Acetaminophen

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Introduction

Acetaminophen (also known as paracetamol and N-acetyl-p-aminophenol [APAP]) is a synthetic central-acting analgesic for mild to moderate acute and chronic pain.1-3 Unlike NSAIDs, APAP is not a peripheral-acting analgesic, and has negligible COX inhibitory and anti-inflammatory effects at the site of surgical injury.2,3 APAP is recommended as a first-line analgesic in mild to moderate acute pain states and is effective in combination with opioids and other analgesics for more severe pain. APAP’s exact mechanism of analgesic effect is not clearly understood. However, it is believed to activate descending serotonergic inhibitory pathways. This interaction is indirect and not associated with binding to serotonin receptors.2-4 APAP is an inhibitor of central COX-2 and possibly COX-3, and has been shown to decrease prostaglandin synthesis in the spinal cord and brainstem. One of the metabolites (AM404) has cannabinoid agonist activity and inhibits TRPV-1 ion channels in pain-conducting pathways.5 APAP directly inhibits the hypothalamic heat-regulating center, resulting in peripheral vasodilatation and increased dissipation of heat.1-3

Oral and Rectal Formulations

APAP was discovered in 1879; however, widespread distribution and use of oral APAP (Tylenol) in the United States and paracetamol (Panadol) in Europe did not occur until the 1950s. It has since become the most widely administered over-the-counter analgesic worldwide.1-3 In addition, opioid compounds containing APAP (eg, Percocet, Tylox, Vicodin, Lortab) also the most widely prescribed analgesics for the management of postsurgical pain. Oral and rectal APAP are commonly utilized to treat mild to moderately severe incisional and musculoskeletal pain after ambulatory surgery.

Standard oral and rectal doses for short-term use (1 to 5 days) are 325 mg to 650 mg every 4 hours or 1000 mg three to four times per day, with a maximum of 4000 mg/day. Thereafter, the maximum dose should be reduced to 3200 mg/day.2,3 In pediatric patients, the recommended rectal dose is 15 mg/kg every 6 hours (40-60 mg/kg/day). This dose has been shown to significantly reduce morphine requirements in children recovering from day surgery procedures.6 A meta-analysis that assessed 51 double-blind, placebo-controlled trials of oral APAP found that significantly more patients experienced a 50% reduction in postoperative pain over 4 to 6 hours compared with placebo (50% vs 20%).7 In recommended doses, APAP does not irritate the lining of the stomach, inhibit platelet aggregation, or affect kidney function as with NSAIDs. Unlike aspirin, APAP is safe in children as it is not associated with a risk of Reye’s syndrome in children with viral illnesses. In contrast to opioids, APAP is not associated with nausea and vomiting and constipation, nor does it alter mood or pose a risk of dependency, tolerance, or withdrawal.1,2

Intravenous Acetaminophen

Intravenous formulations of acetaminophen (IV-APAP) were developed in Europe in the 1980s specifically for postsurgical pain management and control of fever in patients unable to tolerate oral dosing. An early preparation, IV propacetamol, was associated with burning at the injection site and was replaced by IV paracetamol (Perfalgan), which provided greater stability and fewer adverse events.3,9 IV-APAP offered significant advantages over oral/rectal routes, including:

- A more rapid and more predictable onset
- Higher maximum plasma concentration
- Higher analgesic efficacy.

It has become the most widely administered nonopioid analgesic in the European Union, with over 400,000,000 doses administered since 2002.9,10 IV-APAP was subsequently evaluated in several clinical trials in the United States and gained FDA approval for clinical use in 2010.

