of maternal pre-exposure to paracetamol and language delay in a 30-month-old girl.¹⁴ On the other hand, Oncel et al reported no significant difference in neurological outcome among preterm infants who received either paracetamol or ibuprofen at 18-24 months corrected gestational age.²⁸ Similarly, Harma et al found better cerebral oxygenation and neuroprotective effects with postnatal paracetamol use in extremely premature infants with PDA.⁴⁴

Drug levels

While there is sufficient evidence to support that serum paracetamol levels are a reliable marker of paracetamol toxicity in children and adults, their role in clinical management of preterm infants remains very limited, as far as their relationship to efficacy or toxicity is concerned. McPherson et al⁴⁵ analysed paracetamol serum concentrations in preterm infants treated intravenously for PDA and found no correlation between paracetamol serum levels with infant demographics, hepatic transaminases during treatment or duct size at treatment completion.

This can be partly explained by our current understanding of pharmacokinetics that the metabolism of paracetamol is dependent on the level of prematurity and hence on gestation. As there is no established or validated nomogram on gestation-specific serum paracetamol levels, any attempt in interpreting serum drug levels across the board will be of limited value.

The difficulty in interpretation also extends to the type of serum levels (eg peak, trough or steady state levels). The serum levels used in the literature for extremely premature infants are quite variable in relation to administration of

Continued on page 190

Study					Pharmacokinetics		Pharmacodynamics	
Authors	Year/country/ intervention	Sample size	Eligible population (gestation)	Criteria for inclusion	Regime	Total cumulative dose (mg/kg)	Therapeutic efficacy & statistical significance	Side effects of PCM
Dang et al ²⁴	2013 China PCM (n=80) Ibuprofen (n=80)	160	≤34 weeks	Only echo	15mg/kg every 6h for 3 days	180	81.2% PCM vs 78.8% ibuprofen. Not significant	Hyperbilirubinaemia and GI bleeding significantly more in ibuprofen group (p<0.05)
Oncel et al ²⁷	2014 Turkey PCM (n=40) Ibuprofen (n=40)	80	≤30 weeks/ ≤1,250g	Echo only or poor cardiac function with clinical signs	15mg/kg every 6h for 3 days	180	72.5% PCM vs 77.5% ibuprofen. Not significant	No significant difference in adverse effects observed
Dash et al ³¹	2015 India PCM (n=38) Indomethacin (n=39)	77	≤1,500g	Only echo	15mg/kg every 6h for 7 days	420	100% PCM vs 95% indomethacin. Not significant	No significant difference in adverse effects
Bagheri et al ²²	2016 Iran PCM (n=67) Ibuprofen (n=62)	129	<37 weeks	Only echo	15mg/kg every 6h for 3 days	180	82.1% PCM vs 75.8% ibuprofen. Not significant	No side effects
Yang et al ²⁶	2016 China PCM (n=44) Ibuprofen (n=43)	87	<37 weeks	Echo + clinical	15mg/kg every 6h for 3 days	180	70.5% PCM vs 76.7% ibuprofen. Not significant	Less oliguria in PCM group but not statistically significant
Al-Lawama et al ²⁹	2017 Jordan PCM (n=13) Ibuprofen (n=9)	22	≤32 weeks/ ≤1,500g	Either echo or clinical	10mg/kg every 6h for 3 days	120	69% PCM vs 78% ibuprofen. Not significant	No toxicity in either group
Asadpour et al ³⁰	2018 Iran PCM (n=25) Ibuprofen (n=25)	50	<37 weeks	Echo + clinical	10mg/kg every 6h for 3 days	120	92% PCM vs 88% ibuprofen. Not significant	p>0.05 (mean ALT higher in PCM group; GI complications higher in ibuprofen group)
Babaei et al ²¹	2018 Iran PCM (n=36) No intervention (n=33)	69	<34 weeks	Echo + clinical	15mg/kg every 6h for 3 days	180	75% (vs placebo 15%), Overall closure rates with second course 94.4%. Significant	No side effects
Balachander et al ²³	2018 India PCM (n=51) Ibuprofen (n=59)	110	≤37 weeks/ ≤2,500g	Echo + clinical	15mg/kg every 6h for 2 days Ibuprofen 10/5/5	180	74.5% PCM vs 76.4% ibuprofen. Not significant	No side effects with PCM. Significant acute kidney injury seen with ibuprofen and trial was stopped
El-Farrash et al ²⁵	2018 Egypt PCM (n=30) Ibuprofen (n=30)	60	≤34 weeks	Echo only	15mg/kg every 6h for 3 days	180	First course: 66.7% PCM vs 40% ibuprofen Second course 80% vs 66.7%. Overall, 93.3% (vs 80%). Not significant	No difference in side effects between the two groups
Kluckow et al ³	2018 Australia PCM (n=27) Placebo (n=28)	55	<33 weeks	Echo + clinical	25mg/kg loading dose followed by 15mg/kg every 12h for 5 days	160	Trend towards closure. Significant against placebo	No adverse effects observed. Infants <32 weeks received eight hourly maintenance doses
Kumar et al ²⁷	2020 India PCM (n=81) Ibuprofen (n=80)	161	<32 weeks	Echo only	15mg/kg every 6h for 3 days	180	95.4% PCM vs 94% ibuprofen. Not significant	No statistically significant side effects but study not powered enough to comment on absolute safety of PCM

