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The Three W's of Acetaminophen In Children: Who, Why, and Which Administration Mode?

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Acetaminophen is one of the oldest medications commonly administered in children. Its efficacy in treating fever and pain is well accepted among clinicians. However, the available evidence supporting the use of acetaminophen's different modes of administration remains relatively scarce and poorly known. This short report summarizes the available evidence and provides a framework to guide clinicians regarding a rational use of acetaminophen in children.

ABBREVIATIONS IV, intravenous

KEYWORDS analgesia; antipyretics; fever; infant; pain; paracetamol; pediatrics

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Introduction

Acetaminophen, or paracetamol, was first synthesized in 1878 but was not commercialized before the 1950s in Europe and North America.[1] Since then, it has become one of the most commonly used medications in neonates, infants, and children, recommended as a first-line therapy to treat pain and fever in these populations.[2–4] In the last 20 years, the approval of intravenous (IV) acetaminophen, first in Europe in 2002,[5] followed by the United States in 2011,[6] and more recently in Canada in 2019,[7] brought us to revisit the indications, advantages, and disadvantages of this old medication. This short report summarizes the available evidence regarding the different modes of administration of acetaminophen in children to guide clinicians with a rational choice of route of administration.

General Indications

Usage. Acetaminophen is indicated to treat pain and fever. Its exact mechanism of action remains to be determined, but its analgesic effect is believed to occur mainly through cyclooxygenase inhibition in the central nervous system, although the activation of serotoninergic pathways and inhibition of cannabinoid reuptake may also play a significant role.[8] Similarly, its antipyretic effect may be explained by the inhibition of cerebral prostaglandin production through cyclooxygenase inhibition.[9]

Regarding its role in pain management, acetaminophen is indicated for treating mild to moderate pain and for co-analgesia in severe pain. Together with ibuprofen, it is the most commonly used non-opioid analgesic to manage pain in children.[3] It has notably been shown to reduce pain scores in children following ear, nose, and throat surgeries and orthopedic surgeries,[10–13] and to help manage nonsurgical pain due to vaso-occlusive crisis in patients with sickle cell disease.[14] Acetaminophen use was associated with an opioid-sparing effect on numerous occasions, and therefore appears to be beneficial in combination with opioids for the treatment of moderate to severe pain.[10,11,15–20] Indeed, multimodal analgesia, where non-pharmacologic measures and smaller opioid doses are combined with non-opioids, such as acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, α_2-agonists, and *N*-methyl-D-aspartate antagonists, has become a widely accepted approach.[4,21–23] Optimizing multimodal analgesia is crucial in the face of the current opioid epidemic that is driven by multiple factors, including persistent opioid use after hospitalization.[24,25]

Acetaminophen is also indicated to treat fever.[26] However, few indications justify a strict temperature control. Indeed, fever is a physiologic response from the body under most circumstances and is not harmful in itself.[27] Nonetheless, acetaminophen may help relieve the discomfort associated with fever, although few data are available to support this frequently sought effect.[28–30] Strict temperature control does not prevent new episodes of febrile seizure in children with a history of febrile seizure.[31] However, a single randomized, controlled trial found that strict acetaminophen administration (10 mg/kg administered intrarectally every 6 hours) prevents the recurrence of seizures during the same febrile episode.[32] The antipyretic effect of acetaminophen may be beneficial in situations where fever may worsen the condition of critically ill children, such as after cardiac arrest,[33,34] intracranial

hypertension,[35] status epilepticus,[36–38] and junctional ectopic tachycardia.[39,40]

Efficacy and Safety. Although acetaminophen is generally accepted as a safe and effective medication, some questions arose during the last decade regarding its efficacy and safety. The opioid-sparing effect of acetaminophen has recently been questioned in adults.[41] In pediatrics, this effect was consistently found in children when using IV acetaminophen,[15,17,18] whereas studies on intrarectal and oral acetaminophen yielded conflicting results.[10,11,17,19,20,42–45] Different factors may explain those discordant results. First, the route of administration and its associated bioavailability may affect acetaminophen's effectiveness. Moreover, analgesia management is highly variable between studies, which may render the opioid-sparing effect of a single agent (namely acetaminophen) challenging to identify (e.g., various dosing of opioids and non-opioids, different pain scores, pharmacist-led, nurse-led vs physician-led analgesia). Noninvasive procedures, associated with less postoperative pain and faster recovery, are also increasingly preferred and reduce the total analgesic needs. Based on the available data in pediatrics, particularly the consistently demonstrated opioid-sparing properties of the IV route, we believe acetaminophen contributes to reducing opioid consumption in children, especially following invasive and painful procedures. However, more high-quality studies are needed to better characterize the most suitable route of administration and dosing for specific pediatric populations experiencing surgical and nonsurgical pain.