IV-APAP (Ofirmev) is currently approved for:

- Management of mild to moderate pain
- Management of moderate to severe pain with adjunctive opioid analgesics
- Reduction of fever in adult and pediatric patients.11

It is available as a 1 g/100 mL glass infusion bottle that does not require reconstitution. The solution should not be bolused rapidly but rather infused via peripheral IV over a period of 15 minutes. The recommended dose for adults weighing ≥50 kg is 1000 mg every 4 to 6 hours, with a maximum of 4000 mg/day, and no adjustment in dosage is necessary for patients up to 70 years of age weighing ≥50 kg. As a result of changes in volume of distribution in patients >80 years, the area under the curve of APAP plasma concentration is 54% to 68% higher than in adults <60 years of age.12 The elimination half-life is slightly prolonged (2.7 to 3.2 hours in 70- to 80-year-old patients, and 3.6 hours in 80- to 90-year-old patients). These findings suggest a dose adjustment for IV-APAP of 650 mg to 750 mg every 6 hours in these age groups. The recommended dose for children and adolescents weighing <50 kg, is 15 mg/kg every 4 to 6 hours, with a maximum of 3 g per day.11
IV-APAP offers several advantages in the perioperative setting particularly in patients who are unable to tolerate oral medications or in those with unpredictable GI function. Intravenous administration achieves maximal plasma concentrations (T_max) more rapidly and predictably than that observed with oral and rectal dosing. Maximum plasma concentration (C_max) following a 15-minute IV-APAP infusion was significantly higher than that observed with similar doses given orally. No accumulation of drug is noted with repeated doses given every 6 hours. In clinical trials, IV-APAP is superior to oral APAP and comparable to IV ketorolac 30 mg for the treatment of moderate postoperative pain. Onset of analgesia with IV-APAP occurs within 5 to 10 minutes, peak analgesic effect is noted at 1 hour, and its duration of effect is approximately 4 to 6 hours. The onset of its antipyretic effect occurs within 30 minutes, with a duration of 6 hours.

In a trial of 151 patients with moderate to severe pain after orthopedic surgery, IV-APAP (1 g) resulted in significantly better pain relief from 15 minutes to 6 hours postoperatively when compared with placebo. In addition, the need for rescue IV-PCA morphine was delayed in patients receiving APAP (3 hours vs 0.8 hours) and 24-hour morphine requirements were reduced by 33% (33.8 vs 57.4). The incidence of adverse events was significantly lower in the IV-APAP group (8%) than in the placebo group (17%).

IV-APAP was also evaluated for pain management following abdominal laparoscopic surgery. Patients were randomized to receive either IV-APAP 1000 mg every 6 hours, IV-APAP 650 mg every 4 hours, or placebo over 24 hours. The summed pain intensity differences (total reduction from baseline VAS scores) and subjective pain ratings over the first 24 hours were superior with the 1000-mg and 650-mg IV-APAP groups when compared with placebo. There were no differences in the incidence of serious adverse events or alterations in liver enzymes between treatment groups.

The analgesic effectiveness of IV-APAP for postoperative pain management appears to be enhanced when administered prior to surgical incision. Using a preemptive analgesia protocol, Arici and colleagues randomized 90 patients undergoing total abdominal hysterectomy to receive IV-APAP (1 g) given 30 minutes prior to induction, IV-APAP (1 g) given prior to skin closure, or intravenous saline. During the first 24 hours following surgery, morphine consumption was lowest in the preoperative IV-APAP group (25.93 ± 5.69 mg) than the postsurgical IV-APAP group (35.73 ± 5.24 mg). Morphine requirements were significantly higher in the placebo group (62.93 ± 8.67 mg) than either of the IV-APAP groups. To date, over 22 double-blind randomized trials have demonstrated improvements in analgesic efficacy and opioid-dose sparing. Results of several key studies are summarized in Table 10.1.

**Clinical Advantages**

- IV-APAP offers several clinical advantages for perioperative use:
  - It is well tolerated when employed as either analgesic monotherapy or as a multimodal adjunct.
  - IV-APAP is not associated with excessive sedation, biliary spasm, respiratory depression, nausea, vomiting, ileus, or pruritus observed with opioids.
  - It is not associated with the harmful GI, hematologic, cardiovascular, or renal effects associated with NSAIDs and COX-2 inhibitors.
  - Intravenous administration is associated with a more rapid onset and onset to peak analgesic effect, and is more suitable for titrating and reducing the intensity of postsurgical pain.