TABLE 1 A summary of the pharmacokinetics and pharmacodynamics from RCTs using oral paracetamol for PDA management.

Key: PCM=paracetamol; echo=echocardiography; GI=gastrointestinal; ALT=alanine aminotransferase.

Study					Pharmacokinetics		Pharmacodynamics	
Authors	Year/country/ intervention	Sample size	Eligible population (gestation)	Criteria for inclusion	Regime	Total cumulative dose (mg/kg)	Therapeutic efficacy & statistical significance	Side effects of PCM
Harkin et al ³⁵	2016 Finland PCM (n=23) Placebo (n=25)	48	<32 weeks	Echo only	20mg/kg loading dose followed by 7.5mg/kg every 6h for 4 days	132.5	Early closure of PDA (177 hours vs 338 hours). Significant against placebo	No detectable adverse effects
El-Mashad et al ³²	2017 Egypt PCM (n=100) Ibuprofen (n=100) Indomethacin (n=100)	300	<28 weeks/ <1,500g	Clinical + echo	15mg/kg every 6h for 3 days	180	80% PCM group vs 77% ibuprofen vs 81% indomethacin. Second treatment course: 88% PCM vs 83% ibuprofen vs 87% indomethacin. Not significant	PCM has fewer side effects mainly on renal function, platelet count and GI bleeding. Significant increase in creatinine and BUN in ibuprofen and indomethacin group along with oliguria and thrombocytopenia. No adverse effects in PCM group
Bagheri et al ³⁸	2018 Iran PCM (n=80) Placebo (n=80)	160	≤34 weeks	Clinical examination to rule out duct- dependent congenital heart disease	20mg/kg loading dose followed by 7.5mg/kg every 6h for 3 days	102.5	PDA in PCM group = 15% vs 71.25% in placebo group. Statistically significant	No hepatic complications occurred during hospital stay
Hochwald et al ³⁶	2018 Israel PCM + ibuprofen (n=12) Placebo + ibuprofen (n=12)	24	<32 weeks	Clinical + echo	20mg/kg loading dose followed by 10mg/kg every 6h for 3 days (total = 12 doses)	130	83% PCM vs 42% placebo. Not significant (p<0.08)	No adverse effects clinical or laboratory noted in PCM group
Dani et al ³³	2020 Italy PCM (n=58) Ibuprofen (n=52)	110	<32 weeks	Clinical + echo	15mg/kg every 6h for 3 days	180	PCM 52% closure rate vs ibuprofen 78%. Success rates in constriction were similar. Not significant	No difference in adverse effects between the two groups
Meena et al ³⁴	2020 India PCM (n=35) Oral ibuprofen (n=35) Oral indomethacin (n=35)	105	<37 weeks	Clinical + echo	15mg/kg every 6h for 3 days	180	Cumulative closure rate 71.43% PCM group vs 77.14% ibuprofen vs 68% indomethacin. Not significant	IV paracetamol has better safety profile; serum creatinine and BUN significantly raised in the indomethacin and ibuprofen groups
Schindler et al ³⁹	2021 Australia PCM (n=29) Placebo (n=29)	58	<29 weeks	Echo only	15mg/kg loading dose followed by 7.5mg/kg every 6h for 5 days	157.5	Infants in PCM group required PDA intervention 21% vs placebo group 59%. PDA closure in PCM group 69% vs placebo group 28%. Statistically significant	No adverse effects reported in PCM group
Davidson et al ⁴⁰	2021 USA PCM (n=17) Indomethacin (n=20)	37	≤32 weeks or ≤1,500g	Echo only	15mg/kg every 6h for 3 days	180	One (5.9%) hsPDA in the PCM group had successful treatment compared to 11 (55%) in the indomethacin group	The side effects with both drugs were similar

TABLE 2 Summary of pharmacokinetics and pharmacodynamics from RCTs using IV paracetamol for PDA management. Key: PCM=paracetamol; GI=gastrointestinal; BUN=blood urea nitrogen; echo=echocardiography; hsPDA=haemodynamically significant patent ductus arteriosus.

the dose and timings. Therefore, future studies should not only be designed to evaluate gestation-specific nomograms in extremely premature infants but should also work on improving the understanding of clinically relevant timing of levels.

