REVIEW ARTICLE

Continuous Multimechanistic Postoperative Analgesia: A Rationale for Transitioning from Intravenous Acetaminophen and Opioids to Oral Formulations

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■ **Abstract:** Good surgical outcomes depend in part on good pain relief, allowing for early mobilization, optimal recovery, and patient satisfaction. Postsurgical pain has multiple mechanisms, and multimechanistic approaches to postoperative analgesia are recommended and may be associated with improved pain relief, lowered opioid doses, and sometimes a lower rate of opioid-associated side effects. Acetaminophen (paracetamol) is a familiar agent for treating many types of pain, including postsurgical pain. Oral acetaminophen has been shown to be safe and effective in a variety of acute pain models. Combination products using a fixed-dose of acetaminophen and an opioid have also been effective in treating postsurgical pain. Combination products with acetaminophen have demonstrated an opioid-sparing effect, which inconsistently results in a reduced rate of opioid-associated side effects. Intravenous (IV) acetaminophen and an opioid analgesic administered in the perioperative period may be followed by an oral acetaminophen and opioid combination in the postoperative period. Transitioning from an IV acetaminophen and opioid formulation to a similar but oral formulation of the same drugs appears to be a reasonable step in that both analgesic therapies are known to be safe and effective. For postsurgical analgesia with any acetaminophen product, patient education is necessary to be sure that the patient does not concurrently take any over-the-counter products containing acetaminophen and accidentally exceed dose limits. ■

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INTRODUCTION

According to the most recent data from the Centers for Disease Control and Prevention, about 57 million surgical and nonsurgical procedures were performed in the United States in 2006, of which about 35 million were outpatient procedures.[1] About 20 million Americans underwent general anesthesia in 2005.[2] Postsurgical pain has been reported by 70% of patients[3] and is not always adequately treated in the hospital setting.[4] In the outpatient setting, postsurgical pain management becomes even more challenging, in that there is less opportunity for direct interaction between healthcare providers and patients. The classic analgesia paradigm, based on the World Health Organization (WHO) step–ladder model first issued in 1986, matches pain severity (weak, moderate, and severe) with analgesic strength.[5] Better understanding of analgesic mechanisms of action has led to recognition that pain is more effectively treated by etiology rather than severity.[6,7] A multimodal analgesic approach which addresses the various pain mechanisms may be particularly suitable for postoperative pain management.[8]

Postsurgical pain is complex. Following surgery, cells release inflammatory mediators, including histamine, leukotrienes, prostaglandins, cytokines, bradykinins, nerve growth factor (NGF), and others. These inflammatory mediators exert a hyperalgesic effect at the site of injury and surrounding tissue.[9] Afferent neurons release excitatory amino acids (glutamate and aspartate) or peptide neurotransmitters (substance P, neurokinin A, calcitonin generated peptide, cholecystokinin, and somatostatin) which are integrated with other afferent inputs in the dorsal horn to process and modulate pain.[10] Nociceptive activity in the spinal cord is relayed to the supraspinal centers in the brain which modulate pain, influenced by endogenous opioids, norepinephrine, 5-hydroxytryptamine (5-HT), serotonin, among others. These modulating substances are capable of amplifying or inhibiting pain.

Multimechanistic or multimodal analgesia acts at multiple sites (peripheral, spinal, and supraspinal levels), and may result in more effective pain relief than addressing only a single pain mechanism.[11] Multimechanistic postsurgical analgesic regimens have been shown to confer benefits over conventional postsurgical analgesia in terms of improved pain relief, lowered opioid dosages, and sometimes a lower rate of analgesic-related side effects for different types of surgeries.[8,12–15] Multimechanistic analgesic therapy may also benefit from additive or synergistic effects among analgesic agents.[16]

Intravenous (IV) acetaminophen was approved in the United States in early November of 2010; it has been available in Europe since 2002.[17] This article examines the pharmacology of IV acetaminophen and the safety and efficacy of loose dose IV acetaminophen in multimodal analgesia and provides a rationale for postoperative conversion to fixed-dose opioid/acetaminophen combination analgesic products.

