

Effect of IV Paracetamol (APAP) on Postoperative Morphine Requirements in Neonates and Infants

Journal Club  
Amber Schilling

BACKGROUND																																					
Title of Article	Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Non-cardiac surgery																																				
Authors	Ceelie I, de Wildt SN, van Dijk M, et al.																																				
Journal / Citation	JAMA. 2013; 309(2): 149-154.																																				
Background / Justification of the research	<p>Opioids are used to treat post-operative pain in neonates and infants, but are associated with adverse effects such as respiratory depression and hypotension. Safer alternatives are desired for this patient population.</p> <p>"[APAP] is the most widely used non-opioid analgesic agent"<sup>1</sup> and may have opioid-sparing potential when used as an adjuvant.</p> <p>APAP formulations available on Hospital X Formulary</p> <table border="1"> <thead> <tr> <th>Route</th> <th>Strengths</th> <th>Pricing (Lexi-Comp)</th> </tr> </thead> <tbody> <tr> <td>Oral (liquid, suspension, tablet, &amp; chew)</td> <td>160mg/5mL, 80mg/0.8mL, 325mg (t), 80mg (ch)</td> <td>\$0.72 / 10.15 mL (7c/mL; 0.2c/mg) \$4.57 / 100 tabs (5c/tab; 0.01c/mg)</td> </tr> <tr> <td>Rectal (suppository)                             <ul style="list-style-type: none"> <li>Slower, more erratic absorption compared to oral<sup>1</sup></li> </ul> </td> <td>120, 325, 650 mg</td> <td>\$30 / 50 supp. (60c/supp.; 0.5c/mg)</td> </tr> <tr> <td>Intravenous (10mg/mL)                             <ul style="list-style-type: none"> <li>Quicker onset, but equivalent to oral AUC (equal efficacy)<sup>1</sup></li> <li>Been available in Europe since 2002; FDA approved in U.S. in Nov 2010 for ages 2+</li> <li>Restricted use @ Hospital X (NPO pts only; 24hr automatic stop)</li> </ul> </td> <td>10 mg/mL</td> <td>\$42.48 / 100 mL (42c/mL; 4c/mg)</td> </tr> </tbody> </table> <p>Due to it's favorable safety profile in the pediatric population when dosed correctly, IV acetaminophen may be a good opioid-sparing alternative in neonates and infants, even though this would be an off-label use.</p> <p>Pediatric studies to date on the potential opioid-sparing ability of acetaminophen:</p> <ul style="list-style-type: none"> <li>All studies had an opioid on board (as prn only or continuous infusion+rescue prn on top of study drug)</li> <li>Not expecting APAP to replace opioids post-operatively; just looking for possible decrease in total opioid consumption with APAP as adjuvant</li> </ul> <table border="1"> <thead> <tr> <th>Date</th> <th>Authors</th> <th>Type of study</th> <th>Study Agents</th> <th>Ages and Study Population</th> <th>Results</th> </tr> </thead> <tbody> <tr> <td>1999</td> <td>Korpela et al. <sup>2</sup></td> <td>RCT N=120</td> <td>-APAP (rectal) -Placebo -Morphine prn only</td> <td>1 – 7 yo Hernia repair, adenoidectomy, excision of SQ tumor, etc.</td> <td>Morphine <i>rescue</i> dose significantly less in APAP group</td> </tr> <tr> <td>2007</td> <td>Van der Marel et al. <sup>3</sup></td> <td>RCT N=54</td> <td>-APAP (rectal) -Placebo -Morphine (all pts)</td> <td>0-2 months Non-cardiac thoracic or abdominal surgery</td> <td><i>Total</i> morphine consumption not significantly different</td> </tr> <tr> <td>2010</td> <td>Hong et al. <sup>4</sup></td> <td>Prosp, R, DB N=63</td> <td>-APAP (IV) -Placebo -Fentanyl (all pts)</td> <td>6-24 months Undergoing ureteronecystostomy</td> <td><i>Total</i> fentanyl consumption significantly less in APAP group</td> </tr> </tbody> </table> <p>Additional studies are needed to assess acetaminophen's morphine-sparing ability in neonates and infants in the post-operative setting.