Paracetamol
Newborn use only

2021

<table>
<tr><td>Alert</td><td>Intravenous paracetamol should be considered a high-risk medicine when administered to infants and young children.
Use of paracetamol should always be preceded by a comprehensive risk assessment and reviewed every 24 hours.
Safety data for paracetamol in extreme preterm infants (< 28 weeks) is limited. It should be used with caution, particularly in the treatment of patent ductus arteriosus.</td></tr>
<tr><td>Indication</td><td>Analgesia
Antipyretic
Adjunct to post-operative analgesia
Treatment of patent ductus arteriosus (PDA)</td></tr>
<tr><td>Action</td><td>Centrally acting analgesic and antipyretic with minimal anti-inflammatory properties. The mechanism of action of paracetamol in reducing pain is not completely defined. Potential mechanisms include inhibition of central prostaglandin synthesis and inhibition of the cyclooxygenase (COX) isoenzyme, particularly the COX-2 isoform.</td></tr>
<tr><td>Drug type</td><td>Non-narcotic analgesic and antipyretic.</td></tr>
<tr><td>Trade name</td><td>Intravenous: Paracetamol Actavis; Paracetamol ACT; Paracetamol BNM; Paracetamol IV Pfizer; Paracetamol Kabi; Paracetamol-AFT; Paramat
Oral: Dymadon, Febridol, Panadol (Children)</td></tr>
<tr><td>Presentation</td><td>IV: 500 mg/50 mL, 1000 mg/100 mL (10 mg/mL) vial or infusion bag
Oral: 100 mg/mL drops</td></tr>
<tr><td>Dose</td><td><u>Analgesia/Antipyretic/Adjunct to post-operative analgesia</u>
Oral/Intravenous/Rectal[1-3]:
<table>
<tr><th>Weight*</th><th>Loading</th><th>Maintenance</th></tr>
<tr><td><2.0 kg</td><td>15 mg/kg</td><td>7.5 mg/kg every 6 hours</td></tr>
<tr><td>2.0 – 3.0 kg</td><td>15 mg/kg</td><td>10 mg/kg every 6 hours</td></tr>
<tr><td>>3.0 kg</td><td>20 mg/kg</td><td>10 mg/kg every 6 hours</td></tr>
</table>
*Current/best weight

<u>Patent Ductus Arteriosus (treatment course 3-7 days with 48-hourly monitoring of liver function)</u>
Oral/Intravenous[4,5]:
<table>
<tr><th>Criteria</th><th>Loading</th><th>Maintenance</th></tr>
<tr><td>≥28 weeks CGA/PMA and ≥1000 g*</td><td>15 mg/kg</td><td>15 mg/kg every 6 hours</td></tr>
<tr><td><28 weeks and/or <1000 g*</td><td>15 mg/kg</td><td>7.5 mg/kg every 6 hours**</td></tr>
</table>
*Current/best weight
**Higher maintenance doses (15 mg/kg) in extreme preterm infants have been used but there are limited safety data.</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia –Caution to be applied with associated hepatic and renal impairment.
Renal impairment – Refer to precautions section.
Hepatic impairment – Refer to monitoring and precautions sections.</td></tr>
<tr><td>Maximum dose</td><td>60 mg/kg/day</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV, oral, rectal</td></tr>
<tr><td>Preparation</td><td>Intravenous: Use undiluted. Can be diluted to 2 mg/ml for use in ELBW infants using sodium chloride 0.9% or glucose 5%. If diluted, the solution should be used immediately.</td></tr>
<tr><td>Administration</td><td>Intravenous:
Administer over 15 minutes via syringe driver.
Oral:
Can be given with or without feeds. Shake bottle well before measuring dose.
Rectal:
Dilute oral mixture 1:1 with water for rectal doses. Low dose suppositories are not commercially available but can be prepared by selected pharmacy departments. Do not cut suppositories to make part rectal dose.</td></tr>
<tr><td>Monitoring</td><td>Monitor hepatic and renal function.
If signs of acute liver injury (example, raised ALT >50 IU/L) – refer to acetylcysteine formulary and contact Poisons Information Centre (13 11 26 for New South Wales) or local toxicology service.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to paracetamol, active liver disease.</td></tr>
</table>