ACETAMINOPHEN

Acetaminophen or paracetamol, as the same drug is known in Europe, Africa, Australia, New Zealand, and most of Asia, is a familiar analgesic agent often used orally as monotherapy or as part of a fixed-dose combination (multimodal) analgesic product. It is one of the few nonopioid analgesic agents available in oral, rectal, and IV formulations.[18] Propacetamol is a prodrug of acetaminophen available in powdered form to be dissolved in saline or glucose immediately prior to administration.[19] Propacetamol is hydrolyzed by plasma esterases after IV administration with the result that 1 g of propacetamol yields 0.5 g of acetaminophen (paracetamol). The pharmacokinetic actions of IV propacetamol differ from IV acetaminophen, which has a 20% to 25% greater C_{max} (Figure 1).

Although often classified with nonsteroidal anti-inflammatory agents (NSAIDs), acetaminophen has few anti-inflammatory effects. Acetaminophen is not associated with NSAID-induced gastrointestinal problems or opioid-induced respiratory depression.[20] However, although sold over-the-counter (OTC) and recommended for use in pediatric patients, acetaminophen produces serious hepatoxic effects at high doses.[21]

Oral acetaminophen is an effective analgesic agent following oral surgery.[22] Oral formulations offer convenience and familiarity to patients, but with a slower

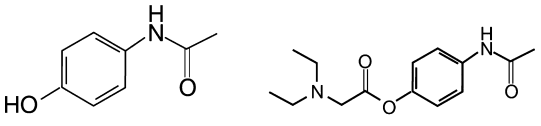

Figure 1. Molecular structure of acetaminophen (paracetamol) on the left and propacetamol on the right. Propacetamol is available as a powder which is dissolved in saline or glucose solution prior to administration.

onset of analgesia. In a study of dental patients (n = 150), the onset of analgesia was more rapid after bolus administration of acetaminophen compared to 15-minute infusion and both were more rapid than oral acetaminophen (3 vs. 5 vs. 11 minutes, respectively).[23]

METABOLISM

Acetaminophen is metabolized mainly in the liver along three different metabolic pathways: glucuronidation, sulfation, and *N*-hydrolyxation, all of which result in products primarily excreted through the kidneys[24] (Figure 2). *N*-hydroxylation produces a potentially alkylating toxic byproduct, *N*-acetyl-*p*-benzo-quinone imine (NAPQI). NAPQI is normally conjugated with the sulfylhydryl groups of glutathione into a nontoxic product but causes hepatic damage if glutathione levels are depleted. Production of NAPQI involves the cytochrome P450 (CYP450) enzyme system, specifically involving isoenzymes CYP2E1, CYP1A2, and CYP2D6. While the latter is not the most significant system for NAPQI production, genetic polymorphisms of this substrate may contribute to inter-patient variability in rates of NAPQI production.[25]

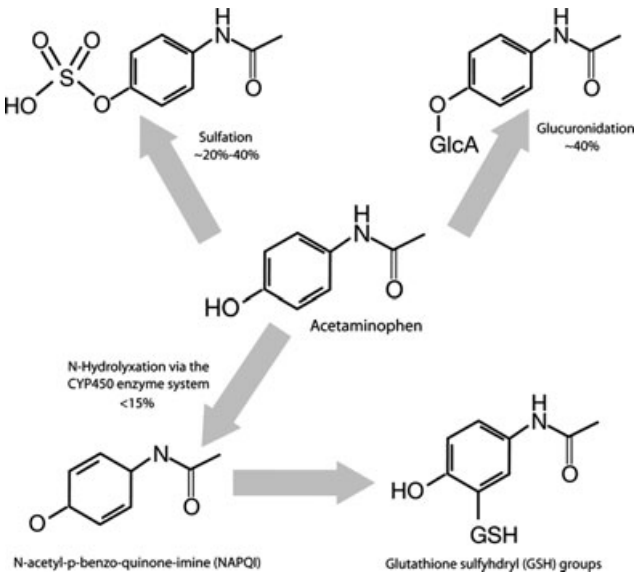

Figure 2. Acetaminophen is metabolized by glucuronidation, sulfation, and *N*-hydrolyxation. The intermediate product, *N*-acetyl-*p*-benzo-quinone-imine (NAPQI) is the only toxic molecule in the sequence and it is usually metabolized into glutathione sulfhydryl unless glutathione levels are depleted.