</p>	Route	Strengths	Pricing (Lexi-Comp)	Oral (liquid, suspension, tablet, & chew)	160mg/5mL, 80mg/0.8mL, 325mg (t), 80mg (ch)	\$0.72 / 10.15 mL (7c/mL; 0.2c/mg) \$4.57 / 100 tabs (5c/tab; 0.01c/mg)	Rectal (suppository) <ul style="list-style-type: none"> <li>Slower, more erratic absorption compared to oral<sup>1</sup></li> </ul>	120, 325, 650 mg	\$30 / 50 supp. (60c/supp.; 0.5c/mg)	Intravenous (10mg/mL) <ul style="list-style-type: none"> <li>Quicker onset, but equivalent to oral AUC (equal efficacy)<sup>1</sup></li> <li>Been available in Europe since 2002; FDA approved in U.S. in Nov 2010 for ages 2+</li> <li>Restricted use @ Hospital X (NPO pts only; 24hr automatic stop)</li> </ul>	10 mg/mL	\$42.48 / 100 mL (42c/mL; 4c/mg)	Date	Authors	Type of study	Study Agents	Ages and Study Population	Results	1999	Korpela et al. <sup>2</sup>	RCT N=120	-APAP (rectal) -Placebo -Morphine prn only	1 – 7 yo Hernia repair, adenoidectomy, excision of SQ tumor, etc.	Morphine <i>rescue</i> dose significantly less in APAP group	2007	Van der Marel et al. <sup>3</sup>	RCT N=54	-APAP (rectal) -Placebo -Morphine (all pts)	0-2 months Non-cardiac thoracic or abdominal surgery	<i>Total</i> morphine consumption not significantly different	2010	Hong et al. <sup>4</sup>	Prosp, R, DB N=63	-APAP (IV) -Placebo -Fentanyl (all pts)	6-24 months Undergoing ureteronecystostomy	<i>Total</i> fentanyl consumption significantly less in APAP group
Route	Strengths	Pricing (Lexi-Comp)																																			
Oral (liquid, suspension, tablet, & chew)	160mg/5mL, 80mg/0.8mL, 325mg (t), 80mg (ch)	\$0.72 / 10.15 mL (7c/mL; 0.2c/mg) \$4.57 / 100 tabs (5c/tab; 0.01c/mg)																																			
Rectal (suppository) <ul style="list-style-type: none"> <li>Slower, more erratic absorption compared to oral<sup>1</sup></li> </ul>	120, 325, 650 mg	\$30 / 50 supp. (60c/supp.; 0.5c/mg)																																			
Intravenous (10mg/mL) <ul style="list-style-type: none"> <li>Quicker onset, but equivalent to oral AUC (equal efficacy)<sup>1</sup></li> <li>Been available in Europe since 2002; FDA approved in U.S. in Nov 2010 for ages 2+</li> <li>Restricted use @ Hospital X (NPO pts only; 24hr automatic stop)</li> </ul>	10 mg/mL	\$42.48 / 100 mL (42c/mL; 4c/mg)																																			
Date	Authors	Type of study	Study Agents	Ages and Study Population	Results																																
1999	Korpela et al. <sup>2</sup>	RCT N=120	-APAP (rectal) -Placebo -Morphine prn only	1 – 7 yo Hernia repair, adenoidectomy, excision of SQ tumor, etc.	Morphine <i>rescue</i> dose significantly less in APAP group																																
2007	Van der Marel et al. <sup>3</sup>	RCT N=54	-APAP (rectal) -Placebo -Morphine (all pts)	0-2 months Non-cardiac thoracic or abdominal surgery	<i>Total</i> morphine consumption not significantly different																																
2010	Hong et al. <sup>4</sup>	Prosp, R, DB N=63	-APAP (IV) -Placebo -Fentanyl (all pts)	6-24 months Undergoing ureteronecystostomy	<i>Total</i> fentanyl consumption significantly less in APAP group																																
Purpose / Objective	To determine if IV paracetamol (acetaminophen) will reduce the cumulative morphine dose needed to provide adequate post-operative analgesia in neonates and infants by at least 30%.																																				
