

**Title: Dosing Recommendations for Acetaminophen in Pediatrics: Guidelines and a Clinical Review**

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**Context and policy issues:**

Acetaminophen is the most widely used antipyretic and analgesic in children.<sup>1</sup> Acetaminophen is the drug of first choice in children for the treatment of fever less than 41°C and mild to moderate pain.<sup>2</sup> Acetaminophen has been available without a prescription since 1960 and the safety of its short-term use is well established.<sup>2-4</sup> However, toxicity can result from the ingestion of massive single overdoses (accidental or suicide attempts) or from multiple supratherapeutic doses administered with therapeutic intent for one or more days.<sup>3</sup>

Most pediatric dosing handbooks cite an oral and rectal acetaminophen dose of 10 to 15 mg/kg, given up to every four to six hours. Appendix 1 provides a sampling of dosing information sources available to health care practitioners for the usual oral and rectal pediatric acetaminophen dosages, derived from various handbooks, review articles and consensus statements. In some cases, these dosing guides may exceed the doses included on the labels of pediatric acetaminophen products, which specifically warn against exceeding a maximum dose of 75 mg/kg/day.<sup>3</sup>

Identical acetaminophen dosages for the oral and rectal administration routes are listed in most dosage handbooks; however it is well known that absorption from the rectum is slow and often erratic, with variable uptake.<sup>1</sup> Several factors may account for this.<sup>5</sup> The relative bioavailability of a suppository may depend on the height of placement in the rectum, rectal pH, rectal vault contents and colonic blood flow. Suppository formulation may also affect the bioavailability, with absorption from lipophilic suppositories being more rapid than from hydrophilic suppositories. The relative bioavailability of rectal acetaminophen compared with oral formulations has been reported as 0.52 (range 0.24 – 0.98).<sup>5</sup> This frequently results in low serum acetaminophen concentrations.<sup>1,6</sup>

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Target therapeutic acetaminophen plasma concentrations for fever and analgesia are controversial. A plasma concentration range of 10 µg/mL to 20 µg/mL is generally accepted as being therapeutic for antipyresis.<sup>1,7-10</sup> A 1978 study by Rumack is generally cited as the source that established this antipyretic therapeutic range, however the study provides no data and makes reference to an unpublished source.<sup>5,11</sup> The acetaminophen plasma concentration for effective analgesia is even less clear. While some investigators cite 10 µg/mL to 20 µg/mL as also being therapeutic for analgesia,<sup>10</sup> others state that this has not been established or validated.<sup>1,7,12</sup>

Because of the delayed absorption with rectal acetaminophen, several investigators have suggested using higher rectal doses of acetaminophen in children, particularly during the perioperative period when a slower absorption rate could provide prolonged analgesia during recovery. In fact, high-dose rectal acetaminophen has become routine in many hospitals,<sup>6</sup> although the efficacy and safety of the therapy is still being debated in the medical literature.

Acetaminophen is metabolized by the liver's cytochrome P450 (CYP) system and eliminated by the kidney as non-toxic glucuronic acid and sulfate conjugates. The metabolism of acetaminophen by the CYP enzyme leads to the formation of *N*-acetyl-*p*-benzoquinone imine (NAPQI), a highly reactive intermediate metabolite that is normally detoxified by conjugation with reduced glutathione. After high doses of acetaminophen are ingested, the capacity for its removal by hepatic conjugation with glucuronide and sulfate is exceeded and more of the toxic metabolite NAPQI is formed.<sup>13</sup> This causes hepatotoxicity, which is sometimes fatal.<sup>13</sup> Acetaminophen has hepatotoxic effects when ingestion of single dosages exceed 140/mg/kg.<sup>4</sup> Plasma concentrations > 120 µg/mL are associated with hepatotoxicity.<sup>9</sup>

Hepatotoxicity can also result from the administration of multiple supratherapeutic doses (larger than 10 to 15 mg/kg per dose) that exceed the maximum recommended daily dosage of 75 mg/kg/day for a period of one or more days.<sup>3</sup> Hepatotoxicity has also been reported in children taking doses as low as 60 mg/kg/day, although more frequently at doses greater than 100 mg/kg/day, particularly in sick, febrile children.<sup>4</sup>