Limitations

Although the RCTs carried out so far have helped to improve our understanding, it is still not any easier for clinicians to make evidence-based decisions for treating a PDA with paracetamol. This is partly attributed to the heterogeneity of the studies. Several aspects of paracetamol use in the neonatal age group remain unclarified in these trials. In particular:

- optimal dosing regimen
- time of initiation of therapy
- route of administration
- direct comparison of different dosing regimens.

The RCTs also have significant limitations, such as:

- uniformity in defining the determinants of hsPDA
- echocardiographic parameters for hsPDA evaluation
- variable inclusion criteria
- inadequate sample power calculations
- absence of intention-to-treat analyses.

While our review has covered case reports, case series and observational studies to identify safety issues, we only used RCTs when evaluating the variability in the dosage regimen and monitoring of safety and effectiveness of paracetamol.

Summary

Paracetamol is establishing itself as an alternative to the conventional treatment of hsPDA by NSAIDs. Although several RCTs have evaluated the efficacy and safety of ibuprofen and paracetamol, a consensus on the practice recommendations has been difficult to establish given the heterogeneity of these trials. The two national surveys conducted in the UK continue to highlight the variability in dosage, duration of treatment and monitoring of infants during paracetamol treatment for PDA closure.^{7,46}

The dose, route of administration, efficacy reports and short- and long-term implications still remain highly variable.⁶ The majority of RCTs involving oral dosing of paracetamol to treat hsPDA have used 15mg/kg/dose (cumulative dose of 60mg/kg/day) safely and effectively. However, it appears that lower cumulative

doses of IV paracetamol (40-50mg/kg/day) may be equally efficacious to higher daily cumulative doses (60-70mg/kg/day) while assuring a better safety profile, given the hepatic and renal immaturity in preterm infants. The data from RCTs combined with experience of its use in older preterm infants, consolidates our understanding of its excellent safety profile.

The review, however, casts doubt on the reliability of therapeutic drug level monitoring of paracetamol as a marker of its safety or efficacy. Data on gestation-specific dosing nomograms should be sought through studies to describe its time concentration profile.

Finally, well-designed multicentre RCTs allowing exploration of the predictive kinetic behaviour of paracetamol through pharmacokinetic multi-compartment modelling are necessary. This will provide the much-needed evidence to help neonatologists confidently use paracetamol as a first-line medication to treat hsPDA.

Conclusion

Paracetamol remains a potential second-line alternative to NSAIDs in managing hsPDA. However, assurance regarding its optimum dosage, route of administration, short- and long-term implications from studies conducted so far is limited.

Contributions

AM (ORCID iD: 0000-0002-3933-7028) and AG conceived and designed the project, reviewed and analysed the data and co-wrote the article.

References

1. **de Klerk JCA, Engbers AGJ, van Beek F, et al.** Spontaneous closure of the ductus arteriosus in preterm infants: a systematic review. *Front Pediatr* 2020;8:541.
2. **Clyman RI, Hills NK, Liebowitz M, Johng S.** Relationship between duration of infant exposure to a moderate-to-large patent ductus arteriosus shunt and the risk of developing bronchopulmonary dysplasia or death before 36 weeks. *Am J Perinatol* 2020;37:216-23.
3. **Kluckow M, Carlisle H, Broom M, et al.** A pilot randomised blinded placebo-controlled trial of paracetamol for later treatment of a patent ductus arteriosus. *J Perinatol Off J Calif Perinat Assoc* 2019;39:102-07.
4. **Sekar KC, Corff KE.** Treatment of patent ductus arteriosus: indomethacin or ibuprofen? *J Perinatol Off J Calif Perinat Assoc* 2008;28 Suppl1:S60-62.
5. **Benitz WE, Committee on Fetus and Newborn, American Academy of Pediatrics.** Patent ductus arteriosus in preterm infants. *Pediatrics* 2016;137.
6. **NICE.** British National Formulary for Children. Online at: <https://bnfc.nice.org.uk/drug/>

[ibuprofen.html#indicationsAndDoses](#) [accessed 26 May 2021].