Funding	ZonMw Priority Medicines for Children grant (ZonMw is The Netherlands Organization for Health Research and Development)																																				
METHODS																																					
Trial Design	<p>Single center, randomized, double-blind, double-dummy trial</p> <ul style="list-style-type: none"> <li>"Placebos could not be distinguished from active study drug in color, odor, or viscosity" (p. 150) → double-dummy</li> </ul> <p>Conducted in a Level 3 pediatric ICU in Rotterdam, the Netherlands</p>																																				
Study Dates	March 2008 – July 2010																																				
Interventions	<p>All patients received morphine load 30 mins b4 end of surgery + rescue doses prn according to protocol</p> <p>Patients randomized to receive either scheduled IV APAP or continuous infusion morphine as their primary post-operative analgesic</p> <table border="1"> <thead> <tr> <th>Study Agent</th> <th>Dose</th> <th>Reference dose from Lexi-Comp</th> <th>Placebo recv'd</th> </tr> </thead> <tbody> <tr> <td>IV Paracetamol (APAP)  Scheduled q6h</td> <td>30 mg/kg/day, divided in 4 doses (=7.5 mg/kg/dose q6h)</td> <td> <ul style="list-style-type: none"> <li>"Limited data available; dose not established" for IV dosing in neonates.</li> <li>"Manufacturer neonatal pharmacokinetic data suggests that 7.5 mg/kg/dose every 6 hours produces a similar pharmacokinetic exposure as standard dosing in children ≥2years."</li> <li>Other studies referenced in Lexi-Comp mention 10 mg/kg/dose q6h</li> </ul> </td> <td>Continuous infusion of normal saline at same rate as equivalent morphine infusion</td> </tr> <tr> <td>IV Morphine  Continuous Infusion</td> <td>                     ≤10 days old: 2.5 mcg/kg<sup>1.5</sup>/hr                      &gt;10 days old: 5 mcg/kg<sup>1.5</sup>/hr                      See below for rationale                 </td> <td>10 – 30 mcg/kg/hr</td> <td>Normal saline administered 4 times daily in a volume similar to the paracetamol dose</td> </tr> </tbody> </table>	Study Agent	Dose	Reference dose from Lexi-Comp	Placebo recv'd	IV Paracetamol (APAP)  Scheduled q6h	30 mg/kg/day, divided in 4 doses (=7.5 mg/kg/dose q6h)	<ul style="list-style-type: none"> <li>"Limited data available; dose not established" for IV dosing in neonates.</li> <li>"Manufacturer neonatal pharmacokinetic data suggests that 7.5 mg/kg/dose every 6 hours produces a similar pharmacokinetic exposure as standard dosing in children ≥2years."</li> <li>Other studies referenced in Lexi-Comp mention 10 mg/kg/dose q6h</li> </ul>	Continuous infusion of normal saline at same rate as equivalent morphine infusion	IV Morphine  Continuous Infusion	≤10 days old: 2.5 mcg/kg <sup>1.5</sup> /hr >10 days old: 5 mcg/kg <sup>1.5</sup> /hr See below for rationale	10 – 30 mcg/kg/hr	Normal saline administered 4 times daily in a volume similar to the paracetamol dose																								
Study Agent	Dose	Reference dose from Lexi-Comp	Placebo recv'd																																		
IV Paracetamol (APAP)  Scheduled q6h	30 mg/kg/day, divided in 4 doses (=7.5 mg/kg/dose q6h)	<ul style="list-style-type: none"> <li>"Limited data available; dose not established" for IV dosing in neonates.</li> <li>"Manufacturer neonatal pharmacokinetic data suggests that 7.5 mg/kg/dose every 6 hours produces a similar pharmacokinetic exposure as standard dosing in children ≥2years."</li> <li>Other studies referenced in Lexi-Comp mention 10 mg/kg/dose q6h</li> </ul>	Continuous infusion of normal saline at same rate as equivalent morphine infusion																																		