Fasting or malnutrition are risk factors for acetaminophen-induced hepatotoxicity because fasting decreases hepatic stores of glutathione.<sup>13,14</sup> This could make children more susceptible to toxicity when sulfation and glucuronidation pathways are saturated. A 1998 position statement by the Canadian Pediatric Society indicates the importance of identifying children who may be at increased risk for acetaminophen-related hepatotoxicity, including children less than two years of age who are acutely malnourished and dehydrated and who have received acetaminophen doses totaling ≥120 mg/kg/day for more than one day.<sup>2</sup>

This report examines the clinical effectiveness and safety of higher doses of acetaminophen in children, and also reviews the guidelines for acetaminophen dosing in children with pain or fever.

## Research question(s):

1. What is the clinical effectiveness and safety of using higher than conventional doses of acetaminophen for the treatment of pain and fever in infants and children?
2. What is the clinical effectiveness and safety of using a loading dose of oral or rectal acetaminophen for the treatment of fever or pain in infants and children?
3. What are the guidelines for acetaminophen dosing in infants and children up to 12 years of age in the community or hospital setting?

**Methods:**

A limited literature search was conducted on key health technology assessment resources, including OVID MedLine and Embase, Pubmed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and April 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analysis, clinical guidelines, and randomized clinical trial (RCT) studies. In addition, the bibliographies of retrieved publications were scanned for further relevant items, including some observational studies.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials, observational studies and evidence-based guidelines.

**Summary of findings:**

The search did not identify any systematic reviews, health technology assessments or meta-analyses. Four RCTs<sup>12,15-17</sup> were identified and two randomized trials.<sup>18,19</sup> Six observational studies were identified,<sup>1,4,5,8,9,20</sup> five of which were pharmacokinetic studies.<sup>1,5,8,9,20</sup> Three guidelines<sup>21-23</sup> and three clinical practice guidance documents/position statements<sup>2,24,25</sup> were retrieved.

*Randomized controlled trials and randomized trials*

A randomized, double-blind, placebo-controlled clinical trial (Korpela *et al.*; 1999)<sup>12</sup> evaluated the analgesic and morphine-sparing effect of three doses of rectal acetaminophen in day-care surgery in 120 children aged one to seven years. Children were randomized to receive placebo or acetaminophen 20, 40, or 60 mg/kg as a single dose pre-operatively. Postoperative pain was evaluated by behavioural assessment and physiologic measurements. The only children to experience severe pain were those who received placebo or 20 mg/kg acetaminophen. Of the children who received placebo, 90% required morphine, with an average of 1.2 doses. For those children receiving 20 mg/kg acetaminophen, 63% required morphine, and 20% required at least two doses. Of the patients receiving 60 mg/kg of acetaminophen, 23% required post-operative morphine, with an average of 0.27 doses. Following discharge, 80% of the children who received placebo had pain at home compared with 17% or 20% of those who received 40 or 60 mg/kg of acetaminophen, respectively ( $p < 0.01$ ). The authors concluded that there was a significant reduction in the need for post-operative morphine in the 40 mg/kg and 60 mg/kg groups and they calculated that 35 mg/kg of rectally administered acetaminophen resulted in morphine-sparing effects for 50% of the children. Rectal doses of 20 mg/kg did not significantly reduce the pain compared with placebo. The study was limited by the use of an invalidated nurse-observer pain evaluation technique to “translate” the child’s pain rating to a visual analog scale (VAS) score. Safety was not evaluated.