MECHANISMS OF ACTION

Acetaminophen appears to act at both central and peripheral pain pathways.[26] A variety of mechanisms of action have been proposed.

- Inhibition of cyclooxygenase 1 (COX-1) in specific brain regions[27] and/or cyclooxygenase 2 (COX-2) pathways involved in prostaglandin (PGE) synthesis.[28,29] This may explain acetaminophen's antipyretic effect.[30] Acetaminophen's ability to inhibit cyclooxygenase action depends in part on a low ambient concentration of peroxides.[31]
- Inhibition of cyclooxygenase 3 (COX-3), a splice variant of COX-1.[32] Since acetaminophen is a weak inhibitor of COX-1 and COX-2, the COX-3 theory proposes that the existence of a third COX enzyme, which could explain how acetaminophen is able to reduce PGE production.[33] However, the role and even existence of COX-3 in humans has been disputed.[34–37] On the other hand, there are proponents who state that the cyclooxygenase system is more complex than currently appreciated and COX-3 is just one of several isoenzymes remaining to be discovered.[38,39]
- Modulation of 5-HT pathways, which regulate spinal nociception.[40] The serotonergic system was supported in acetaminophen action when pretreatment with tropisetron and granisetron (known serotonin 5-HT_3 antagonists) blocked the analgesic effect of oral acetaminophen using an experimental pain model (electrical stimulation) in healthy volunteers.[41] Subsequent placebo-controlled studies in postoperative pain have not been able to replicate this finding. Preclinical studies report that activation of spinal serotoninergic descending pathways is involved in acetaminophen's antinociceptive effect.[42] Central nervous system (CNS) changes in serotoninergic neurotransmission reduce the analgesic effect of acetaminophen.[43]
- Enhancement of the level of endogenous cannabinoids, such as anandamide, by blocking their cellular reuptake.[20] Increased levels of anandamide are associated with analgesia.[44] Acetaminophen may also indirectly activate cannabinoid (CB_1) receptors.[20,45] Related studies suggest that acetaminophen may potentiate the vanilloid tone in the brain and dorsal root ganglia.[46,47]
- Inhibition of the *N*-methyl-D-aspartate receptor (NMDAR) which, in turn, stimulates the substance P-dependent synthesis of nitric oxide (NO), a

primary mediator of nociception.[48,49] But direct inhibition has not been verified.[50]

These multiple mechanisms may not be as contradictory as they appear at first glance. A model has been proposed, whereby acetaminophen acts as a reducing co-substrate in the two-step process for converting arachidonic acid to prostaglandin H2 (PGH2). This enzymatic action combines with the ambient peroxide, which may explain acetaminophen's lack of anti-inflammatory effect.[51] An active metabolite of acetaminophen has been identified in mice as *p*-aminophenol,[52] which is conjugated with arachidonic acid by fatty acid amide hydrolase to form AM404 (*N*-(4-hydroxyphenyl)arachidonoylethanolamide). AM404 is a potent activator of the vanilloid subtype 1 receptor (TRPV1), a ligand at cannabinoid-1 (CB1) receptors and an inhibitor of cellular anandamide reuptake. Activation of TRPV1 at the CB1 receptors would result in higher levels of endogenous cannabinoids, although AM404 does not have a direct effect on the CB1 receptors.