IV Morphine  Continuous Infusion	≤10 days old: 2.5 mcg/kg <sup>1.5</sup> /hr >10 days old: 5 mcg/kg <sup>1.5</sup> /hr See below for rationale	10 – 30 mcg/kg/hr	Normal saline administered 4 times daily in a volume similar to the paracetamol dose																																		

	<p>Morphine dosing schedule rationale (mg/kg<sup>1.5</sup>/hr)</p> <ul style="list-style-type: none"> <li>Based off of pharmacokinetic studies performed by Knibbe and colleagues<sup>5</sup></li> <li>Morphine has two major metabolites: morphine-3-glucuronide and morphine-6-glucuronide (both are formed by glucuronidation)</li> <li>Neonates less than 10 days old have lower rates of morphine glucuronidation than do children older than 10 days. Glucuronidation capacity and subsequent clearance of morphine metabolites increase with bodyweight by an exponential scaling factor of 1.5.</li> <li>Example calculation: 10 day old pt weighing 3 kg: (2.5 mcg/kg<sup>1.5</sup>)*(3<sup>1.5</sup>) = 12.99 mcg → 12.99 mcg/3 kg = 4.33 mcg/kg/hr (Compare to traditional Lexi-Dosing of 10-30 mcg/kg/hr)</li> <li>Dosing suggested: mg/kg<sup>1.5</sup>/hr. For neonates less than 10 days old, this dose should be reduced even further by 50%.</li> </ul>
Inclusion Criteria	<p>Infants undergoing major thoracic (non-cardiac) or abdominal surgery at Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands</p> <p>Post-conceptual age 36 and 1/7 week – 1 year old</p> <p>Body weight &gt;1.5 kg</p>
Exclusion Criteria	<p>ECMO (extracorporeal membrane oxygenation)</p> <p>Neurological dysfunction</p> <p>Hepatic dysfunction</p> <p>Renal insufficiency</p> <p>Prenatal or postnatal administration of opioids or psychotropic drugs (anti-epileptics, BDZs, or antidepressants) for &gt;24 hrs</p> <p>Known allergy or intolerance to morphine or APAP</p> <p>Administration of opioids in the 24 hours PRIOR to surgery</p>
Primary Endpoint	<p>Cumulative morphine dose in first 48 hrs post-op (mcg/kg)</p> <ul style="list-style-type: none"> <li>= Intraoperative loading dose (100 mcg/kg) + Morphine study dose + Amt of morphine rescue required</li> </ul>
Secondary and Safety Endpoints	<p>All are for 48 hours post-op:</p> <ul style="list-style-type: none"> <li>Amt of morphine rescue required (mcg/kg)</li> <li>Number of morphine rescue doses required (all counted as 1: each rescue bolus given, the start of a rescue infusion, or an increase in the infusion dose)</li> <li>Number of patients receiving rescue doses</li> <li>Average NRS-11 and COMFORT-B scores</li> <li>Morphine-related adverse events <ul style="list-style-type: none"> <li>✓ Need for mechanical ventilation, reintubation, or both</li> <li>✓ Apnea (O2 sats by pulse ox &lt;94% or RR &lt;20 for longer than 30 secs)</li> <li>✓ Naloxone administration</li> <li>✓ Bradycardia (HR &lt;80 for longer than 30 secs)</li> <li>✓ Hypotension (need for vasoactive meds or fluid boluses)</li> <li>✓ Seizures (r/o other causes)</li> <li>✓ GI (ileus, need for anti-emetics or laxatives)</li> <li>✓ Urinary retention</li> </ul> </li> </ul>
Statistical Analyses	<p>Number of patients required to provide 80% power and minimize type 1 error to 5% = 37 pts / group</p> <ul style="list-style-type: none"> <li>(<math>\alpha = 0.05</math>, 2-tailed; <math>\beta = 0.20</math>)</li> <li>Takes into account 15% drop-out rate (minimum of 32 required/group if drop-outs occur)</li> <li>Anticipates a 30% reduction in cumulative morphine dose at 48 hours post-op (480 mcg/kg → 336 mcg/kg) in the IV paracetamol group (30% reduction considered by investigators to be clinically relevant)</li> </ul> <p>Tests used</p> <ul style="list-style-type: none"> <li>Non-parametric, ordinal data: Mann-Whitney U test, Kolmogorov-Smirnov</li> <li>Non-parametric, nominal data: Chi-Squared (for n&gt;20), Fisher's exact (for n≤20)</li> <li>Parametric data: t-test</li> </ul>