A double-blind RCT (Bremerich *et al.*; 2001)<sup>15</sup> compared the effects of three different doses of pre-operatively administered rectal acetaminophen with placebo in 80 infants and children from two weeks to 12.5 months of age undergoing cleft palate repair. The outcomes of interest were early post-operative pain control (as measured by the observational Children’s and Infants Postoperative Pain Score (CHIPPS) and opioid requirements. After anesthesia induction, all children were randomized to receive either placebo, or a single dose of 10, 20, or 40 mg/kg acetaminophen via a rectal suppository. Plasma acetaminophen concentrations were measured at the end of the surgical procedure, which ranged in duration from 110 minutes to 136 minutes. Rectal acetaminophen was found to have no effect on early post-operative pain scores and had no opioid-sparing effect. After

20mg/kg dosing, the maximum plasma concentration was 13 µg/mL; after 40 mg/kg dosing it was 21 µg/mL. The authors concluded that single doses of rectal acetaminophen up to 40 mg/kg were not effective for early post-operative pain control and did not reduce the use of narcotic analgesics in infants and small children undergoing cleft palate repair. They also concluded that “analgesic plasma concentrations” were not achieved with rectally administered acetaminophen. However, a generally accepted analgesia therapeutic range for acetaminophen has not been established. A limitation of the study was that plasma samples were available for only 50 of the 80 children due to technical difficulties with blood work. Another limitation was the timing of the single blood sampling: absorption after rectal administration is erratic and peak plasma concentrations occur, on average, two to three hours after rectal acetaminophen. It is possible that earlier or later peaks may have been missed.

A double-blind parallel group randomized trial (Tréluyer *et al.*; 2001)<sup>19</sup> compared the antipyretic efficacy of a 30 mg/kg oral acetaminophen loading dose versus a 15 mg/kg maintenance dose in 121 children four months to nine years of age who had a rectal temperature of 39°C to 40.5°C. If temperature did not decline by at least 0.5°C within four hours, a 15 mg/kg dose of acetaminophen was given. The primary endpoint was the time to obtain a rectal temperature below 38.5°C. In an intention-to-treat analysis, the time to obtain a temperature lower than 38.5°C was significantly shorter in the 59 children who received a 30 mg/kg dose compared with 62 children who received 15 mg/kg (110.7 ± 94.3 minutes versus 139.4 ± 112.6 minutes,  $p < 0.05$ ). The mean difference between the two groups was 29 minutes (95% CI -66.5 to -8.9). The maximum temperature difference was also significantly higher in the 30 mg/kg group than in the 15 mg/kg group (2.3 ± 0.7 °C versus 1.7 ± 0.6 °C,  $p < 0.05$ ). The duration of rectal temperature below 38.5°C was significantly longer in the 30 mg/kg group than in the 15 mg/kg group (250 ± 92 minutes versus 185 ± 121 minutes,  $p < 0.05$ ). Adverse events (hyperthermia, hypothermia, vomiting) were reported in six children in the 30 mg/kg group compared with five children in the 15 mg/kg group). The authors concluded that an initial 30 mg/kg loading dose could be an efficient way to obtain a significant temperature decrease (0.5 °C) thirty minutes sooner and that lasts one hour longer than a 15 mg/kg dose in febrile children. The limitations of this study include the small sample size. In addition, tolerability observed after a single dose cannot predict safety after repeated doses.

A randomized trial (Howell *et al.*; 2003)<sup>18</sup> evaluated acetaminophen plasma concentrations in 24 children greater than 25 kg who were given a single pre-operative rectal acetaminophen dose of either 1 g (the adult dose for rectal acetaminophen) or 40 mg/kg prior to elective spinal surgery. The objective of the study was to determine if the adult rectal dose of 1 g was sufficient to achieve therapeutic levels in older children or whether the higher dose of 40 mg/kg was required. The mean maximum serum concentration was 7.8 µg/mL for children who received 1 g of acetaminophen compared with 5.9 µg/mL in the group of children who received 40 mg/kg ( $p = 0.009$ ). The children receiving 40 mg/kg achieved the maximum concentration on average one hour before those receiving the 1 g dose (The time to reach maximum serum concentration, or  $T_{max}$ , was 2.6 hours versus 3.8 hours,  $p = 0.009$ ). The maximum plasma level recorded in the study was 45 µg/mL (in a child dosed at 40 mg/kg). The authors concluded that 1 g of rectal acetaminophen is insufficient in children weighing > 25 kg. The authors acknowledged that acetaminophen’s therapeutic range for analgesia is not well established; however, they cited previous studies that have demonstrated little or no analgesia below levels of 10 µg/mL and those that suggest better analgesia is attained with increasing plasma concentrations up to levels of 25 µg/mL to 30 µg/mL. No parameters other than plasma concentrations were evaluated.