7. **Mukherjee A, Jadhav V, Gupta A.** Off-label use of paracetamol in managing patent ductus arteriosus across neonatal intensive care units in the UK. *Arch Dis Child Fetal Neonatal Ed* 2021;106:113-14.
8. **Xiao Y, Liu H, Hu R, You Q, et al.** Efficacy and safety of paracetamol for patent ductus arteriosus closure in preterm infants: an updated systematic review and meta-analysis. *Front Pediatr* 2019;7:568.
9. **Allegaert K, Van der Marel CD, Debeer A, et al.** Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F25-28.
10. **Fortuny J, Kogevinas M, Garcia-Closas M, et al.** Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. *Cancer Epidemiol Biomark Prev* 2006;15:1696-702.
11. **Allegaert K, Palmer GM, Anderson BJ.** The pharmacokinetics of intravenous paracetamol in neonates: size matters most. *Arch Dis Child* 2011;96:575-80.
12. **Palmer GM, Atkins M, Anderson BJ, et al.** IV acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008;101:523-30.
13. **van der Horst J, Manville RW, Hayes K, et al.** Acetaminophen (paracetamol) metabolites induce vasodilation and hypotension by activating Kv7 potassium channels directly and indirectly. *Arterioscler Thromb Vasc Biol* 2020;40:1207-19.
14. **Bornehag C-G, Reichenberg A, Hallerback MU, et al.** Prenatal exposure to acetaminophen and children's language development at 30 months. *Eur Psychiatry J Assoc Eur Psychiatr* 2018;51:98-103.
15. **Cakir U, Tayman C, Karacaglar NB, et al.** Comparison of the effect of continuous and standard intermittent bolus paracetamol infusion on patent ductus arteriosus. *Eur J Pediatr* 2021;180:433-40.
16. **Ohlsson A, Shah PS.** Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. *Cochrane Database Syst Rev* 2018;4:CD010061.
17. **Oncel MY, Yurttutan S, Degirmencioglu H, et al.** Intravenous paracetamol treatment in the management of patent ductus arteriosus in extremely low birth weight infants. *Neonatology* 2013;103:166-69.
18. **Terrin G, Conte F, Scipione A, et al.** Efficacy of paracetamol for the treatment of patent ductus arteriosus in preterm neonates. *Ital J Pediatr* 2014;40:21.
19. **Tekgunduz KS, Ceviz N, Caner I, et al.** Intravenous paracetamol with a lower dose is also effective for the treatment of patent ductus arteriosus in preterm infants. *Cardiol Young* 2015;25:1060-64.
20. **Terrin G, Conte F, Oncel MY, et al.** Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F127-36.
21. **Babaei H, Nemati R, Daryoshi H.** Closure of patent ductus arteriosus with oral acetaminophen in preterm neonates: A randomized trial. *Biomed Res Ther* 2018;5:2034-44.
22. **Bagheri MM, Niknafs P, Sabsevari F, et al.** Comparison of oral acetaminophen versus ibuprofen in premature infants with patent ductus arteriosus. *Iran J Pediatr* 2016;26:e3975.
23. **Balachander B, Mondal N, Bhat V, et al.** Comparison of efficacy of oral paracetamol versus ibuprofen for