Precautions	Hepatic impairment, renal impairment, sepsis, dehydration
Drug interactions	Paracetamol absorption is increased by substances that increase gastric emptying. Paracetamol absorption is decreased by substances that decrease gastric emptying. Paracetamol may increase chloramphenicol concentrations. The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as anticonvulsant agents.
Adverse reactions	Vomiting, fever, rash, neutropenia, leucopoenia, thrombocytopenia. May cause liver toxicity at high plasma concentrations.
Compatibility	Sodium chloride 0.9%, glucose 5%
Incompatibility	Do not mix with any other intravenous fluids or medications.
Stability	Vials should be used immediately after opening. Any unused solution should be discarded. After dilution in 0.9% sodium chloride or 5% glucose do not store for more than 1 hour (infusion time included).
Storage	IV: Do not store above 30°C. Do not refrigerate or freeze. Oral: Store below 25°C.
Excipients	
Special comments	Preterm infants may be at increased risk of paracetamol toxicity. Review indications if IV paracetamol is needed for more than 48 hours. Antidote of choice for overdose is acetylcysteine IV infusion. Rectal bioavailability is variable depending on the formulation used. Oral or intravenous routes are preferred.
Evidence	**Efficacy and safety (analgesia/adjunct to post-operative analgesia)** A systematic review of nine studies reported comparisons in 728 infants of paracetamol versus placebo or other pain-reducing interventions.[6] Paracetamol for heel lance did not reduce pain when compared with water, cherry elixir or EMLA cream. Paracetamol use was associated with a stronger response to pain than was seen with glucose. Paracetamol did not reduce pain in infants exposed to vacuum extraction or forceps at birth and their response to a subsequent heel lance at two to three days of life was increased compared with placebo. For eye examination, paracetamol was effective in reducing pain compared with water in one study, but the pain response was stronger among paracetamol-treated infants than in infants given 24% sucrose. In infants treated with paracetamol (30 mg/kg/day) and morphine compared with morphine alone, the total amount of morphine required during the first 48 hours following major surgery to the chest or the abdomen was less in the paracetamol group. Recommendation: The paucity and low quality of existing data do not provide sufficient evidence to establish the role of paracetamol in reducing the effects of painful procedures in neonates. Paracetamol given after assisted vaginal birth may increase the response to later painful exposures. Paracetamol may reduce the total need for morphine following major surgery, and for this aspect of paracetamol use, further research is needed.[6] (LOE I GOR B) **Efficacy and safety (patent ductus arteriosus)** A systematic review of eight studies reported comparisons in 916 infants of paracetamol versus placebo, ibuprofen and indomethacin.[4] Two studies (80 infants) showed a lower rate of failure of ductal closure after 4 to 5 days of treatment compared to placebo or no intervention (typical RR 0.49 (95% CI 0.24 to 1.00; P = 0.05); typical RD −0.21 (95% CI −0.41 to −0.02); I^2 = 0 % for RR and RD; NNTB 5; 95% CI 2 to 50; low quality of evidence). A third randomised controlled trial [in press] comparing paracetamol to placebo showed less infants in the intervention group required intervention for PDA up to 5 days (6 [21%] vs 17 [59%] infants [p=0.003]; relative risk reduction 0.35 [95%CI 0.16-0.77; NNT 2.6]).[5] Five studies (559 infants) showed no significant difference between paracetamol and ibuprofen for failure of ductal closure (typical risk ratio (RR) 0.95, 95% confidence interval (CI) 0.75 to 1.21; typical risk difference (RD) −0.02, 95% CI −0.09 to 0.09; I^2 = 0% for RR and RD; moderate quality of evidence). Gastrointestinal bleeding was lower in the paracetamol group versus the ibuprofen group (typical RR 0.28, 95% CI 0.12 to 0.69; typical RD −0.06, 95% CI −0.09 to −0.02; I^2 = 0% for RR and RD; number needed to treat for an additional beneficial outcome (NNTB) 17 (95% CI 11 to 50); moderate quality of evidence). The serum levels of creatinine were lower in the paracetamol group compared with the ibuprofen group in four studies (moderate quality of evidence), as were serum bilirubin levels following treatment in two studies (n = 290). There were no significant differences in the neurological outcomes at 18 to 24