A double-blind randomized placebo-controlled study (van der Marel *et al.*; 2001)<sup>16</sup> evaluated plasma acetaminophen levels and pain scores (using two validated pain measurement instruments) in 40 children between the ages of three months and three years undergoing major craniofacial surgery. All children received a 40 mg/kg rectal acetaminophen loading dose and were randomized to one of two

maintenance interventions every 6 hours for three doses: 20 mg/kg given as an oral elixir, plus a placebo suppository; or 20 mg/kg as a rectal suppository, plus a placebo oral elixir. Investigators, care givers and patients were blinded to the route of the actual acetaminophen administration. A secondary aim of the study was to determine a dose-plasma concentration and a plasma concentration-effect relation of both orally and rectally administered acetaminophen. Acetaminophen plasma concentrations were higher in children receiving rectal acetaminophen (mean area under the concentration-time curve 171.2 mg/h/L) compared with children receiving oral acetaminophen (mean area under the concentration-time curve 111.9 mg/h/L,  $p=0.004$ ). Vomiting occurred in 11 children receiving rectal acetaminophen and in 12 children receiving oral acetaminophen; however, vomiting with oral administration was a confounder since this would decrease plasma concentrations. After excluding children who vomited, acetaminophen plasma concentrations and pain scores did not differ between the two groups. Therefore, no relationship was found between plasma acetaminophen concentration and pain scores. Nine of 40 children (22.5%) did not reach acetaminophen plasma concentrations of 10 µg/mL to 20 µg/mL, although they did achieve plasma levels of  $\geq 5$  µg/mL. Since more than 92.5% of all children had visual analog scale pain scores  $> 4$  (what is commonly considered to be satisfactory analgesia) the authors speculated that analgesic plasma concentrations for this age group could be  $< 10$  µg/mL. Safety was not evaluated.

A double-blind randomized placebo-controlled study (Hamers *et al.*, 1999)<sup>17</sup> evaluated the effectiveness of two pain protocols used to manage early post-operative tonsillectomy and/or adenoidectomy pain. Eighty-three children aged three to 12 years were randomized to one of the two protocols. In the first protocol, children received an intra-operative acetaminophen rectal loading dose of 30 to 50 mg/kg, followed by regular acetaminophen doses (20 mg/kg) three times a day to a maximum of 70 to 100 mg/kg per 24 hours, including the loading dose. They also received an intra-operative intramuscular placebo injection. In the second protocol, children received the same acetaminophen doses described in the first protocol plus intra-operative intramuscular fentanyl at 1 µg/kg. A second objective of the study was to investigate whether nurses' systematic pain assessments improved pain management. Pain was measured using two validated pain scales. Neither pain protocol sufficiently relieved post-operative tonsillectomy/adenoidectomy pain. About 60% of the children in each group said they suffered too much pain. Systemic pain assessment by nurses did not improve the effectiveness of analgesics. The authors concluded that a high-loading dose of acetaminophen (30 to 50 mg/kg) combined with fentanyl (1 µg/kg) given intra-operatively to relieve early tonsillectomy/adenoidectomy postoperative pain did not lead to improved analgesia compared with a high-loading dose of acetaminophen (30 to 50 mg/kg) combined with a placebo. Limitations of the study include a high percentage of missing values (33% and 37%) on two self-report pain scales.

