Intravenous Acetaminophen

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Acetaminophen was first used clinically in 1887 but only much later—during the mid-1950s—was it widely marketed in the United States. It has since gone on to become one of the mostly widely used and safest antipyretic and analgesic drugs available. Acetaminophen has a high therapeutic index (approximately 10), indicative of its efficacy-to-safety ratio and a long and respected legacy as a safe and effective choice for treating pain and fever in a wide range of patient types. This is particularly true in the hospital setting, where it may be successfully combined with other analgesics to manage postoperative pain.

Acetaminophen is a synthetic, nonopiate, centrally acting analgesic and antipyretic derived from p-aminophenol. It has not been shown to affect platelet function, increase surgical bleeding, or affect kidney function and is, therefore, appropriate for use at any time during the perioperative period. The opioid-sparing qualities of acetaminophen have been recognized, and these properties may lead to acetaminophen being incorporated effectively as an adjunct therapy. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen has no substantial peripheral anti-inflammatory activity.

Despite more than a century of study, the mechanism of action of acetaminophen is not definitively known, although it is believed that part of its analgesic action may be associated with centrally acting cyclooxygenase (COX) inhibition with weak peripheral effects. This central action could explain the antipyretic effect of acetaminophen, and the minimal peripheral effects could be responsible for the lack of gastric irritation and clotting abnormalities often associated with NSAIDs. Owing to its efficacy, safety, and lack of the side effects associated with other analgesics, acetaminophen has been considered a fundamental component of the multimodal analgesic approach to which NSAIDs and other drugs are added. Moreover,
Acetaminophen has been formally recommended for first-line use as one of the possible components of multimodal analgesic regimens for postoperative pain management by the American Society of Anesthesiologists.\textsuperscript{10}

In the postoperative period, effective acute pain control is essential for optimal recovery and patient satisfaction. Nonetheless, management of postoperative pain remains suboptimal—in one survey, approximately 80% of patients reported moderate to acute pain after surgery,\textsuperscript{11} and other reports indicate that approximately 50% of patients experience uncontrolled pain.\textsuperscript{12} Postsurgical pain is associated with more than patient discomfort; it is also the most common cause of unanticipated readmissions for same-day surgery.\textsuperscript{12} The need to address postoperative pain complications is compounded by the increasing number of surgical procedures performed in the United States. In 2006 alone, 46 million inpatient procedures were reported.\textsuperscript{13}

Adequate postoperative pain control provides advantages to patients beyond immediate clinical benefits, such as increased satisfaction and improved sleep. Recovery may be more rapid, resulting in less time in the postanesthesia care unit; shorter hospital stays; less need for rehabilitative services; lower risks of postoperative complications, such as the development of long-term or chronic pain conditions,\textsuperscript{12} which may be associated with acute postoperative pain\textsuperscript{14}; fewer neuroendocrine side effects of injury; and a lower risk of deep vein thrombosis and pulmonary effects.\textsuperscript{15}

Acetaminophen is commonly available in oral and suppository formulations, which are not always appropriate for perioperative use. The recent clinical development of an intravenous (IV) formulation for use in the United States may have important implications for the perioperative management of pain, because IV delivery allows for administration of analgesics for pre-emptive management of pain. IV administration of analgesics is the preferred route in the immediate postoperative period, especially in situations where a patient is unable to take medications by mouth (eg, nothing by mouth status, severe nausea, odynophagia, or dysphagia), when a faster onset of analgesia is desired, or when it may be prudent to attenuate postoperative pain as early and effectively as possible, before the onset of acute pain.\textsuperscript{16} IV acetaminophen supports this need for rapid analgesia, in part because patients do not have to be fully recovered from general anesthesia before receiving the medication, permitting the initiation of effective analgesic therapy in the early phase of the postoperative period.\textsuperscript{16–18}

Recent evidence-based developments in postoperative pain management have focused on balancing effective analgesia with patient safety by optimizing analgesic delivery and refining multimodal analgesia techniques. The conceptual framework of multimodal analgesia was introduced approximately 2 decades ago as a method for improving pain control and reducing the incidence of opioid-related adverse events.\textsuperscript{19,20} One multimodal strategy for the management of postoperative pain is represented in a stepwise structure (Fig. 1).\textsuperscript{21} The rationale for this strategy is based on the known additive or synergistic effects between different classes of analgesics, which allow a reduction in any one individual drug dose, thus potentially lowering the incidence of that medication’s adverse effects. Several studies have described the clinically significant beneficial effects of multimodal analgesia on pain control and the recovery process.\textsuperscript{19} The reduced incidence of adverse effects and improved pain control demonstrated with multimodal analgesia techniques may result in shorter hospitalization times, improved recovery and function, and decreased health care costs.\textsuperscript{22}

IV acetaminophen has been approved for the treatment of acute pain and fever in approximately 80 countries outside of the United States since its approval in 2001,
as reported in mid-2009; more than 437 million doses had been distributed in Europe. As development of IV acetaminophen continues in the United States, it is intriguing to explore how such a formulation may have an impact on the current state of postoperative analgesia. IV administration of acetaminophen may provide rapid and predictable analgesia that can be subsequently maintained by oral delivery. IV administration may also result in a more rapid onset of analgesia with more predictable pharmacokinetics than the oral or rectal formulations. Speed of onset compared with the oral route may at times be especially important. The advantages afforded by IV acetaminophen may result in its assuming a key role in multimodal pain management, because it has been found safe to use along with other drugs and has few clinically significant drug interactions.

**PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES**

IV delivery of acetaminophen results in rapid and high plasma concentrations and a clinical analgesic effect that occurs within 5 minutes of administration. IV acetaminophen has been shown to achieve higher maximum concentration ($C_{\text{max}}$) and earlier time to maximum concentration ($T_{\text{max}}$) than bioequivalent oral or rectal formulations with less intrasubject variability. The standard dose used in US adult clinical trials was 1 g, infused over 15 minutes, every 4 to 6 hours to a daily maximum of 4 g. The mean $C_{\text{max}}$ after a standard 15-minute infusion has been reported to be 29.9 mg/L, which is approximately 70% higher than the mean $C_{\text{max}}$ observed at an equivalent oral dose. The higher $C_{\text{max}}$ with IV acetaminophen does not seem to
compromise the safety profile or the production of glutathione conjugates compared with oral acetaminophen, because the C$_{\text{max}}$ at this dose remains far below the 150 mg/L concentration considered the threshold for potential hepatotoxicity.31 The median time to reach T$_{\text{max}}$ for IV acetaminophen, which occurs at the end of the 15-minute infusion,30 is much faster than typically reported for oral or rectal formulations (>45 minutes).1

With respect to its analgesic and antipyretic effects, acetaminophen’s pharmacodynamic effect seems to correlate well with cerebrospinal fluid (CSF) levels. Acetaminophen readily penetrates an intact blood-brain barrier, and acetaminophen concentrations in the CSF are linearly dose proportional, with plasma levels after IV doses of 500 mg to 2000 mg.32 In children and adults, acetaminophen is detectable in the CSF within minutes after IV administration (studies evaluated both IV acetaminophen and IV propacetamol, the prodrug to acetaminophen, which required reconstitution before administration and resulted in frequent injection-site pain reactions, leading to its replacement by the ready-to-use and better tolerated IV acetaminophen).33,34 The rapid CSF penetration and earlier and higher C$_{\text{max}}$ observed with IV acetaminophen seem responsible for its more rapid onset of action and peak efficacy compared with oral or rectal acetaminophen.35

Acetaminophen metabolism is well characterized and is not dependent on route of administration. Acetaminophen is metabolized by the liver via three pathways: glucuronidation (approximately 85%), sulfation, and oxidation.36 The oxidation pathway produces N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive intermediate, primarily by cytochrome P450 isoenzyme, CYP2E1.37 NAPQI conjugation with intracellular glutathione results in products excreted in the urine as thiol metabolites.36,37 NAPQI may cause hepatotoxicity if glutathione stores are depleted, most commonly after a massive, acute acetaminophen overdose.

Regardless of route of delivery, the terminal elimination half-life of acetaminophen is approximately 2 to 4 hours in children, adolescents, and adults. It is slightly longer in infants and neonates and is longer still in premature neonates.1 Compared across age groups, pharmacokinetic (PK) parameter estimates for IV acetaminophen were similar in children, adolescents, and adults, when normalized for body weight.38 Acetaminophen clearance in adults averaged 0.27 L/h/kg and 0.28 and 0.33 L/h/kg in children and adolescents, respectively.38 Maturational effects in acetaminophen metabolism in neonates and infants are well characterized and have demonstrated a limited ability to metabolize acetaminophen via glucuronide.39 Neonates and infants, therefore, predominantly metabolize acetaminophen via the sulfation pathway, which may help explain reduced clearance.39,40 This maturational effect may result in less production and accumulation of NAPQI and, consequently, a decreased susceptibility to acetaminophen hepatotoxicity in infants and children.41

PK considerations indicate that oral doses of acetaminophen are likely to expose the liver to maximal amounts of acetaminophen, due to its near complete absorption in the proximal small intestine, delivery into the portal vein, and first-pass metabolism. Conversely, IV dosing is expected to expose the liver to less acetaminophen, because the dose is distributed in the systemic circulation before being delivered to the liver via the hepatic artery. First-pass PK models have shown that the IV route of administration reduced initial hepatic acetaminophen exposure by approximately 2-fold as compared with the oral route.42 Thus, the lack of a first-pass effect with IV acetaminophen administration may result in reduced hepatic acetaminophen exposure and an improved safety profile compared with equivalent doses of oral acetaminophen.
CLINICAL EFFICACY IN ADULTS: POSTOPERATIVE PAIN

Many randomized and controlled studies have been conducted outside of the United States demonstrating the efficacy and safety of IV acetaminophen. These studies have been reviewed in great detail by Duggan and Scott and Malaise and colleagues. More recently, and in anticipation of its availability in the United States, the results of several US clinical trials with IV acetaminophen have been completed with favorable results. Although the results of these studies have yet to be formally presented and are pending publication, they have essentially confirmed the favorable findings of the European experience with IV acetaminophen for the treatment of acute pain and fever.