A recent systematic review and meta-analysis in children younger than 2 years showed better pain and fever control with ibuprofen compared with acetaminophen.[46] In a previous study, ibuprofen showed superior antipyretic effect vs acetaminophen, with similar analgesic effect,[47] Current data remain insufficient to consider ibuprofen superior, and both agents are first-line therapies in children ages >6 months with fever and pain, in line with the American Academy of Pediatrics recommendations.[48] Combining or alternating both therapies modestly improves fever control, but the benefits of such an approach in terms of comfort remain unproven.[49] Therefore, because of an increased risk of overdosing, most pediatric societies do not recommend this strategy.[50] Although the safety of both medications appears similar in a general outpatient population,[46] some conditions may contraindicate ibuprofen, such as dehydration, gastrointestinal bleeding, and high bleeding risk. Acetaminophen is also preferred in infants ages <6 months because ibuprofen use is off-label in this population and based on limited safety data.[50] Moreover, our understanding of the ontogeny of renal function dependence on prostaglandins during the first 6 months of life discourages ibuprofen (nonsteroidal anti-inflammatory drug) use in infants <6 months of corrected age.[51]

Acetaminophen overdosing may occur not only secondary to intentional, but also unintentional ingestions and dosing errors. Acetaminophen's relatively narrow therapeutic index implies that overdosing may lead to significant hepatocellular injury caused by the accumulation of *N*-acetyl-*p*-benzoquinone imine, a toxic metabolite.[52,53] Repeated or major dosing errors leading to hepatotoxicity may occur at home[54] but also in hospital settings and have recently been described following IV administration.[55] Despite staying within the recommended dosing range, chronic exposure to acetaminophen may contribute to the deterioration of an underlying liver injury and sometimes even be the primary cause of hepatic failure, particularly if associated with fasting, excessive alcohol consumption, and administration of concomitant antiseizure medications.[56–58] Acute liver failure secondary to chronic exposure leads to higher incidences of liver transplantation and mortality compared with single toxic exposure.[56,57] Unintentional overdose is particularly common in young children, whereas intentional overdose is more common in adolescents and adults. In a recent retrospective study, the most common causes of dosing errors in children were the inadvertent administration of the medication twice, dosing intervals that were too short, confusion in the units of measure, wrong formulation or concentration used, and dispensing cup errors.[59] Unintentional overdosing may also occur due to the coadministration of different products containing acetaminophen.[60] This is not a frequent cause in children younger than 6 years, representing less than 1% of the dosing errors,[59] but it may be more common in adolescents and adults for whom a wider variety of combined medication products are available.[61] To mitigate this risk, the US Food and Drug Administration and Health Canada limited the amount of acetaminophen in combined prescription drug products to 325 mg per dosing unit.[62,63] However, this limit does not apply to non-prescription medications in North America. Moreover, to avoid confusion and associated dosing errors, the United States removed its more concentrated infant formulation from the market, leaving a single available concentration for all oral liquid formulations labeled for use in children younger than 12 years.[64] Regulatory agencies' efforts to limit acetaminophen overdosing also include warning labels and public advisories.[62,65]

Acetaminophen was associated with hypotension following administration in adults[66–69] and children,[70–72] raising concerns about its innocuity. Hypotension occurs more frequently following IV acetaminophen compared to enteral administration[67] but may happen regardless of the administration route.[73,74] In children following cardiac surgery, hypotension followed 5% of the administered IV doses,[70] whereas 27% of the children with septic shock receiving acetaminophen required fluid boluses or increased inotropic support following IV administration to maintain adequate

Table. Acetaminophen Drug Products Available as Uncombined Products in the United States and Canada