<b>RESULTS</b>	
Enrollment / Assignment	<p>Stratified randomization, as well as blocking</p> <ul style="list-style-type: none"> <li>Initially stratified into 4 age groups (0-10 days, 11 days – 3 months, 3-6 months, and 6-12 months)</li> <li>After 9 months, stratification changed to 2 age groups (0-10 days, 11 days – 1 year) based on low numbers in older age groups</li> </ul> <p>71 patients analyzed</p> <ul style="list-style-type: none"> <li>33 in paracetamol group (1 required termination of APAP and replacement of morphine; analyzed via ITT)</li> <li>38 in morphine group</li> <li>Keeps statistical power</li> </ul>
Monitoring	Pain and distress monitored q8h using NRS-100 and COMFORT-B scales, respectively
Baseline Characteristics	<p>Table 1</p> <p>None were statistically significant between groups; however, some could be clinically significant:</p> <ul style="list-style-type: none"> <li>Subjects in acetaminophen group slightly younger, smaller weights, longer surgeries, and longer duration of post-operative intubations</li> <li>More abdominal surgeries than thoracic (repairs of diaphragmatic hernia, intestinal atresia, or esophageal atresia most common)</li> </ul>
Withdrawal or lost to f/u	3 (74 pts randomized, 3 drop outs = 71 analyzed)

<p>Results: Primary Endpoint</p>	<p>Table 2</p> <p>Cumulative morphine dose in paracetamol group significantly less than morphine group</p> <ul style="list-style-type: none"> <li>• 66% less, p&lt;0.001 → statistically significant</li> <li>• Medians: 121 mcg/kg/48hrs vs 357 mcg/kg/48hrs</li> </ul> <p>Cumulative morphine dose in paracetamol group also significantly less when broken down by age group</p> <ul style="list-style-type: none"> <li>• 0-10 days old: 111 mcg/kg/48hrs in APAP group; 218 mcg/kg/48hrs in morphine group → 49% reduction, p =0.002</li> <li>• 11 days – 1 year: 152 mcg/kg/48hrs in APAP group; 553 mcg/kg/48hrs in morphine group → 73% reduction, p&lt;0.001</li> <li>• Bonferonni correction for multiple comparisons: 0.05/3 comparisons = 0.017 → both results still reach statistical significance</li> </ul>
<p>Results: Secondary Endpoints</p>	<p>Total morphine needed as rescue, number of morphine rescue doses required, and number of patients requiring rescue doses of morphine → none were statistically significant</p> <ul style="list-style-type: none"> <li>• However, median amount of rescue morphine needed slightly higher in paracetamol group could be clinically significant</li> </ul> <p>Median NRS-11 and COMFORT-B scores (provided in narrative, but not in Table 2)</p> <ul style="list-style-type: none"> <li>• Scores not statistically significant between the 2 groups</li> </ul> <p>Morphine-related AE:</p> <ul style="list-style-type: none"> <li>• Apnea requiring naloxone statistically less in paracetamol group (NNT = 1/0.079 = 13)</li> <li>• 1 episode of urinary retention observed in paracetamol group; 0 in morphine group; 95% CI does not cross 1 (stat. signif.)</li> <li>• None of the other AE reached statistical significance, but study not powered to detect differences because these were secondary endpoints</li> </ul>
<p><b>AUTHORS' CONCLUSIONS</b></p>	