US Studies: Acute Pain After Total Hip or Knee Arthroplasty

The primary evidence for efficacy and safety for IV acetaminophen in the treatment of moderate to severe pain in adults has been found in patients undergoing major orthopedic surgery. Sinatra and colleagues conducted a randomized, double-blind, placebo- and active-controlled, single- and repeated-dose, 24-hour study at nine study centers in the United States. The primary objective of the study was to compare the analgesic efficacy and safety of a single and repeated (every 6 hours) doses of IV acetaminophen (1000 mg) to placebo in the treatment of adults with moderate to severe postoperative pain after total hip or knee replacement. Pain intensity (PI) was measured on a four-point verbal PI categorical scale and a four-point visual analog scale (VAS). The study included 101 patients, 49 in the IV acetaminophen group and 52 in the placebo group (an additional 50 patients were included in a propacetamol comparator arm).

Statistically significant differences favoring IV acetaminophen compared with placebo were observed for pain relief at 15 and 30 minutes ($P$.05) and from 45 minutes to 6 hours ($P$.001). Statistically significant differences favoring IV acetaminophen compared with placebo were also observed for the mean sum of PI differences from 15 minutes through 6 hours ($P$.05).

Patients who received IV acetaminophen and required rescue analgesia had a significantly longer elapsed time to first-rescue medication and a significantly lower dose of medication (patient-controlled analgesia [PCA] morphine) over the first 6 hours. The median time to first rescue medication was 3 hours for those receiving IV acetaminophen and 0.8 hours for those in the placebo group ($P$.001). Mean ($\pm$SD) patient-controlled analgesia (PCA morphine) consumption through 6 hours after the first dose of study medication was significantly lower for the IV acetaminophen group (9.7 $\pm$ 10.0 mg) than for the placebo group (17.8 $\pm$ 16.7 mg, $P$.01), representing a 46% reduction in opioid consumption during the first 6 hours with IV acetaminophen. This trend was maintained over the 24 hours of evaluation (representing doses of study medication administered every 6 hours): mean ($\pm$SD) PCA morphine consumption was lower in the IV acetaminophen group (38.3 $\pm$ 35.1 mg) than in the placebo group (57.4 $\pm$ 52.3 mg), representing a 33% reduction in opioid consumption.

Patients’ global satisfaction at 24 hours was significantly higher in the IV acetaminophen group than in the placebo group ($P$.01). Fair to excellent ratings were reported by 39 (80%) of 49 patients in the IV acetaminophen group compared with 34 (65%) of 52 placebo patients.

US Studies: Acute Pain After Abdominal Laparoscopic Surgery

A second randomized, double-blind, placebo-controlled, multicenter, acute pain efficacy and safety study was conducted at 17 US sites in adults undergoing abdominal laparoscopic surgery. A total of 244 patients experiencing moderate to
acute postsurgical pain (measured by a 4-point PI categorical scale and a VAS score ≥40 mm and ≤70 mm at rest on a 100-mm scale) were randomized to receive IV acetaminophen (1000 mg every 6 hours or 650 mg every 4 hours or matched placebo over 24 hours).45

For weighted sum of PI score differences using VAS 100 mm over 24 hours and weighted sum of PI scores using VAS 100 mm over 24 hours, IV acetaminophen (1000 mg) was significantly better than the combined placebo group at reducing pain (P = .0068). Statistically significant differences in weighted sum of pain relief scores and subject global evaluation scores favoring IV acetaminophen (1000 mg) over the combined placebo group (P = .0006 and P = .0004, respectively) were also reported. Time to meaningful pain relief after the first dose was significantly shorter in subjects who received IV acetaminophen (1000 mg) (<25 minutes) compared with subjects in the combined placebo group (P = .0028). The time to rescue medication and amount of rescue medication consumption favored IV acetaminophen but did not achieve statistical significance. Of all patients in both study arms, 40% to 50% required no rescue medication during the 24-hour treatment period, and this may have contributed to a reduced chance of demonstrating statistical significance. Results with the 650-mg dose were consistent with the 1000-mg dose; however, not all comparisons to placebo reached statistical significance.45

The preliminary summary results of these two multicenter US postoperative pain studies reveal the rapid and sustained pain relief provided by IV acetaminophen after surgical procedures and are significant additions to the already large body of clinical studies performed with IV acetaminophen. Single- and repeated-dose IV acetaminophen efficacy has been well documented in a variety of postoperative settings and patient populations across PI scores from mild to severe pain for periods up to 72 hours. A comprehensive list of published IV acetaminophen studies conducted in adults can be found in Table 1. In summary, these studies demonstrate the efficacy of IV acetaminophen across a broad range of pain types and intensities. In many studies, the onset of analgesic action for IV acetaminophen has been documented to occur just before or at the end of the 15-minute infusion. The peak effect as measured by PI or pain relief (PR) endpoints for the IV acetaminophen comparison with placebo has been shown in multiple studies not only statistically significant but also clinically meaningful. The opioid-sparing effect of IV acetaminophen remains somewhat controversial, however. Some, but not all, studies show a statistically significant reduction in opioid consumption. Certain studies have even shown that a substantial percentage of patients have been able to avoid the need for opioid rescue altogether.