#### *Observational studies (including pharmacokinetic studies)*

A retrospective study (Heubi *et al.*; 1998)<sup>4</sup> that compiled reports of acetaminophen toxicity from published literature and US Food and Drug Administration files, identified 47 children aged five weeks to 10 years who had acetaminophen-induced hepatotoxicity after multiple overdoses of acetaminophen administered with therapeutic intent. The acetaminophen dose, which could be estimated for 39 children, ranged from 60 to 420 mg/kg/day. The duration of overdosing was available for 33 children and varied from one day to 42 days. Twenty-four of 43 (55.8%) children died, with three more children surviving after liver transplantation. Fourteen children received excessive dosing either because of dosage miscalculation or the inadvertent administration of drops (a more concentrated formulation) in the dose recommended for suspension. Of note, six children received reported doses that were only slightly above the recommended 10 to 15 mg/kg dose for up to five doses per day or 50 to 75 mg/kg/day. The authors surmised that in most multiple accidental overdoses, infants and children were febrile and acutely malnourished. The combination of fasting

and repeated acetaminophen may lead to hepatotoxicity due to a depletion of glutathione, the liver enzyme that normally removes a toxic acetaminophen metabolite. The limitations of this analysis were that data collected retrospectively can be imprecise and data were not available for all children.

A pharmacokinetic study (Anderson *et al.*; 1999)<sup>8</sup> determined how serum concentrations of acetaminophen are related to analgesia in 120 children undergoing adenotonsillectomy. A pre-operative acetaminophen dose of almost 40 mg/kg was given orally (n=20) or rectally (n=100) to children aged two to 15 years before an outpatient tonsillectomy. Individual concentrations of acetaminophen in serum and pain scores (0 to 10) measured over a four-hour post-operative period were analyzed using a nonlinear mixed-effects model. The results revealed that the relative bioavailability of the rectal suppository with the oral formulation was 0.54. Fifteen children from the suppository group required rescue intravenous morphine within the first 30 minutes after surgery compared with two children from the group administered oral elixir. Simulation modeling determined that an acetaminophen effect compartment concentration of 10 µg/mL is required to achieve a mean post-tonsillectomy pain score of 3.6 out of 10, which would be considered satisfactory pain control. This pharmacokinetic-pharmacodynamic modeling study in tonsillectomy may have limited applicability to other painful procedures. Many samples were missing because of patient or parent refusal. Safety was not evaluated.

A pharmacokinetic study (Hansen *et al.*; 1999)<sup>1</sup> evaluated the plasma acetaminophen concentrations and pharmacokinetics of a single dose of rectal acetaminophen in 17 neonates and young infants ≤ 160 days of age. The mean dose administered was 23.9 mg/kg. The resulting mean maximum plasma acetaminophen concentration ( $C_{max}$ ) was 11 µg/mL (±5.1 µg/ml) at a mean time ( $T_{max}$ ) of 102.4 minutes (±59.1 min). The maximum plasma concentration did not exceed 24.2 µg/mL in any infant. The authors concluded that the absorption of acetaminophen in young infants is variable, often prolonged, and that mean doses of 23.9 mg/kg achieve plasma concentrations that are below the “antipyretic” therapeutic range of 10 µg/mL to 20 µg/mL. Limitations of this pharmacokinetic study include the small number of patients and the limited number of blood samples obtained (actual number not reported) in many of the children.

A pharmacokinetic/pharmacodynamic study (van Lingen *et al.*; 1999)<sup>9</sup> evaluated serum concentrations following rectal administration of acetaminophen in 10 term neonates. The relationship between dose and effect and between concentration and effect was also examined. The infants were given 20 mg/kg/dose every six hours for a total of four doses. Serum concentrations were analyzed from nine serial samples and pain assessment performed with a validated pain score. The mean peak serum concentration was 10.79 µg/mL ± 6.39 µg/mL (range 1.7 to 23.2 µg). There was no correlation between dose and serum concentrations or between pain scores and serum concentrations. Pain scores from 0 to 1 were obtained when serum concentrations were > 2.61 µg/mL. No drug accumulation was observed. The authors concluded that since no drug accumulation was found, it is appropriate to administer rectal acetaminophen to term infants on the first day of life using a loading dose of 30 mg/kg, followed by 20 mg/kg rectally every 6 to 8 hours to a maximum of 90 mg/kg/day. Limitations of the study include the small number of infants and the very short period of dose administration.