United States	Canada
Oral route of administration	
Tablets (regular, extra strength): 325 mg, 500 mg	Tablets (regular, extra strength): 325 mg, 500 mg
Tablets, extended release: 650 mg	Tablets, extended release: 650 mg
Oral liquid (elixir, gel): 160 mg/5 mL (dye-free available)	Oral liquid (elixir, gel): 80 mg/mL, 160 mg/5 mL (dye-free available)
Chewable tablets: 80 mg, 160 mg, 325 mg	Chewable tablets: 80 mg, 160 mg, 325 mg
Dissolve packs (powder): 160 mg, 500 mg	Easy dissolve (powder): 160 mg
	Fast melts: 160 mg
Rectal route of administration	
Suppositories: 80 mg, 120 mg, 325 mg, 650 mg	Suppositories: 120 mg, 160 mg, 325 mg, 650 mg
Intravenous route of administration	
Solution; intravenous 10 mg/mL (1 g/100 mL and 500 mg/50 mL)	Solution; intravenous 10 mg/mL (1 g/100 mL)

blood pressure.[71] Acetaminophen-related hypotension has not been clearly associated with acetaminophen infusion rate, and its underlying mechanisms remain poorly understood.[75] Decreased systemic vascular resistance and, more rarely, cardiac output have been described.[69,76,77] A reduction in preload caused by the diuretic effect of mannitol, which is often included in the IV formulation, has been suggested as a potential explanation.[78] However, no association was found between hypotensive episodes and urine output in 28 adolescents following orthopedic surgery.[72] Another explanation relies on acetaminophen metabolites, which may activate potassium channels located in peripheral vessels and induce direct vasodilatation.[79] This potential mechanism could explain the occurrence of hypotension following both enteral and parenteral administration.

Administration Modes

Oral Administration. Oral acetaminophen is easy to administer and readily available for outpatient therapy. The usual recommended dose is 10 to 15 mg/kg given every 4 to 6 hours as needed, with a maximum recommended dose of 75 mg/kg/day not to exceed 4000 mg/day. The dosing interval should be longer in neonates, with suggested doses of 10 to 15 mg/kg given every 6 to 8 hours (maximum 60 mg/kg/day), not to exceed 40 mg/kg/day in preterm neonates less than 33 weeks of gestational age.[80] Available formulations, concentrations, and packaging vary by country. The Table summarizes the different available formulations in Canada and the United States. In neonates and infants, liquid formulations are favored for their ease of administration and precision of weight-based dosing. The inclusion of a measuring device also depends on the country's legislation. A wider range of options is available in older children, including chewable tablets, quick-dissolving powder, rapid-release capsules, and regular or long-lasting tablets (Table). Pediatric formulations of acetaminophen are available in a variety of fruit flavors, including cherry, grape, and berry. Despite their lower precision compared with precise weight-based dosing, solid formulations with fixed dosing are more convenient and preferred in older children because of the flavoring and large volumes required with liquid formulations.

Acetaminophen's pharmacokinetics is generally more predictable when given orally than rectally, although the interindividual variability is high with both formulations.[81] In adults, oral (tablets and solution) acetaminophen's bioavailability was shown to vary between 63% and 94%.[82–84] Few data are available in children, but a single study in critically ill children showed a bioavailability of 70% with significant interindividual variability (range, 11–91).[85] For the purpose of this study, enteral acetaminophen-containing radioactive carbon isotope was administered via a nasogastric tube concomitantly with a therapeutic IV dose. It has also been shown that concomitant morphine administration delays and reduces oral acetaminophen absorption in adults while not affecting the pharmacokinetics of IV acetaminophen.[86] This is presumably because of an opioid-induced decrease in gastrointestinal motility and delayed gastric emptying.

Rectal Administration. Rectal acetaminophen is relatively easy to administer and may be the only tolerated administration mode in young children with severe gastrointestinal disturbance in an outpatient setting. The usual recommended doses vary between 10 and 20 mg/kg/dose every 4 to 6 hours (max 75 mg/kg/day). In neonates ≥33 weeks of gestational age, 15 to 20 mg/kg/dose every 6 to 8 hours is recommended, with a preference for the 8-hour dosing interval in preterm neonates.[80] In neonates, if the weight-based dose cannot be given using a half or a whole suppository, the oral solution may be administered rectally, as suggested in previous studies[87,88] and routinely done in our institution in premature and low–

