

## **IV Acetaminophen: On the horizon? Should it be used for analgesia in children? Is there evidence for safety and efficacy?**

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Choices for management of postoperative pain in children include opioids, NSAIDs, acetaminophen, and regional and local anesthetic techniques. Opioids are the only class of drugs labeled for parenteral administration for treatment of acute pain in children. Use of opioids may be associated with adverse events such as nausea and vomiting which may prolong postoperative recovery and hospital stay as well as require administration of prophylactic or rescue medications which increase cost. Opioids also increase risk of respiratory depression, especially in children with history of sleep apnea (obstructive or central). Regional techniques are effective for some procedures of the chest, abdomen, and extremities but require extra time and expertise.

Only one parenteral NSAID (ketorolac) is approved in the US for treatment of acute pain. However, even ketorolac is not labeled for use as an antipyretic or as an analgesic in pediatric patients under the age of 2 years; in children 2 to 16 years of age its use is limited to a single dose. Additionally, ketorolac has a detailed black box warning regarding adverse gastrointestinal, renal and bleeding effects.

Acetaminophen is known to be effective as an analgesic and antipyretic. Pharmacokinetic parameters of enterally administered acetaminophen have been well characterized in children of all ages, including neonates. The relationship between plasma level and antipyretic efficacy has been well established in children (concentration: response relationship) but data is lacking for the plasma concentration that correlates with analgesic efficacy. What is also revealed by these previous studies is that oral and especially rectal are unreliable routes of administration because of delayed and variable absorption resulting in a wide range of plasma concentrations, with sub-therapeutic concentrations most likely.<sup>1</sup> For example, the coefficient of variation of maximal concentration for rectal administration was found to be 43%.<sup>2</sup> In neonates, use of higher doses administered rectally raise concern for outliers (more complete absorption) when recommended higher doses (30-40 mg/kg) are used. Concern also exists regarding recommendations for dose interval in the youngest patients as clearance is slower in these patients and plasma concentrations may rise with repeated doses. Use of intravenous acetaminophen would be expected to result in faster onset of more predictable plasma levels in the therapeutic range with resultant better efficacy, eliminating uncertainty about these parameters.

Analgesic effect of acetaminophen has been less well correlated with plasma concentration than what is seen for antipyretic effect,<sup>3</sup> although Anderson et al have data which leads them to conclude that a plasma concentration of 10 mg/L will provide adequate analgesia to 50% of children after tonsillectomy.<sup>4</sup> The time delay between peak plasma concentration and peak

analgesic effect may be due to the time it takes for equilibration with a central compartment with the time to analgesic effect more correlated with time to peak CSF concentration.<sup>5</sup> IV acetaminophen may have a faster onset of analgesia because of faster plasma:CSF equilibration time<sup>6</sup> than that seen with oral or rectally administered acetaminophen.<sup>7</sup>

## History

Efforts had been made for many years to develop an intravenous formulation of acetaminophen. Its insolubility was a problem that was difficult to overcome. Prior to the availability of the current formulation, a prodrug, propacetamol, was developed and approved for use in the EU. Propacetamol was shown to have analgesic efficacy and safety profile children.<sup>8</sup> However, its use was associated with a high rate of pain on injection in the adult patients who were studied (20-40% vs 2% for other injectable analgesics [ketorolac, paracetamol]).<sup>9,10</sup> Intravenous propacetamol has been shown to be a more effective analgesic than rectal paracetamol in children after major craniofacial surgery, associated with a higher mean plasma concentrations more likely to be in the therapeutic range.<sup>11</sup> Propacetamol was never approved in the US.

More recently, the problem with solubility of the native drug has been resolved, having been formulated in a very dilute solution (1000mg/100mL) which must be reconstituted immediately before use. Intravenous acetaminophen has been approved and is in use for the treatment of acute pain and fever in almost 80 countries. It is the most commonly prescribed injectable analgesic in the EU, having been approved there in 2002. Recently in the UK, labeling has been extended to use in neonates and infants < 1 year of age. Adult and pediatric clinical trials of IV acetaminophen (Acetavance™, Cadence Pharmaceuticals, Inc.) have been completed in the United States and the drug is under review by the FDA.