The efficacy and safety of IV acetaminophen has also been shown in other unpublished but completed double-blind, placebo-controlled studies in a variety of postoperative pain models, including total hip arthroplasty76,77 and vaginal hysterectomy.78 In addition to demonstrating clinically relevant pain relief, reductions in opioid usage of up to 64% were observed in the IV acetaminophen groups compared with the placebo groups.76–78 In those patients requiring rescue treatment, IV acetaminophen patients typically demonstrated a prolonged time to administration of such rescue.

**CLINICAL EFFICACY IN ADULTS: FEVER**

In addition to the treatment of acute pain, the possible usefulness of a parenteral antipyretic for the urgent treatment of fever/hyperthermia in patients who are unable to receive oral or rectally administered acetaminophen (eg, nothing by mouth status, immunocompromised patients, or immobilized patients) has also been examined.
The efficacy of IV acetaminophen (1000 mg) in the treatment of fever was evaluated in two randomized studies in 141 healthy adult men, 76 of whom received IV acetaminophen: a placebo-controlled trial and a second active-controlled trial versus oral acetaminophen (1000 mg). Both trials evaluated the safety and efficacy of a single dose of IV acetaminophen in the treatment of fever induced by reference standard endotoxin.

A single dose of IV acetaminophen (1000 mg) had a superior and sustained antipyretic effect compared with placebo in blunting endotoxin-induced fever over a 6-hour study period (weighted sum of temperature differences over 6 hours, \( P < .0001 \)). The onset of the antipyretic effect was rapid, with a statistically significant difference from placebo detected by 30 minutes \( (P = .0085) \), 15 minutes after the end of the IV acetaminophen infusion. The durability of the treatment effect with IV acetaminophen was demonstrated by a substantially lower mean temperature compared with placebo at each time point from 30 minutes to 5.5 hours.

When compared with an equivalent dose of oral acetaminophen, a single dose of IV acetaminophen (1000 mg) demonstrated a faster onset of temperature reduction, with a more pronounced blunting of the reference standard endotoxin–induced fever during the first 2 hours compared with oral acetaminophen (1000 mg) (weighted sum of temperature differences over 2 hours, \( P = .0039 \)). The onset of the antipyretic effect was rapid, with a statistically significant difference from oral acetaminophen detected by 30 minutes, 15 minutes after the end of the IV acetaminophen infusion \( (P = .0202) \). For an hour afterwards, statistically significant reductions in mean temperature in favor of the IV acetaminophen group compared with the oral acetaminophen group were observed.

The antipyretic effect of IV acetaminophen in these two fever studies demonstrates that 1000 mg produces a rapid temperature-reducing effect that begins approximately 15 minutes after completion of the infusion, peaks at approximately 1 hour and may last for up to 6 hours. In addition, the results of several published studies with oral acetaminophen support the antipyretic efficacy of doses ranging from 500 to 1000 mg in fever of infectious origin and in endotoxin-induced fever.

**CLINICAL EFFICACY IN PEDIATRIC PATIENTS: POSTOPERATIVE PAIN AND FEVER**

Acetaminophen has a long history of safe and effective clinical use and is the first-line choice for the treatment of pain and fever in pediatric patients. Despite this, oral delivery may not represent an ideal route of administration, especially in an inpatient setting. Rectally administered acetaminophen has been routinely used in its place, but absorption via this route may be slow and erratic, which may produce subtherapeutic plasma levels or expose neonates and infants to potentially toxic levels of the product. Because of the delayed absorption, using higher doses has been suggested when administering acetaminophen by the rectal route in children as well as adults. Higher rectal doses (45 mg/kg), however, may expose some children to the potential risk of drug accumulation and possible toxicity.

European studies on IV formulations of acetaminophen have characterized its PK profile and shown its safety in a wide range of pediatric patients. A summary of published studies of IV acetaminophen in pediatric patients can be found in Table 2. Despite the strict and ethical limitations of pediatric clinical studies, two recent reports highlight the usefulness of IV acetaminophen for the management of acute pain and fever in this population.