A 24-hour pharmacokinetic study (Birmingham *et al.*; 2001)<sup>20</sup> evaluated whether a rectally administered acetaminophen loading dose of 40 mg/kg followed by a 20 mg/kg dose every six hours would result in serum concentrations within a target range of 10 µg/mL to 20 µg/mL without evidence of accumulation. Children were included in the study if they were two to 12 years old, weighed more than 12 kg and were to be hospitalized after elective orthopedic surgery. Sixteen children were given acetaminophen 40 mg/kg after induction of anesthesia and up to three subsequent doses of 20 mg/kg at six-hour intervals. Large inter-individual pharmacokinetic characteristics were seen. The initial

loading dose resulted in a serum level in the 10 µg/mL to 20 µg/mL target range 38% ± 25% of the time. With subsequent dosing, the target range was maintained 60% ± 29% of the time. The highest serum concentration achieved with initial dose or subsequent dosing was 38.6 µg/mL. There was no evidence of accumulation during the 24-hour sampling period. Safety was not specifically evaluated. Limitations of the study include small sample size and the short time period. The authors presumed that 10 µg/mL to 20 µg/mL is the therapeutic range for analgesia; however, this has not been definitively established.

A pharmacokinetic study (Cormack *et al.*, 2006)<sup>5</sup> measured serum acetaminophen levels in 17 children aged three to 15 years with chronic liver disease who were given a single rectal loading dose of 40 mg/kg during a minor surgical procedure under general anesthesia. The objective of the study was to establish whether serum concentrations in children with liver disease were similar to children with normal liver function. Blood samples were taken at 2, 3, 4, 6, 8, 16 and 24 hours after the single rectal dose administration. The mean maximum concentration ( $C_{max}$ ) reached was 11.4 µg/mL at a mean time of 2.7 hours ( $T_{max}$ ). The highest plasma acetaminophen concentration reached was 27.6 µg/mL. Six patients failed to attain a serum concentration > 10 µg/mL at any time. The authors concluded that it is likely safe to administer a single rectal acetaminophen dose of 40 mg/kg in children with liver disease who undergo minor surgery. Limitations of the study include small sample size and the use of a surrogate marker rather than a biologic marker to monitor possible hepatotoxicity in children with liver disease.

#### *Clinical practice guidelines*

Three clinical practice guidelines<sup>21-23</sup> and three clinical practice guidance documents/position statements<sup>2,24,25</sup> were identified. However, only one of these documents, a guideline from the British Association for Emergency Medicine<sup>23</sup> included acetaminophen dosing information for the management of pain in children. This information is included in the Appendix. Of note, there was no description of the methods or evidence used to formulate the dosage recommendations.

#### **Conclusions and implications for decision or policy making:**

Some dosing guides (see the Appendix) continue to recommend identical acetaminophen doses for oral or rectal administration at a traditional dose of 10 – 15 mg/kg every 4 to 6 hours for children < 12 years. Other dosing guides recommend the use of higher rectal doses, at 20 mg/kg/dose every 4 to 8 hours, depending on the age of the child. For example, several dosing guides recommend rectal doses of 20 mg/kg in term infants less than 90 days old.<sup>6,26-28</sup> The use of high-dose rectal acetaminophen has become routine in many hospitals.<sup>6</sup> The rationale for using a higher rectal dose is based on the poor, delayed and erratic absorption of acetaminophen from suppositories. Peak plasma concentrations have been reported to occur two to three hours after rectal suppository insertion compared with 30 to 60 minutes following oral acetaminophen.<sup>12</sup>

The safety of repeated dosing of acetaminophen in children has been questioned and cases of hepatotoxicity after repeated therapeutic doses and supratherapeutic doses administered with therapeutic intent have been reported.<sup>4</sup> Children less than two years of age may be more susceptible to acetaminophen hepatotoxicity at doses of 90 mg/kg/day or more if they are acutely malnourished and dehydrated due to vomiting, diarrhea or decreased liquid and nutrient intake.<sup>29</sup> In 1999, Heubi *et al.* searched the published literature and US Food and Drug Administration files and identified reports of 47 children who had acetaminophen-induced hepatotoxicity. Among these children, 55% died, and half of the deaths occurred in children less than two years old. Administered doses ranged from 60 - 420 mg/kg/day and the duration of treatment ranged from one to 42 days. Six children in the series may have received as little as 50 – 75 mg/kg/day of acetaminophen. According to the Canadian