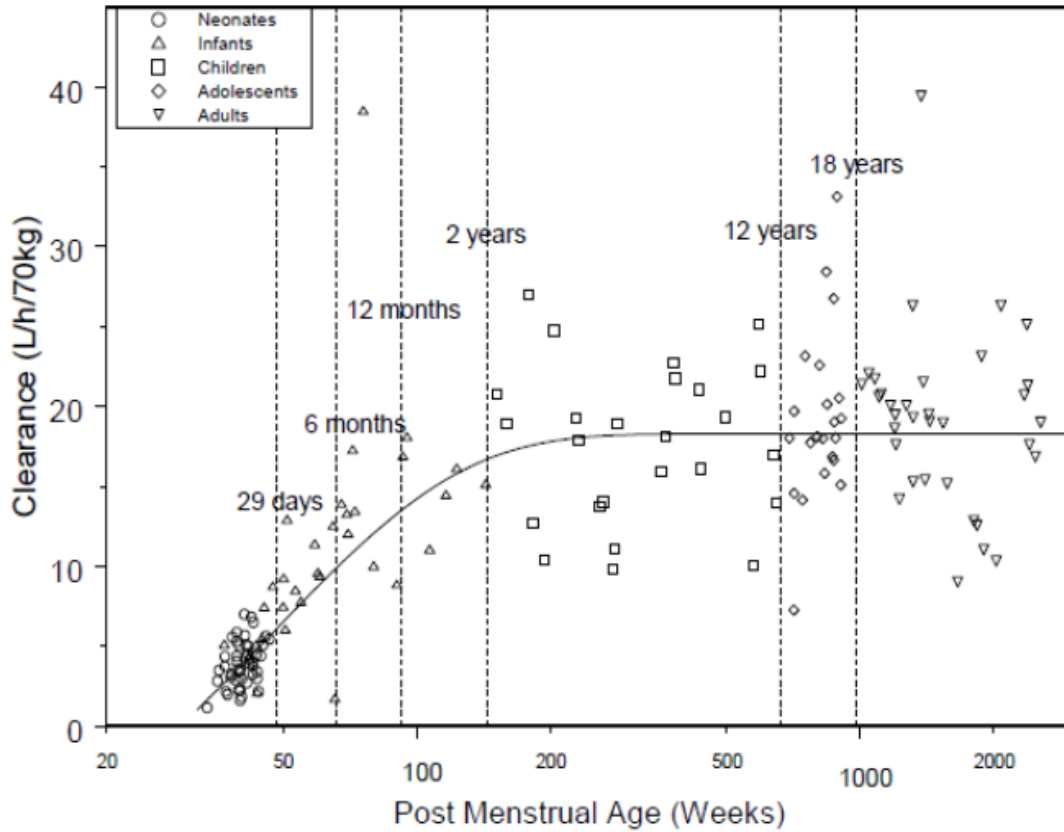
## Evidence for safety:

Two completed pediatric clinical trials have been sponsored by Cadence in the US. One was a prospective, multi-center, randomized, open-label, single and repeated dose, 48-hour study of intravenous acetaminophen in pediatric inpatients to determine pharmacokinetics and safety in acute pain and fever. The second was a multi-center, open-label, prospective, repeated dose, multi-day study of the safety and efficacy of intravenous acetaminophen in pediatric inpatients. Both of these studies were designed to assess the safety of repeated doses of IV acetaminophen in pediatric populations from full-term neonates to adolescents. In the first pharmacokinetic/safety study, subjects were randomized to receive either 12.5 or 15 mg/kg, with neonates dosed on a q6 or q8h schedule and older children dosed q4 to q6h. Outcome included adverse event reporting and pK parameters. In the multiday safety study, investigators selected the dose which ranged from 30-45 mg/kg/day for neonates and 60 – 75 mg/kg/day for older children; the study population ranged from > 37 weeks GA to < 17 years of age and totaled 75 inpatients at 5 sites. Total enrollment for the two studies was 175, of which 4 were neonates and 33 infants. Safety outcomes included adverse event reporting and clinically meaningful changes from baseline of laboratory test parameters (urine and blood tests, including liver function tests).

Of the patients enrolled, no neonates or infants had elevation of hepatic enzymes; 4.5% of children and 6.9 % of adolescents had transient hepatic enzyme elevation (total 8 patients). Six of eight patients had posterior spinal fusions and had a pattern of enzyme elevation consistent with muscle injury from surgery. Two patients continued on IV or oral acetaminophen with

normalization of enzymes. Patients and/or parents were also asked to complete global evaluations of treatment satisfaction and adverse side effects.