Achieving earlier and higher plasma and cerebrospinal fluid (CSF) levels is most likely responsible for the rapid and surprisingly high analgesic efficacy of the IV preparation compared with what surgeons have come to expect with oral APAP. As there is no contraindication to preemptive dosing, effective blood concentrations of IV-APAP can be achieved intraoperatively prior to emergence from anesthesia. We recommend that the infusion be initiated, as part of standard protocol, in the holding area immediately following placement of the peripheral IV catheter. The IV-APAP bottle can be spiked and piggy-backed into the main IV line delivering standard lactated ringers or sodium chloride solutions. Alternatively, the drug can be started by the anesthetist, ideally prior to initiation of neural blockade or induction of general anesthesia. If this is not possible, IV-APAP can be started anytime during the procedure or upon patient arrival in the postanesthesia care unit.

Since IV-APAP is a central-acting analgesic without anti-inflammatory effects, it may be combined with an NSAID or coxib to gain additive multimodal analgesic effects. This additivity may be of particular benefit in patients recovering from colectomy or those presenting with histories of opioid-induced constipation. The combination of central and peripheral analgesic effects can further reduce opioid consumption and potential dose-dependent inhibition of bowel function.

**Hepatic Toxicity**

The main concern with any form of APAP dosing is hepatic toxicity. APAP has a narrow therapeutic window, and even minor overdoses may cause severe hepatic injury. Liver necrosis occurs at 7.5 g to 10 g of APAP. For this reason, it is important not to administer IV-APAP in doses higher than the maximum recommended. IV-APAP is contraindicated in patients with severe hepatic impairment or severe active liver disease. Pharmacokinetic modeling suggests that IV-APAP may have a reduced risk of hepatotoxicity when compared with oral dosing, as it is not associated with high GI first-pass delivery to the liver. It is reassuring to know that hepatotoxicity does not occur when recommended doses of IV-APAP are administered to healthy patients.

In pivotal clinical trials involving >400 patients treated with multiple doses of IV-APAP, elevations twice upper limit of normal in key liver enzymes ALT and AST were very low and equivalent to that observed in patients treated with placebo. Singla and coworkers evaluated the safety of IV-APAP vs standard analgesic care in >200 patients. They found a numerically lower proportion of patients with elevated liver function tests in the IV-APAP group compared with standard of care. The safety and tolerability of IV-APAP (up to 15 mg/kg) was also tested in 175 pediatric patients requiring analgesic and antipyretic therapy. They found that IV-APAP was well tolerated in this relatively complicated pediatric population and no clinically relevant differences, severe, or overall treatment-emergent adverse events were noted.
APAP-induced hepatotoxicity is not caused by the drug itself but from its metabolite NAPQI. Normally, NAPQI undergoes conjugation with glutathione but at toxic doses, glutathione is markedly depleted. APAP doses exceeding the recommended daily limit and potential toxicity can be treated with N-acetylcysteine. N-acetylcysteine is a precursor of glutathione and increases the availability of glutathione for NAPQI metabolism. It is most effective if given within 8 to 10 hours of APAP ingestion.9

Conclusion

The development and availability of IV-APAP offers the surgeon a new therapeutic option for postsurgical pain management. It offers benefits of:
- High patient safety
- Rapid onset
- Improved analgesic when compared with traditional routes of APAP administration.

For many day surgical procedures, IV-APAP monotherapy will provide sufficient for many day surgical procedures with mild to moderate pain.22 This can obviate the need or minimize opioid dosing and associated adverse events. When employed in multimodal regimens that employ neural or epidural blockade, IV-APAP can be used for breakthrough pain relief, once again obviating the need for opioid analgesics. When employed with adjunctive IV-PCA or IV opioids, IV-APAP offers benefits of further reductions in pain intensity scores and total opioid dose requirement.15,23 Despite demonstrated improvements in pain scores, opioid dose, and overall patient satisfaction, studies to date have not been powered to detect significant reductions in opioid–related adverse effects or improvements in postsurgical outcome. In addition, there is an added cost of the IV preparation versus relatively inexpensive PO and Rectal formulations. These phase 4 evaluations may demonstrate important pharmacoeconomic benefits associated with IV-APAP treatment and to satisfy pharmacist and administrator concerns regarding increased drug acquisition costs.