Pediatric Society, similar reports of acetaminophen-induced hepatotoxicity have not been identified in the provinces of Ontario and Quebec. A review of liver transplants performed in children between 1986 and 1996 in these two provinces found that no transplants were performed because of acetaminophen-induced damage.<sup>2</sup>

This report identified five small randomized controlled trials that evaluated the perioperative use of rectal loading doses of acetaminophen > 30 mg/kg in children. The authors of these studies have concluded that the administration of rectal acetaminophen loading doses (ranging from 30 to 60 mg/kg) in the perioperative period appears to be safe and effective. A comparison of these trial results is impractical due to differences in the populations studied, dose and interval regimens, suppository formulations, methods to assess pain and the types of surgical procedures. Many trials reported missing data due to the challenges of sample collection from children. It must also be pointed out that none of the studies specifically assessed the potential toxicity of higher doses of acetaminophen, apart from the surrogate marker of plasma concentration.

Five small observational studies evaluated various aspects of acetaminophen pharmacokinetics in children after single high-dose rectal acetaminophen alone or followed by multiple dosing. One small study in 10 infants found no correlation between dose and serum levels or between serum concentration and pain scores. The target therapeutic serum concentrations for antipyresis and pain control in children have not been clearly established. Pharmacokinetic studies of acetaminophen for use in pain control may even be of limited value since higher plasma concentrations are not correlated with better pain control. A ceiling effect may be present at acetaminophen plasma concentrations of approximately 14 µg/mL above which no additional analgesic benefit is derived.<sup>7</sup> Many of the pharmacokinetic trials reported missing data due to the challenges of sample collection from children. None of the studies specifically assessed the potential toxicity of higher doses of acetaminophen, apart from the surrogate marker of plasma concentration.

On the basis of data from these limited studies, several dosage guides recommend the use of a single rectal acetaminophen loading dose in the perioperative period,<sup>30</sup> or for postoperative<sup>27</sup> or hospital emergency room pain control<sup>23</sup>. However, as the Lexi-Comp Pediatric Dosage Handbook points out, the routine perioperative use of high-dose rectal acetaminophen remain controversial and further studies are needed to establish optimal dose and dosing interval for efficacy and safety.

For policy makers, the clinical effectiveness and safety of using higher than conventional doses of oral or rectal acetaminophen (including loading doses) in infants and children remains controversial. While several of the dosage guides included in the Appendix recommend higher than conventional rectal doses, including a loading dose in the perioperative period, additional research is needed to establish the safety and efficacy of these higher doses. Although several Clinical Practice Guidelines address the treatment of fever and pain in infants and children, only one guideline provides specific acetaminophen dosing for acute, mild pain in children, and the evidence to support the recommended dosage is not stated.<sup>23</sup>

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Appendix: Acetaminophen Dosing Guides for Term Neonates, Infants, Children and Adolescents