Evidence of efficacy and safety of IV acetaminophen in the treatment of acute pain in pediatric subjects has been investigated for patients undergoing unilateral inguinal...
Table 1
Published randomized controlled trials supporting the efficacy and safety of IV acetaminophen in adults

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<tr>
<th>Author (Year)</th>
<th>Pain Model Studied</th>
<th>Comparator/Control</th>
<th>Study Medication Regimen</th>
<th>Total No. of Subjects (Completers/Group)</th>
<th>Study Summary</th>
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<tr>
<td>Alhashemi, 2006&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Cesarean section</td>
<td>Oral ibuprofen</td>
<td>IV APAP 1000 mg/PO placebo vs PO ibuprofen 400 mg/IV placebo q6h × 48 h</td>
<td>N = 45, IV APAP: 22, PO ibuprofen: 23</td>
<td>IV APAP provided comparable analgesia to PO ibuprofen</td>
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<td>Api, 2009&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Fractional curettage</td>
<td>Placebo</td>
<td>IV APAP 1000 mg vs placebo, single dose</td>
<td>N = 70, IV APAP: 36, Placebo: 34</td>
<td>No significant differences noted in pain response; however, all patients had mild to moderate pain (&lt;4 on 10-pt VAS)</td>
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<tr>
<td>Arici, 2009&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Total abdominal hysterectomy</td>
<td>Placebo</td>
<td>IV APAP 1000 mg before Ind or before EOS vs placebo, single dose</td>
<td>N = 90, IV APAP Ind: 30, IV APAP EOS: 30, Placebo: 30</td>
<td>Pain response and morphine consumption were significantly better for IV APAP than for placebo; placebo group had significantly greater incidence of nausea, vomiting and pruritus; and significantly longer hospital stays</td>
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<tr>
<td>Atef, 2008&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Tonsillectomy</td>
<td>Placebo</td>
<td>IV APAP 1000 mg vs placebo q6h × 24 h</td>
<td>N = 76, IV APAP: 38, Placebo: 38</td>
<td>100% of Patients in the placebo group required rescue analgesia over 24 h vs 29% in the IV APAP group</td>
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<td>Study, Year</td>
<td>Procedure(s)</td>
<td>Treatment(s)</td>
<td>Intervention</td>
<td>N</td>
<td>Outcome</td>
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<td>Bektas, 2009&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Renal colic</td>
<td>Morphine and placebo</td>
<td>IV APAP 1000 mg vs IV morphine 0.1 mg/kg vs placebo, single dose</td>
<td>N = 146</td>
<td>IV APAP: 46 IV morphine: 49 Placebo: 51</td>
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<tr>
<td>Cakan, 2008&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Lumbar laminectomy/discectomy</td>
<td>Placebo</td>
<td>IV APAP 1000 mg vs placebo q6h × 24 h</td>
<td>N = 40</td>
<td>IV APAP: 20 Placebo: 20</td>
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<td>Canbay, 2008&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Propofol injection pain</td>
<td>IV lidocaine and placebo</td>
<td>IV APAP 50 mg or IV lidocaine 40 mg in saline vs placebo, single dose</td>
<td>N = 150</td>
<td>IV APAP: 50 Lidocaine: 50 Placebo: 50</td>
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<tr>
<td>Cattabriga, 2007&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Cardiac surgery</td>
<td>Placebo</td>
<td>IV APAP 1000 mg vs placebo q6h × 72 h</td>
<td>N = 113</td>
<td>IV APAP: 56 Placebo: 57</td>
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IV APAP produced comparable pain relief to IV morphine and significantly better pain relief than placebo.

Pl was significantly higher in the placebo group at 12, 18, and 24 h than in the IV APAP group; no significant differences in morphine consumption; reduced vomiting in the IV APAP group.

Incidence of pain on injection of propofol with IV APAP (22%) and IV lidocaine (8%) was significantly better than with placebo (64%).

At 12, 18, and 24 h after surgery, the IV APAP group had significantly less pain at rest than the placebo group; cumulative morphine consumption was ~50% less with IV APAP (not statistically significant).