<p>“Infants who receive IV paracetamol as primary analgesic after major surgery require significantly less morphine than those who receive a continuous morphine infusion” (p. 153).</p> <p>“Judging from the rescue morphine doses, a similar level of analgesia was obtained in either group” (p. 153).</p> <p>Scheduled IV paracetamol may be a reasonable alternative to continuous infusion morphine in the post-operative setting in neonates and infants.</p>	
<p><b>STRENGTHS / LIMITATIONS</b></p>	
<p>Strengths:</p> <ul style="list-style-type: none"> <li>• This study investigated a topic that has not historically been well-studied, but where information is greatly needed.</li> <li>• Ethical design (rescue pain protocol ensured that infants did not suffer while receiving study drugs).</li> </ul> <p>Limitations / Weaknesses:</p> <ul style="list-style-type: none"> <li>• The statistical significance of the primary endpoint is promising, but may be a little misleading. The cumulative dose of morphine will of course be less in the paracetamol group because they did not receive it as study drug. Since the endpoint was more of a composite (loading dose of morphine + morphine study dose + rescue morphine), there is always a possibility that the acetaminophen group actually had a higher morphine rescue requirement, offset by not having received morphine at the study dose. Rescue morphine dose would have been a more definitive primary endpoint, but was a secondary endpoint and the study was not adequately powered to detect a difference here (and indeed, none was found, so we must consider this as a potential issue).</li> <li>• How many received accurate dosing of paracetamol according to protocol? Of morphine?</li> <li>• Limited patient demographic (non-cardiac patients) → may limit extrapolation to other patients, such as those undergoing cardiac surgery</li> <li>• Unique morphine dosing regimen (mg/kg<sup>1.5</sup>/hr) may also limit external validity → more standard morphine dosing gives smaller, younger infants higher doses → if IV acetaminophen is compared to these higher doses typically seen in practice, then APAP may actually appear to provide less analgesia</li> </ul> <p>Author reported:</p> <ul style="list-style-type: none"> <li>• Single center limits external validity of findings</li> <li>• Not powered to detect a difference in adverse effects</li> <li>• Liver function not monitored in paracetamol group → unable to determine which treatment is safest</li> </ul>	
<p><b>DISCUSSION / CLINICAL UTILITY</b></p>	
<p>Paracetamol IV did not eliminate the need for morphine rescue. It may be a reasonable agent to spare infants from a morphine continuous infusion, but the study was not powered to determine whether the IV paracetamol spared patients from a higher morphine rescue requirement and more AE.</p>	

References:

1. Johnson PN, Miller JL, and Hagemann TM. Sedation and analgesia in critically ill children. *American Association of Critical Care Nurses*. 2012; 23(4): 415-34.
2. Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology*. 1999; 91:442-7.
3. Van der Marel CD, Peters JWB, Bouwmeester NJ, et al. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *British Journal of Anaesthesia*. 2007; 98(3): 372-9.
4. Hong JY, Kim WO, Koo BN, et al. Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. *Anesthesia*. 2010; 113: 672-7.
5. Knibbe CAJ, Krekels EHI, et al. Morphine glucuronidation in preterm neonates, infants, and children younger than 3 years. *Clin Pharmacokinetics*. 2009; 48(6):371-385.