birth weight neonates without any reported adverse effects despite more than 30 years of use. The main disadvantage of the rectal route, in addition to the discomfort associated with its administration, is its erratic absorption. Acetaminophen absorption following rectal administration is slow and unpredictable, with a reported relative bioavailability compared with oral administration anywhere between 30% and 65%, which varied greatly between patients.[89–93] For this reason, single or first doses between 20 and 45 mg/kg have been suggested for perioperative pain management in infants and children when using the intrarectal route, followed by doses of 20 to 25 mg/kg/dose.[92,94] However, because of the high interindividual variability in absorption, caution should be applied, and prolonged repeated dosing may lead to hepatotoxicity. Indeed, repeated high doses may induce toxicity in the subset of patients with high absorption. On the contrary, even higher doses may fail to reach adequate concentrations and provide adequate comfort and pain control in the subset of patients with lower absorption.[92,95] Intrarectal administration should be avoided in cases of high bleeding risk (low platelet count), severe neutropenia (potential risk of bacterial translocation and secondary bloodstream infection), or anal lesion (e.g., early postoperative from an anal procedure). Alternative administration routes should be considered in those patients unresponsive or poorly responsive to rectal acetaminophen administration.

Intravenous Administration. Intravenous acetaminophen is generally used in hospitalized patients. In Canada and the United States, it is available as a 10 mg/mL solution in a ready-to-use vial or bag (Table). The approved dose is 15 mg/kg given every 6 hours, although some teams advise lower doses in neonates and infants younger than 2 years (range, 10–12.5 mg/kg) based on population pharmacokinetic studies.[96,97] According to the product monograph, patients weighing more than 50 kg can receive an entire 100-mL bag, which should be administered during 15 minutes. When doses do not match the ready-to-use bags, it is recommended to withdraw the dose to be administered in a separate container and discard the residual amount because the bags are labeled for single use. Centers might adopt a different cost-effective strategy as data supporting the stability of the product for up to 84 hours in a syringe are available.[98]

Unlike the oral and rectal routes, IV acetaminophen's pharmacokinetics is predictable and reliable. Its main disadvantages include safety concerns, with, as noted above, hypotensive episodes reported following administration, and higher cost compared with rectal or oral formulations. In a retrospective study including data from 49 pediatric hospitals, the total costs associated with acetaminophen use increased from USD $2.7 million to $18.1 million following the introduction of the IV formulation in the United States.[6,99] Although approved in Europe across the pediatric age spectrum, IV acetaminophen is officially approved in United States and Canada for the treatment of mild to severe pain only in children ages ≥2 years.[6,7] The lack of labeling could theoretically keep clinicians from using it in children younger than 2 years. However, this does not appear to be the case, and it is widely used as an off-label medication in this population across North America based on data supporting its use, efficacy, and safety in neonates and infants.[100,101]

Comparison of Different Administration Modes. Few studies compare acetaminophen's different administration modes in children. Studies focusing on oral vs rectal administration showed conflicting results. A randomized controlled study compared the analgesic efficacy and plasma concentrations between oral (elixir) and rectal (suppository) acetaminophen (both given as 20 mg/kg every 6 hours) in 40 children ages 3 months to 3 years following craniosynostosis surgery.[42] The authors concluded that rectal acetaminophen led to better analgesia and higher plasma concentrations (compared using the area under the curve), although the differences in both comfort and exposure (area under the curve) were not significant when removing patients who vomited shortly after oral administration. Another randomized controlled trial in 100 children ages 3 to 15 years undergoing tonsillectomy showed lower pain scores and higher plasma concentrations following singles doses of oral acetaminophen (elixir; 40 mg/kg) compared with rectal administration (suppositories; 40 mg/kg).[102] Regarding temperature control, oral and rectal acetaminophen were found to have similar efficacies in reducing fever.[103]

Only 1 study compared IV and oral acetaminophen analgesic effect in 45 children following a primary cleft palate repair.[17] This randomized, controlled study showed that IV acetaminophen (12.5 mg/kg every 6 hours) was associated with better pain control and provided a more significant opioid-sparing effect when compared to the oral formulation (suspension; 15 mg/kg every 6 hours). This may be explained by reduced bioavailability in young postoperative children using the oral formulation, although no drug concentration or pharmacokinetic data were obtained to confirm this hypothesis. Regarding acetaminophen's antipyretic effect, a single study in children with high fever (>103°F [39.4°C]) showed that IV acetaminophen (single dose of 15 mg/kg) decreased body temperature more quickly than oral acetaminophen (single dose of 15 mg/kg), but no difference was observed 4 hours following administration.[104] The pharmacokinetic profiles of the respective formulations probably explain this. Indeed, IV administration has a higher bioavailability and leads to a more rapid increase in concentrations and higher maximal plasma concentration, explaining the quicker decrease in body temperature, whereas oral administration leads to lower exposure, a slower rise

in concentrations, and a lower maximal concentration.