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<tr>
<th>Author (Year)</th>
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<tr>
<td>Celik, 2009</td>
<td>Hand surgery with IVRA</td>
<td>IVRA lidocaine and placebo</td>
<td>IV APAP 200 mg in the IVRA vs IV APAP 200 mg IV (in nonoperative arm) vs placebo, single dose</td>
<td>N = 90</td>
<td>IV APRA/IV APAP: 30 IV APAP: 30 Placebo: 30</td>
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<td>IV APAP added to the IVRA produced superior pain relief and significantly reduced morphine consumption compared with placebo or IV APAP infusion in the nonoperative arm</td>
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<td>Evron, 2008</td>
<td>Spontaneous labor</td>
<td>CE vs CE + IV PCA remifentanil vs CE + IV APAP vs IV PCA remifentanil alone</td>
<td>CE with 0.2% ropivacaine vs CE + IV remifentanil vs CE + IV APAP 1 g vs CE alone: 50 Remifentanil alone: 44</td>
<td>N = 192</td>
<td>IV APAP reduced the temperature compared with the other groups; the pain scores were comparable across the groups</td>
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<tr>
<td>Grundmann, 2006</td>
<td>Lumbar microdiscectomy</td>
<td>IV parecoxib, IV metamizol, and placebo</td>
<td>IV APAP 1000 mg vs IV parecoxib 40 mg vs IV metamizol 1000 mg vs placebo, single dose</td>
<td>N = 80</td>
<td>IV APAP was comparable to IV parecoxib in terms of pain response</td>
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<td>Holmér Pettersson, 2005</td>
<td>CABG/cardiopulmonary bypass</td>
<td>Oral acetaminophen</td>
<td>IV APAP 1000 mg vs oral acetaminophen 1000 mg q6h × 24 h</td>
<td>N = 77</td>
<td>IV APAP produced comparable pain relief to oral, but significantly reduced consumption of rescue medication</td>
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<tr>
<td>Study</td>
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<td>Dosage</td>
<td>Outcome</td>
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<tr>
<td>Holmér Pettersson, 2006&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Cardiac surgery</td>
<td>IV APAP 1000 mg vs rectal acetaminophen 1000 mg q6h × 24 h</td>
<td>Plasma APAP peaked within 40 min of IV administration but after rectal administration</td>
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<tr>
<td>Hong, 2010&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Thyroidectomy</td>
<td>IV APAP 1000 mg vs placebo, single dose, before surgery and q6h × 24 h after surgery</td>
<td>IV APAP patients had significantly lower pain scores over at 1, 3, 6, and 24 h after surgery; significantly fewer required rescue medication; and significantly reduced incidence of nausea and vomiting</td>
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<tr>
<td>Juhl, 2006&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Oral surgery: third molar surgery</td>
<td>IV APAP 1000 mg vs IV APAP 2000 mg vs placebo, single dose</td>
<td>IV APAP 1000 mg produced increased magnitude of pain relief and duration of analgesia effect vs placebo; IV APAP 2000 mg was associated with better and longer pain relief; there were no significant safety differences among the 3 groups</td>
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<td>Jokela, 2010&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Laparoscopic hysterectomy</td>
<td>Placebo, IV APAP + OND</td>
<td>IV APAP 1000 mg vs placebo at the induction of anesthesia and then 6 h × 24 h; in patients who received IV APAP, OND 4 mg or placebo 1 × at end of surgery</td>
<td>( N = 120 )</td>
<td>IV APAP reduces opioid consumption vs placebo; OND (a 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonist) does not block IV APAP analgesia</td>
</tr>
<tr>
<td>Kampe, 2006&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Breast cancer surgery</td>
<td>IV metamizol</td>
<td>IV APAP 1000 mg vs IV metamizol 1000 mg q6h × 24 h</td>
<td>( N = 40 )</td>
<td>IV APAP provided clinically equivalent pain relief to IV metamizol</td>
</tr>
<tr>
<td>Kemppainen, 2006&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Endoscopic sinus surgery</td>
<td>Placebo</td>
<td>IV APAP 1000 mg vs placebo, single dose</td>
<td>( N = 74 )</td>
<td>Significantly fewer patients in the IV APAP group (25%) required rescue medication than in the placebo group (71%); patients in this group had a significantly longer time to rescue medication (126 min vs 70 min with placebo)</td>
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<tr>
<td>Khan, 2007&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Knee arthroscopy</td>
<td>IV morphine</td>
<td>IV APAP 1000 mg vs IV morphine 0.1 mg/kg as a bolus, single dose</td>
<td>( N = 84 )</td>
<td>IV APAP produced comparable pain relief to IV morphine 0.1 mg/kg with lower incidence of nausea, vomiting, and dizziness</td>
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<tr>
<td>Study, Year</td>
<td>Procedure/Condition</td>
<td>drugs and dosages</td>
<td>comparators and doses</td>
<td>N</td>
<td>findings</td>
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<td>Ko, 2010&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Hand or forearm surgery with IVRA</td>
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<td>IV APAP 300 mg vs IV ketorolac 10 mg vs placebo</td>
<td>N = 60</td>
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<td>Total hip arthroplasty or surgery of the femoral shaft</td>
<td>IV parecoxib and placebo</td>
<td>IV APAP 1000 mg q6h or parecoxib 40 mg q12h vs placebo × 72 h</td>
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<td>Korkmaz Dilmen, 2010&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Lumbar disc surgery</td>
<td>IV metamizol, IV lornoxicam, and placebo</td>
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<td>N = 77</td>
<td>IV APAP: 20 IV metamizol: 18 IV lornoxicam: 20 Placebo: 19 IV APAP and metamizol significantly reduced pain vs placebo; the rate of morphine consumption with IV APAP decreased significantly over 24 h; total opioid consumption over 24 h did not differ between groups</td>
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<td>N = 60</td>
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<td>Sinatra, 2005</td>
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<td>Tasmacioglu, 2009</td>
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<td>Tiippana, 2008</td>
<td>Laparoscopic cholecystectomy</td>
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<td>IV APAP followed by PO APAP was as effective for pain as IV parecoxib/PO valdecoxib; IV/PO APAP significantly reduced rescue medication consumption on day 1 compared with IV/PO coxibs</td>
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**Abbreviations:** APAP, acetaminophen; CE, continuous epidural; EOS, end of surgery; IM, intramuscular; Ind, induction; IVRA regional anesthetic; OND, ondansetron; PO, oral.
hernia repair. Murat and colleagues98 conducted a randomized, active-controlled, double-blind, parallel group, multicenter study in 183 children ranging in age from 1 to 12 years. Patients were randomized 1:1 to receive either a single dose of IV acetaminophen (15 mg/kg) or a bioequivalent dose of IV propacetamol (30 mg/kg) when their postoperative PI as rated by the investigator was greater than 30 on a 0- to 100-mm VAS. Both treatments rapidly reduced pain scores, with a steep reduction from baseline PI during the first 15-minute interval after infusion. The duration of analgesia, measured as the time to first rescue, was more than 4 hours for both groups. Similarly, only approximately 20% of the patients in both groups required rescue medication, and global evaluations of “excellent” were reported for 76% of patients receiving IV acetaminophen.