It is also possible that multiple mechanisms might be involved. A preclinical study found that acetaminophen induced spinally mediated antinociception and a simultaneous "self-synergy" between spinal and supraspinal sites. This suggests that acetaminophen mediates synergistic interaction between the brain and spinal cord.[53] This self-synergistic response is attenuated by the opioid receptor subtype selective antagonists β-funaltrexamine hydrochloride (β-FNA; μ), naltrindole (δ), and nor-binaltorphine hydrochloride (nor-BNI; k).[54] This suggests that endogenous opioids (endorphins, enkaphalins, and dynorphins) might contribute to the antinociceptive actions of acetaminophen.

ANALGESIC EFFICACY OF ACETAMINOPHEN IN POSTSURGICAL PATIENTS

Postoperative pain is known to be most severe immediately after surgery, decreasing in intensity over time.[55–57] Pre-emptive analgesia administered in the perioperative period may address this most severe pain, but the best regimen remains unclear.[59,60] Intravenous acetaminophen has been shown to be a safe, effective and well-tolerated analgesic agent in the treatment of pain following a variety of surgical interventions (Table 1).

Table 1. Selected Randomized Clinical Trials Comparing IV Acetaminophen or IV Propacetamol Against a Control Group Using Intravenous Saline as Placebo

Investigators	Surgery	Route	*N*	Results
Api[58]	Fractional curettage	IV	70	No difference in pain scores
Bektas[116]	Renal colic	IV	146	IV morphine or acetaminophen provided significantly greater pain relief than placebo (VAS, $P = 0.005$), but no significant difference between morphine and acetaminophen ($P = 0.74$)
Cattabriga[117]	Cardiac	IV	113	IV acetaminophen patients had significantly less pain at rest at 12, 18 and 24 hours postop ($P = 0.0041$) and used less rescue morphine (48 vs. 97 mg, NS)
Hernandez-Palazon[57]	Spinal fusion	IV Prop	42	Propacetamol patients used significantly less PCA morphine ($P < 0.001$) and had significantly lower pain scores
Juhl[103]	Oral	IV	297	IV acetaminophen provided significantly greater pain relief ($P < 0.0001$) and significantly greater median duration of analgesia ($P < 0.0001$)
Kemppainen[118]	Endoscopic sinus	IV	74	Significantly fewer IV acetaminophen patients needed rescue analgesics ($P = 0.001$)
Korkmaz Dilmen[119]	Lumbar disc	IV	80	IV metamizol, acetaminophen, lornoxicam and placebo compared, with significantly greater pain relief provided by metamizol and acetaminophen ($P = 0.001$ and $P = 0.04$, respectively)
Lahtinen[120]	Cardiac	IV Prop	79	No difference in pain scores but a *post hoc* analysis showed propacetamol patients used less PCA oxycodone in the first 24 hours postop ($P = 0.036$)
Moon[95]	Abdominal hysterectomy	IV	76	Premedication with IV acetaminophen reduced postsurgical opioid consumption by 30% over 24 hours ($P = 0.013$)
Ohnsesorge[93]	Breast surgery	IV	87	Significantly fewer IV acetaminophen patients required rescue analgesia in the first 24 hours postop ($P < 0.001$) and IV acetaminophen patients had more rapid time to ambulation (4.0 ± 0.2 hours vs. 5.5 ± 1.0 hours, $P < 0.05$)
Salihoglu[77]	Lapaproscopic cholecystectomy	IV	40	IV acetaminophen patients had significantly lower verbal and visual pain scores ($P < 0.05$) and significantly decreased morphine requirement and total morphine dose ($P < 0.05$)
Sinatra[121]	Major orthopedic	IV	151	IV acetaminophen patients had significantly greater pain relief from 15 minutes to 6 hours postop ($P < 0.05$) and reduced rescue morphine consumption

IV, intravenous; h, hour; min, minute; NS, not significant; PCA, patient-controlled analgesia; Prop, propacetamol; postop, postoperative or postoperatively; VAS, visual analog scale.