- PDA closure in preterms - a prospective randomized clinical trial. *J Matern-Fetal Neonatal Med* 2020;33:1587-92.
24. **Dang D, Wang D, Zhang C, et al.** Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. *PLoS One* 2013;8:e77888.
 25. **El-Farrash RA, El Shimy MS, El-Sakka AS, et al.** Efficacy and safety of oral paracetamol versus oral ibuprofen for closure of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Matern-Fetal Neonatal Med* 2019;32:3647-54.
 26. **Yang B, Gao X, Ren Y, et al.** Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. *Exp Ther Med* 2016;12:2531-36.
 27. **Kumar A, Gosavi RS, Sundaram V, et al.** Oral paracetamol vs oral ibuprofen in patent ductus arteriosus: a randomized, controlled, noninferiority trial. *J Pediatr* 2020;222:79-84.e2.
 28. **Oncel MY, Eras Z, Uras N, et al.** Neurodevelopmental outcomes of preterm infants treated with oral paracetamol versus ibuprofen for patent ductus arteriosus. *Am J Perinatol* 2017;34:1185-89.
 29. **Al-Lawama M, Alamkori I, Abdelghani T, Badran E.** Oral paracetamol versus oral ibuprofen for treatment of patent ductus arteriosus. *J Int Med Res* 2018;46:811-18.
 30. **Asadpour N, Harandi PS, Hamidi M, et al.** Comparison of the effect of oral acetaminophen and ibuprofen on patent ductus arteriosus closure in premature infants referred to hajar hospital in Shahrekord in 2016-2017. *J Clin Neonatol* 2018;7:224.
 31. **Dash SK, Kabra NS, Avasthi BS, et al.** Enteral paracetamol or intravenous indomethacin for closure of patent ductus arteriosus in preterm neonates: a randomized controlled trial. *Indian Pediatr* 2015;52:573-78.
 32. **El-Mashad AE-R, El-Mahdy H, El Amrousy D, Elgeddy M.** Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. *Eur J Pediatr* 2017;176:233-40.
 33. **Dani C, Poggi C, Cianchi I, et al.** Effect on cerebral oxygenation of paracetamol for patent ductus arteriosus in preterm infants. *Eur J Pediatr* 2018;177:533-39.
 34. **Meena V, Meena DS, Rathore PS, et al.** Comparison of the efficacy and safety of indomethacin, ibuprofen, and paracetamol in the closure of patent ductus arteriosus in preterm neonates - a randomized controlled trial. *Ann Pediatr Cardiol* 2020;13:130-35.
 35. **Harkin P, Harma A, Aikio O, et al.** Paracetamol accelerates closure of the ductus arteriosus after premature birth: a randomized trial. *J Pediatr* 2016;177:72-77.e2.
 36. **Hochwald O, Mainzer G, Borenstein-Levin L, et al.** Adding paracetamol to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a double-blind, randomized, placebo-controlled pilot study. *Am J Perinatol* 2018;35:1319-25.
 37. **Oncel MY, Yurttutan S, Erdev O, et al.** Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Pediatr* 2014;164:510-14.e1.
 38. **Bagheri MM, Bahman-Bijari B, Torabi-Nejad MH, et al.** Is prophylactic parenteral paracetamol effective to diminish incidence of PDA in preterm neonates? A randomized trial. *Iran J Pediatr* 2018;28:e11735.
 39. **Schindler T, Smyth J, Bolisetty S, et al.** Early PARacetamol (EPAR) trial: a randomized controlled trial of early paracetamol to promote closure of the ductus arteriosus in preterm infants. *Neonatology* 2021;118:274-81.
 40. **Davidson JM, Ferguson J, Ivey E, et al.** A randomized trial of intravenous acetaminophen versus indomethacin for treatment of hemodynamically significant PDAs in VLBW infants. *J Perinatol* 2021;41:93-99.
 41. **Jacqz-Aigrain E, Anderson BJ.** Pain control: non-steroidal anti-inflammatory agents. *Semin Fetal Neonatal Med* 2006;11:251-59.
 42. **Bucarechi F, Fernandes CB, Branco MM, et al.** Acute liver failure in a term neonate after repeated paracetamol administration. *Rev Paul Pediatr* 2014;32:144-48.
 43. **Bauer AZ, Kriebel D.** Prenatal and perinatal analgesic exposure and autism: an ecological link. *Environ Health* 2013;12:41.
 44. **Harma A, Aikio O, Harkin P, et al.** Subgroup analysis of the early paracetamol trial to preterm infants found haemodynamic changes and improved oxygenation. *Early Hum Dev* 2020;145:105042.
 45. **McPherson C, Luecke CM, Liviskie CJ, et al.** Acetaminophen serum concentrations in infants treated intravenously for patent ductus arteriosus. *J Pediatr Pharmacol Ther* 2019;24:134-37.
 46. **Noureldein M, Hu K, Groucutt J, et al.** Paracetamol for patent ductus arteriosus in preterm infants: a UK national survey. *J Matern Fetal Neonatal Med* 2020;14:1-4.

Don't miss the November 2021 issue of *Infant* journal

Annual subscriptions
start from just £35.*

*Rate increases from January 2022



Subscribe online at
www.infantjournal.co.uk
or email
subscriptions@infantjournal.co.uk
or call Tricia on 01279 714511.

 **VAPOTHERM®**

The Vapotherm Transfer Unit (VTU)

Delivering High Velocity
Therapy on the GO



Transfer patients while providing continuous therapy

Used across many NHS Trusts, the Vapotherm Transfer Unit (VTU) is designed to make patient transfer easier and more efficient by adding a mobile power supply and seamless switching between air, oxygen tanks and wall gas supply.