Evidence for the efficacy of IV acetaminophen in the treatment of fever of infectious origin has been investigated in 67 children ranging in age from 1 month to 12 years.96 Patients were randomized to receive IV acetaminophen (15 mg/kg) or a bioequivalent dose of IV propacetamol (30 mg/kg). From a baseline mean of 39.4°C, 79% of the IV acetaminophen group had temperature readings below a median of 38°C by 2 hours, reductions that were maintained for a mean of 3.42 hours. In addition, 69.7% of children in the IV acetaminophen group became afebrile by 3 hours, and 72.7% of children were thought to have had a “good” or “excellent” response on the investigator’s global evaluation. IV acetaminophen was well tolerated and resulted in significantly fewer injection-site reactions than seen with IV propacetamol (5.7% vs 28.1%; \( P = .0134 \)).

Additional published studies have reported similar positive results for IV acetaminophen in the treatment of pain associated with tonsillectomy in 80 children and adolescents93 and adenotonsillectomy in 50 children.95 Finally, Kumpulainen and colleagues33 studied the CSF penetration of a single dose of IV acetaminophen (15 mg/kg) in 32 children (3 months to 12 years of age, median 55 months) who were undergoing lower body surgery with spinal anesthesia and demonstrated rapid CSF penetration of IV acetaminophen, with time to peak levels in the CSF occurring in under 1 hour.

CLINICAL TOLERABILITY AND SAFETY

IV acetaminophen is well tolerated and shares many safety aspects of the oral and rectal formulations. Like the oral formula, IV acetaminophen is not associated with the potentially serious adverse events that may occur with NSAIDs, COX-2 inhibitors, and opioids, including gastrointestinal complications, sedation, and bleeding risks.43,44 In contrast to NSAIDs, such as diclofenac and ketorolac, which can significantly impair platelet aggregation,99,100 acetaminophen has little or no effect on platelet function. Adverse reactions related to the use of IV acetaminophen are rare—less than 1 in 10,000—and are usually mild and transient. It has demonstrated a safety profile similar to that of placebo, with comparable frequency of adverse events in clinical studies.43 Treatment-emergent adverse events (TEAEs) reported include hypotension, malaise, hypersensitivity reaction, elevated hepatic transaminases, and thrombocytopenia.43 Recent open-label, multiple-dose US safety studies in both pediatric and adult inpatients have confirmed these tolerability reports.101,102