Source	Age	Oral acetaminophen dose	Rectal acetaminophen dose	Maximum daily dose
<b>Pediatric Dosage Handbook 14<sup>th</sup> edition. Lexi-Comp, Inc., 2007<sup>26</sup></b>	Term neonates > 10 days (and up to 90 days)	10 – 15 mg/kg/dose every 4-6 hours	Loading dose: 30 mg/kg/dose; then 20 mg/kg/dose every 6-8 hours.	90 mg/kg/day
	Infants and children	10 – 15 mg/kg/dose every 4-6 hours as needed;	10 – 20 mg/kg/dose every 4-6 hours as needed. Note: Although the perioperative use of high-dose rectal acetaminophen (i.e. 25-45 mg/kg/dose) has been investigated in several studies, its routine use remains controversial; optimal dose and dosing frequency to ensure efficacy and safety have not yet been established; further studies are needed.	<b>Oral dosing:</b> 5 doses in 24 hours
	Children ≥ 12 years and adults	325 – 650 mg every 4-6 hours or 1000 mg 3-4 times daily.	325 – 650 mg every 4-6 hours or 1000 mg 3-4 times daily.	4 g/day
<b>Drug Handbook and Formulary 2007 – 2008. Toronto, Hospital for Sick Children.<sup>30</sup></b>	Newborns and Infants > 38 weeks	10 – 15 mg/kg every 4-6 hours	10 – 15 mg/kg every 4-6 hours	60 mg/kg/day *Single rectal loading doses of 30 mg/kg may be used for perioperative analgesia
	Infants and older children	10 – 15 mg/kg every 4-6 hours	10 – 20 mg/kg every 4-6 hours	<b>Oral dosing:</b> 75 mg/kg/day or 4 g/day for children > 12 years <b>Rectal dosing:</b> 80 mg/kg/day or 4 g/day for children > 12 years *Single rectal loading doses of 40 mg/kg may be used for perioperative analgesia

Source	Age	Oral acetaminophen dose	Rectal acetaminophen dose	Maximum daily dose
<b>Morton NS. Dosing guide for postoperative pain. Archives of Disease in Childhood Education and Practice. 2007.<sup>27</sup></b>	0 to 3 months	20 mg/kg up to every 8 hours	30 mg/kg loading dose; then 20 mg/kg up to every 12 hours	60 mg/kg/day for a maximum duration of 48 hours
	> 3 months	20 mg/kg loading dose; then 15 mg/kg up to every 4 hours	40 mg/kg loading dose; then 20 mg/kg up to every 6 hours	90 mg/kg/day for a maximum duration of 72 hours
<b>Walker P. Acetaminophen dosing recommendations. Journal of Pharmacy Practice 2003.<sup>28</sup></b>	Term infants < 10 days	10 – 15 mg/kg every 6 – 8 hours	20 – 30 mg/kg every 6-8 hours	60 mg/kg/day for oral dosing only
	Term infants > 10 days	10 – 15 mg/kg every 6 – 8 hours	20 – 30 mg/kg every 6-8 hours	90 mg/kg/day for oral dosing only
	Children < 60 kg	10 – 15 mg/kg every 4 – 6 hours	No rectal dose provided	100 mg/kg/day up to 2.6 g/day; do not exceed 5 doses in 24 hours
	Children ≥ 60 kg	650 – 1000 mg every 4 – 6 hours	No rectal dose provided	4 g/day
<b>British Association for Emergency Medicine. Guideline for the Management of Pain in Children. 2004.<sup>23</sup></b>	Children with acute pain	20 mg/kg loading dose, then 15 mg/kg every 4-6 hours	20 mg/kg loading dose, then 15 mg/kg every 4-6 hours	Not specified
<b>Anand KJS. Consensus statement for the prevention and management of pain in the newborn. International Evidence-Based Group for Neonatal Pain. 2001.<sup>6</sup></b>	Term infants < 10 days	10 – 15 mg/kg (no interval specified – see max dose)	20 – 30 mg/kg	60 mg/kg/day
	Term infants ≥ 10 days	10 – 15 mg/kg (no interval specified – see max dose)	20 – 30 mg/kg	90 mg/kg/day

Source	Age	Oral acetaminophen dose	Rectal acetaminophen dose	Maximum daily dose
<b>Berde CB. Oral dosage guidelines for commonly used non-opioid analgesics. New England Journal of Medicine 2002.<sup>10</sup></b>	Infants and neonates	10 – 15 mg/kg every 4 hours	Not provided	60 mg/kg for term neonates
	Children < 60 kg	10 – 15 mg/kg every 4 hours	35 to 45 mg/kg loading dose followed by 20 mg/kg every 6 – 8 hours	100 mg/kg
	Children ≥ 60 kg	10 – 15 mg/kg every 4 hours	Not provided	4 g/day