	months (n = 61); (low quality of evidence). Two studies (277 infants) showed no significant difference between paracetamol and indomethacin for failure of ductal closure (typical RR 0.96, 95% CI 0.55 to 1.65; I^2 = 11%; typical RD −0.01, 95% CI −0.09 to 0.08; I^2 = 17%); low quality of evidence). Serum creatinine levels were significantly lower in the paracetamol group compared with the indomethacin group and platelet counts and daily urine output were significantly higher in the paracetamol group. A second systematic review of studies involving the use of paracetamol in preterm infants reported on sixteen studies: Two randomised controlled trials and 14 uncontrolled studies. The quality of selected studies was rated as poor. Proportion meta-analysis of uncontrolled studies demonstrated a pooled ductal closure rate of 49% (95% CI 29% to 69%) and 76% (95% CI 61% to 88%) after 3 and 6 days of treatment with paracetamol, respectively.[7] The majority of studies used 15 mg/kg every 6 hours for 3–7 days. Recommendation: Low-moderate quality evidence suggests that paracetamol is more effective than placebo and as effective as ibuprofen and indomethacin for ductal closure. There was no difference in neurodevelopmental outcome in children exposed to paracetamol compared to ibuprofen, however, the quality of evidence is low and comes from only one study. In view of concerns raised regarding neurodevelopmental outcomes following prenatal and postnatal exposure to paracetamol, long-term follow-up to at least 18 to 24 months' postnatal age must be incorporated in any studies of paracetamol in the newborn population. Further research is required before recommendations for the routine use of paracetamol in the newborn population can be made.[4] (LOE I GOR B) **Hepatic toxicity** Individual cases with hepatic toxicity related to paracetamol in newborns have been reported. Overall, the number of cases reported is limited to significant overdoses (75–446 mg/kg), most commonly as a result of an in-hospital, 10-fold drug error.[8] In infants and children, hepatotoxicity has been reported over a wide dosage range (60–420 mg/kg/day for 1–42 days).[9] **Pharmacokinetics** Model-based dosing regimen of intravenous paracetamol aiming for a target paracetamol concentration of 9 mg/l based on population pharmacokinetic analysis from preterm neonates to adults, including 108 neonates (post-natal age 1–76 days, gestational age 27–42 weeks):[1] • BW 0.5 kg – Loading 11.2 mg/kg; maintenance q6h 5.1 mg/kg • BW 1.0 kg – Loading 12.1 mg/kg; maintenance q6h 6.0 mg/kg • BW 1.5 kg – Loading 12.2 mg/kg; maintenance q6h 6.8 mg/kg • BW 2.0 kg – Loading 13.3 mg/kg; maintenance q6h 7.4 mg/kg • BW 3.0 kg –Loading 12.8 mg/kg; maintenance q6h 8.5 mg/kg • BW 5.0 kg – Loading 13.5 mg/kg; maintenance q6h 10.4 mg/kg NB. The above numbers can be converted to any target concentration by dividing by 9 and multiplying by the desired target concentration. Population pharmacokinetic analysis of 943 paracetamol observations from 158 neonates (27–45 weeks' postmenstrual age [PMA]) showed a mean paracetamol serum concentration of 11 mg/l is predicted in neonates of 32–44 weeks' PMA given a standard dose of intravenous paracetamol of 10 mg/kg every 6 hours.[2] A population pharmacokinetic analysis of acetaminophen time-concentration profiles in 283 children (124 aged ≤ 6 months) reported that a mean, steady state, target concentration greater than 10 mg/l at trough can be achieved by an oral dose of 25 mg/kg/day in premature neonates at 30 weeks' post-conception, 45 mg/kg/day at 34 weeks' gestation, 60 mg/kg/day at term. Similar concentrations can be achieved with maintenance rectal doses of 25 (capsule suppository) or 30 (triglyceride suppository) mg/kg/day in premature neonates at 30 weeks' gestation, increasing to 90 (capsule suppository) or 120 (triglyceride suppository) mg/kg/day at 6 months.[3]
Practice points	**General** The dosing schedule in this formulary is equivalent to a target paracetamol concentration of approximately 11 mg/l.[1] **Dose** <u>Analgesia/antipyretic/adjunct to post-operative analgesia</u>

	Recommendations are primarily based on intravenous pharmacokinetic analyses as paracetamol has good oral bioavailability. The rectal dosing is safe but may not achieve target paracetamol concentrations as rectal bioavailability is variable depending on the formulation used. Oral or intravenous routes are preferred.[1-3] (LOE IV GOR C) Patent Ductus Arteriosus Recommendations are adapted from dosing schedules used in randomised controlled trials. The majority of studies have used 15 mg/kg every 6 hours for 3–7 days. The maintenance doses in extreme preterm infants are lower, consistent with studies focused on this population. Safety data are limited for higher maintenance doses.[5,6] (LOE I GOR B)
References	1. Wang C, Allegaert K, Tibboel D, Danhof M, van der Marel CD, Mathot RA, et al. Population pharmacokinetics of paracetamol across the human age-range from (pre)term neonates, infants, children to adults. Journal of Clinical Pharmacology. 2014;54:619-29. 2. Allegaert K, Palmer GM, Anderson BJ. The pharmacokinetics of intravenous paracetamol in neonates: size matters most. Arch Dis Child 2011;96:575-80. 3. Anderson BJ, van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: a pooled population analysis. Anesthesiology 2002;96:1336-45. 4. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2020;1:CD010061. 5. Schindler T, Smyth J, Bolisetty S, Michalowski J, Mallitt KA, Singla A, 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 [in press]. 6. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. Cochrane Database of Systematic Reviews. 2020;1:CD011219. 7. Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, 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. 8. Pacifici GM, Allegaert K. Clinical Pharmacology of Paracetamol in Neonates: A Review. Curr Ther Res Clin Exp. 2015;77:24–30. 9. Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: hepatoxicity after multiple doses in children. J Pediatr. 1998;132:22-7.

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