REFERENCES


### TABLE 10.1 — Randomized, Controlled Trials With IV Acetaminophen for Postoperative Pain

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Patients</th>
<th>Treatment</th>
<th>Anesthesia</th>
<th>Treatment</th>
<th>Scale</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic re-pain and morphine</td>
<td>Hospitalized adults 22-87 years old</td>
<td>2 g PROP vs PBO</td>
<td>General</td>
<td>Given postop 1 g IV APAP vs PBO</td>
<td>VAS, q6h x 24h</td>
<td>IV APAP significantly reduced pain and morphine consumption over 24-h period</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>Ambulatory adults 16-40 years old</td>
<td>1 g IV APAP vs PBO</td>
<td>General</td>
<td>Given postop q6h x 24h</td>
<td>VAS</td>
<td>IV APAP significantly reduced meperidine consumption over 24-h period</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Adults 45-79 years old</td>
<td>1 g IV APAP vs PBO</td>
<td>General</td>
<td>15 min before end of surgery and q6h x 72h</td>
<td>VAS</td>
<td>IV APAP significantly reduced pain at rest and at 12 hours, nonsignificant reduction in morphine consumption</td>
</tr>
<tr>
<td>Total abdominal hysterectomy</td>
<td>Hospitalized women</td>
<td>1 g IV APAP vs PBO</td>
<td>General</td>
<td>Given once either 30 min before surgery or prior to skin closure</td>
<td>VAS</td>
<td>Preemptive IV APAP significantly reduced postop morphine consumption, no hemodynamic effects</td>
</tr>
</tbody>
</table>

Key: APAP, acetaminophen; PBO, placebo; PROP, proparacetamol; VAS, visual analogue scale; VRS, visual rating scale.


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### FIGURE 10.1 — Pharmacokinetics of IV vs PO Acetaminophen

Mean acetaminophen concentration over time: 6-hour dosing regimen (arrows) of IV or PO acetaminophen in healthy adults.\(^1\)

- \(C_{\text{MAX}}\) is up to 70% higher in IV than in PO acetaminophen.\(^{1,2}\)
- Overall exposures (AUC) are very similar for IV and PO acetaminophen.\(^2\)
- IV acetaminophen accumulation is similar to that of PO acetaminophen.\(^1\)

- Of the 38 randomly assigned patients, 34 patients who received IV acetaminophen 1 g and 33 patients who received PO acetaminophen 1 g had plasma concentrations measured.
- \(^a\)Rapid-release liquid PO acetaminophen.

1. Data on file Cadence Pharmaceuticals, Inc.

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### FIGURE 10.2 — Pain Relief Scores in Patients Recovering From Major Orthopedic Surgery\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>IV Acetaminophen</th>
<th>PBO</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient satisfaction: good to excellent at 24 hours</td>
<td>40.8%</td>
<td>23.1%</td>
<td>0.004(^{a,2})</td>
</tr>
<tr>
<td>Median time to first use of rescue</td>
<td>3.0 hours</td>
<td>0.8 hours</td>
<td>0.0001</td>
</tr>
<tr>
<td>Morphine consumption over 24 hours(^b)</td>
<td>38.3 mg (33% ↓)</td>
<td>57.4 mg</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Safety (adverse reactions)</td>
<td>IV APAP is comparable with PBO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Based on Cochran-Mantel Haenszel test.
\(^b\) Clinical benefit of reduced opioid consumption was not demonstrated.

2. Data on file Cadence Pharmaceuticals, Inc.