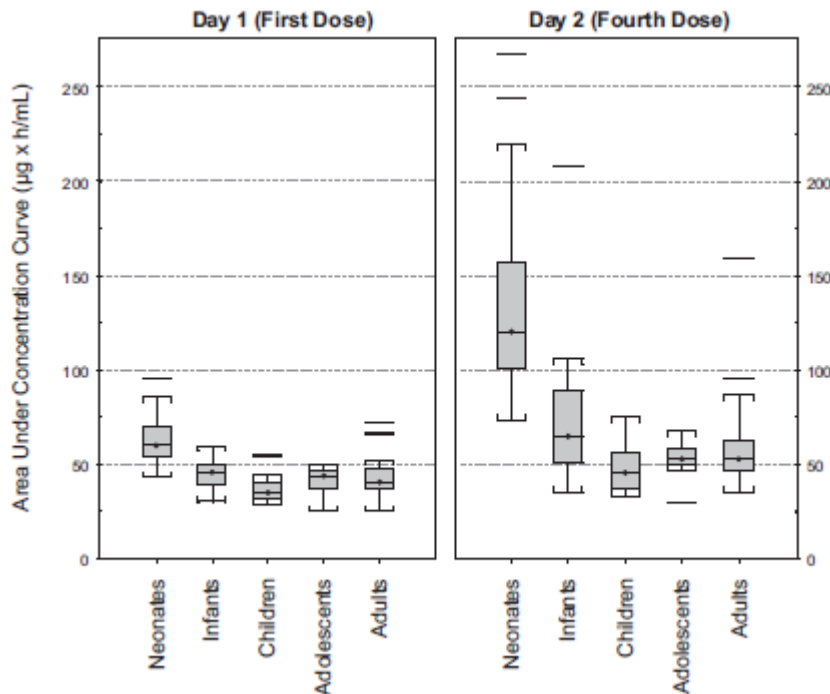
Pharmacokinetic parameters were similar to those previously determined after oral or rectal administration with clearance reduced in neonates and young infants, reaching adult levels at approximately 2 years of age.



#### Safety in neonates

In addition, two investigator initiated studies of pharmacokinetics and safety have been published in which repeated doses of acetaminophen were administered to 239 neonates (32 weeks GA to 29 days of age) and some older infants (up to post menstrual age of 55 weeks) of which most were treated for postoperative pain.<sup>12,13</sup> Dosing regimens were 20 mg/kg loading dose followed by 10 mg/kg q6h (>36 weeks), q8h (31 to 36 weeks), and q12h (<31 weeks) in the Allegaert study and 15 mg/kg q6h ( $\geq$  36weeks), 12.5 mg/kg q6h (32 to <36 weeks), and 10 mg/kg q6h (<32 weeks) in the Palmer study. In both of these studies, IV acetaminophen was well-tolerated with only a single case of significant but transient liver enzyme elevation.

Unconjugated hyperbilirubinemia was associated with reduced clearance in the Palmer study leading the authors to suggest dose reduction in this event.<sup>7</sup> In addition, in neonates, drug levels continue to rise after repeated dosing, reinforcing the necessity for dose reduction and/or lengthening of dose interval for the youngest patients.



#### Evidence for analgesic efficacy

Although many studies have been published which have established analgesic efficacy of IV acetaminophen in adults, relatively few pediatric studies are available for review. Alhashemi and Daghistani showed in a randomized double-blind study that IV acetaminophen provided analgesia comparable to IM meperidine for post-tonsillectomy pain with less sedation and shorter time to readiness for PACU discharge.<sup>14</sup> Most pediatric studies of efficacy of IV acetaminophen have used propacetamol or rectal acetaminophen as a comparator, rather than an opioid,<sup>6</sup> and many have looked at efficacy only after a single dose.<sup>15,16</sup> In the multi-day Cadence sponsored study referred to above, pain was a secondary endpoint and pain scores were not recorded. Future investigator-initiated studies should be designed to evaluate efficacy in inpatients receiving IV acetaminophen. Outcome measures should include pain scores and rescue medication (time to first rescue as well as total rescue medication/time).

#### Administration issues

Acetaminophen must be diluted (1000 mg/100 ml) immediately prior to administration and given by infusion over 15 minutes. Although many intravenous analgesics are administered by syringe pump on inpatient units, this practice is unusual in PACUs, where analgesics are more commonly administered “IV push”.

Implementation of intravenous acetaminophen administration after FDA approval will require education and careful monitoring of compliance with maximal dosing recommendations based

on age and weight. Auditing practice after implementation can provide important feedback of utility in maintaining safe practice.<sup>17,18</sup>

## Conclusion

Available evidence suggests that IV acetaminophen may be safe and effective for postoperative analgesia in children, including neonates, if dosing guidelines are followed. IV acetaminophen may suffice as a sole analgesic for patients with mild to moderate postoperative pain and to supplement regional analgesic techniques. It may prove to be opioid-sparing in patients at high risk for adverse effects of opioids (central and obstructive sleep apnea, respiratory failure, neuromuscular disease).

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