The primary safety concern with acetaminophen is its potential hepatic toxicity when used at higher-than-recommended doses (>4g/d for adult patients).103 Hepatic toxicity associated with acetaminophen is rare less than 1 in 500,000 treated patients44 and is primarily associated with unintentional or uncontrolled oral and rectal overdoses. It is likely that hepatic concerns associated with IV acetaminophen would
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<td>N = 80 IV APAP: 40 IM meperidine: 40</td>
<td>IV APAP was equivalent to IM meperidine with less sedation and pruritus and significantly faster readiness for PACU discharge</td>
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<td>Alhashemi, 2007</td>
<td>Pediatric dental restoration</td>
<td>IM meperidine</td>
<td>IV APAP 15 mg/kg vs IM meperidine 1 mg/kg, single dose</td>
<td>N = 40 IV APAP: 20 IM meperidine: 20</td>
<td>IV APAP was equivalent to IM meperidine with significantly less sedation and faster readiness for PACU discharge</td>
</tr>
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<td>Capici, 2008</td>
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<td>Duhamel, 2007</td>
<td>Pediatric fever</td>
<td>IV propacetamol</td>
<td>IV APAP 15 mg/kg vs IV propacetamol 30 mg/kg, single dose</td>
<td>N = 67 IV APAP: 35 IV propacetamol: 32</td>
<td>IV APAP was equivalent to IV propacetamol in antipyretic activity; 79% and 75% of subjects achieved temperature goal of 38°C; IV APAP was associated with significantly fewer injection-site reactions</td>
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<td>Study, Year</td>
<td>Procedure</td>
<td>Comparator 1</td>
<td>Comparator 2</td>
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<td>Hong, 2010[97]</td>
<td>Pediatric inguinal herniorrhaphy</td>
<td>Placebo</td>
<td>IV APAP 20 mg/kg + IV ketorolac 1 mg/kg vs placebo, single dose</td>
<td>N = 55</td>
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<td>Murat, 2005[98]</td>
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<td>IV APAP: 95</td>
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<td>Palmer, 2008[40]</td>
<td>Postoperative pain in pediatric neonates</td>
<td>N/A</td>
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<td>N = 50 (median PMA 38.6)</td>
<td>IV APAP: 50</td>
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*Abbreviations: APAP, acetaminophen; IM, intramuscular; N/A, not applicable; PACU, post anesthesia care unit; PMA, postmenstrual age.*
be further minimized by controlled dosing in the clinical setting. A recent analysis of eight (4 single-dose and 4 multiple-dose studies) multicenter, double-blind, randomized, placebo-controlled studies conducted in the United States (total N = 1064; IV acetaminophen = 649; placebo = 415) was performed to evaluate the safety of IV acetaminophen in a variety of postoperative environments and endotoxin-induced fever for hepatic TEAEs.104 The placebo group had a slightly higher rate of hepatic TEAEs (26/415; 6.3%) than the IV acetaminophen group (20/649; 3.1%). In one of the trials, in which patients received repeated doses over 48 hours, the placebo group reported a higher rate and greater severity of hepatic enzyme (alanine aminotransferase/aspartate aminotransferase) elevations (6/165; 3.6%) than the IV acetaminophen group (3/166; 1.8%).104 Therefore, the risk of hepatotoxicity with repeated dosing of IV acetaminophen 1 g every 6 hours up to 48 hours may be no different from placebo. Nonetheless, IV acetaminophen, as with all forms of acetaminophen, should be used with great caution in patients with impaired liver function.

SUMMARY

The efficacy and safety of single and repeated doses of IV acetaminophen have been well documented in a variety of postoperative settings and patient populations across PI scores from mild to severe for periods up to 72 hours. In many studies, the onset of analgesic action for IV acetaminophen has been documented to occur just before or at the end of the 15-minute infusion. The peak effect, as measured by PI or pain relief, compared with placebo has been shown in several studies not only statistically significant but also clinically meaningful. IV acetaminophen (1000 mg) in the treatment of moderate to severe postoperative pain has an efficacy comparable to ketorolac (30 mg), diclofenac (75 mg), metamizol (0.5 g), or morphine (10 mg).105

In the perioperative setting, the parenteral form of acetaminophen may be preferred because patients may be unable to tolerate oral medications and/or may have unpredictable gastrointestinal function after surgery. There may also be a need for parenteral alternatives to treat adult patients who have a relative or absolute contraindication to the use of NSAIDs and who may require urgent treatment of fever/hyperthermia. IV administration can achieve effective levels in a shorter time with more predictable drug levels compared with oral and rectal forms. Additionally, it has demonstrated superior analgesia at least in the first hour after it is administered as well as a longer duration of action. It has demonstrated an adverse reaction profile similar to that of placebo and is, therefore, an appropriate analgesic option for adult and pediatric patients undergoing ambulatory surgery. IV acetaminophen is also effective for the treatment of fever in adults and pediatric patients. Parenteral administration results in higher plasma concentrations, which may contribute to enhanced CSF penetration and more rapid and effective antipyresis.

The opioid-sparing effect of IV acetaminophen remains somewhat controversial. In some but not all studies of IV acetaminophen, a statistically significant reduction in opioid consumption has been documented, with some studies showing that a substantial percentage of patients have been able to avoid the need for opioid rescue altogether. Avoiding or even delaying the use of opioids for moderate to acute pain may help avoid undesirable side effects, hyperalgesic responses, and possible dependency issues. Additionally, the use of IV acetaminophen and decreased use of opioids postoperatively may improve overall patient comfort and satisfaction, allow for earlier ambulation, and possibly translate to a shorter hospital stay.

Owing to its broad compatibility characteristics, IV acetaminophen may also be considered as an adjunct to other analgesics where synergy through complementary
mechanisms of action\textsuperscript{106,107} may be clinically useful, especially in multimodal analgesic regimens. As technical advances have made many surgical procedures less invasive, there has been a concomitant and associated trend to initiate physical therapy sooner to enhance long-term rehabilitation and healing. Therefore, it may be increasingly important to manage pain effectively and with minimal tolerability and safety issues to effectively transition patients to primary rehabilitative services. Although the emerging clinical picture for IV acetaminophen demonstrates its potential in fulfilling the unmet needs and requirements for the treatment of fever and pain in the perioperative setting, future studies should help clearly define its utility and scope of use in multimodal pain management.

ACKNOWLEDGMENTS

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REFERENCES

46. Alhashemi JA, Alotaibi QA, Mashaat MS, et al. Intravenous acetaminophen vs oral ibuprofen in combination with morphine PCA after Cesarean delivery: [L'acetaminophene intraveineux vs l'ibuprofene par voie orale comme \\alu-