The analgesia provided by IV acetaminophen did not show any clear benefit compared with rectal administration in children following adenoidectomy, and rectal acetaminophen provided analgesia lasting for a slightly longer period of time.[105–107] However, in children following craniofacial surgery, lower pain scores were observed and fewer rescue medications were needed in children receiving IV vs rectal acetaminophen.[89] The delayed rectal absorption may explain the longer-lasting effect after intrarectal administration. However, if therapeutic concentrations are not achieved in the subset of patients with low rectal absorption, intrarectal administration may be less effective than IV administration.

Our Approach to Acetaminophen Routes of Administration: Who, Why, and Which

Context. In Canada, the daily cost of the injectable solution is approximately 10-fold higher than for the oral products (e.g., in a 20-kg child, CAD $4.50 vs $0.42, respectively). To avoid excessive hospital costs, it is imperative to carefully determine the precise indications and populations for which IV acetaminophen is most beneficial. Our institutional group focusing on optimizing analgesics use (in French, Comité de Gouvernance des Analgésiques) provided the following recommendations, which are currently applied in our center.

Oral. For its ease of administration, effectiveness, and low cost, we believe that oral acetaminophen should be the preferred administration mode in most instances.

Rectal. Because of its low and variable bioavailability, and therefore unpredictable effectiveness, rectal use should be limited to patients unable to tolerate oral intake and for whom IV acetaminophen is not indicated. Rectal acetaminophen should mostly be used for mild pain not requiring opioids. Rectal acetaminophen may also be indicated for fever control in all common pediatric conditions to improve comfort. Contrary to common beliefs, no temperature threshold justifies fever reduction in most instances,[108] and comfort is the main indication for temperature control. Alternative administration routes should be considered in patients unresponsive or poorly responsive to rectal acetaminophen administration. Outside of research purposes, we do not recommend routine serum concentration monitoring (therapeutic drug monitoring). However, serum concentrations should be assessed if acetaminophen toxicity is suspected. Rectal administration should be avoided in cases of high bleeding risk, severe neutropenia, or anal lesion.

Intravenous. After conducting an extensive literature review, our institutional group better defined IV acetaminophen's indications to include 1) moderate to severe surgical or nonsurgical (e.g., significant trauma, mucositis, and severe mucosal involvement caused by a dermatologic disorder, such as Stevens-Johnson syndrome) pain where oral administration is difficult and/or enteral absorption may be compromised and given in addition to opioids, and 2) specific critical situations where strict temperature control may be beneficial (e.g., status epilepticus, intracranial hypertension, post–cardiac arrest care, junctional ectopic tachycardia, and septic shock). The decision to include major surgeries when the enteral route is available was motivated by the frequent occurrence of postoperative nausea and vomiting that interfere with oral administration and the predictable pharmacokinetics and complete bioavailability of the IV route that may improve control of severe pain. Moreover, the opioid-sparing effect may be greater with IV acetaminophen than with oral and rectal administration.[16]

For fever, IV acetaminophen is only indicated in the rare occurrences where strict temperature control may be beneficial. This applies to situations of hemodynamic instability where limiting the oxygen demand, which is increased by fever, may be beneficial (e.g., traumatic brain injury, refractory status epilepticus, refractory septic shock, refractory pulmonary hypertension).

With cost reduction in mind, the indications justifying IV acetaminophen should be revisited frequently. Transition to enteral acetaminophen should be attempted as soon as pain scores decrease, enteral intakes are tolerated, and hemodynamic stability is achieved. Close monitoring should be pursued when administering IV acetaminophen to critically ill children given the potential for hypotension.

Conclusion

Acetaminophen is effective in treating pain and fever in children. Oral and rectal acetaminophen are generally well tolerated when staying within the recommended dosing range, whereas IV acetaminophen may cause hypotension in critically ill patients. In most instances, oral acetaminophen is the preferred administration route. Rectal administration should be reserved for children unable to tolerate the oral route. Intravenous acetaminophen is restricted to inpatient care to manage moderate to severe pain or for strict temperature control in critical situations when oral absorption may be compromised.

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