FIXED-DOSE ACETAMINOPHEN COMBINATIONS

Combining acetaminophen with an opioid creates an analgesic that acts via multiple targets and, ideally, produces the desired analgesic effect with a lower dose of opioid compared to opioid monotherapy.[61] Nonopioid analgesics are increasingly used as adjuvant agents with opioids for surgical pain as a way to provide analgesic benefit while reducing opioid consumption.[62,63] Opioid analgesics for postoperative pain are associated with dose-dependent side effects, including, but not limited to respiratory depression, constipation, nausea, vomiting, headache, and somnolence.[62]

Fixed-dose formulations of oral acetaminophen with various other analgesic agents have had good clinical results in treating postsurgical pain.[64–67] A selection of clinical studies of oral acetaminophen combination agents is given in Table 2.

OPIOID-SPARING EFFECTS OF ACETAMINOPHEN COMBINATION THERAPY

Synergistic Effects

The demonstration of synergy for agonist combinations requires experimental design and quantitative analysis that are often conducted with isobolographic and related procedures. The theoretical basis of this analysis has been described in several reviews.[68–71] The combination of oral acetaminophen with opioids has been explored for synergistic analgesic benefits.[72] In an isobolographic analysis from a preclinical study, acetaminophen combined with NSAIDs has been shown to have synergistic action.[73] These results seem to align with those of clinical studies in humans showing that adding an NSAID to acetaminophen improves analgesic efficacy over acetaminophen alone.[74] In an experimental study of intraperitoneal co-administration of acetaminophen with diclofenac, ibuprofen, keoprofen, meloxicam, metamizol, naproxen, nimesulid, parecoxib, and piroxicam, all were found to have synergistic effects, in that the experimental point of 50% antinociception was significantly smaller than the theoretically calculated point of 50% antinociception.[73]

Synergistic effects have been reported for the oral formulations of acetaminophen combined with oxycodone,[75] codeine,[67] morphine,[73] and tramadol.[76]

Safety and Effectiveness

The opioid-sparing effects of acetaminophen have been observed in several studies.[77–82] A meta-analysis of seven randomized controlled clinical studies (n = 265) found that acetaminophen reduced morphine consumption by about 20% (mean reduction 9 g, 95% CI, −15 to −3 g, P = 0.003) in the first 24 hours after surgery, but this was not associated with a reduction in morphine-associated adverse effects.[83] This meta-analysis included propacetamol and oral acetaminophen as well as IV acetaminophen. Further, this analysis excluded studies allowing patient-controlled analgesia (PCA) systems and studies that used loading doses of acetaminophen, which have been associated with opioid-sparing effects.[84]

A larger meta-analysis of COX-2 inhibitors, NSAIDs, and acetaminophen combined with morphine alone (n = 52 studies, 4,893 adult patients) found that acetaminophen significantly decreased morphine consumption in the first 24 hours following surgery by an average of 8.3 mg, but it did not significantly decrease

Table 2. Representative Studies of Acetaminophen Combination Analgesics in Fixed-Dose Oral Formulations for the Management of Postoperative Pain

Investigators	Application	*n*	Results
Desjardins[122]	Oral surgery	270	Both oral rofecoxib 50 mg and 10 mg oxycodone + 650 mg acetaminophen (followed by 5 mg oxycodone + 325 mg acetaminophen every 6 hours) provided significantly better pain relief than placebo (P < 0.001)
Franceschi[123]	Polytrauma	60	Oral acetaminophen 100 mg + codeine 60 mg provided effective pain relief (difference between acetaminophen + codeine vs. ketorolac not significant)
Gammaitoni[124]	Oral surgery	141	Oxycodone 10 mg + acetaminophen 325 mg provided greater analgesia than controlled-release oxycodone 20 mg and placebo
Rajpal[125]	Spine surgery	200	Patients who received a perioperative oral multimodal regimen (oxycodone, gabapentin, acetaminophen) had significantly lower ratings of ''least pain'' (P < 0.01) and less opioid consumption (P < 0.001) than those who received conventional IV PCA.
Trabulsi[126]	Radical prostatectomy	60	Multimodal analgesia patients (pregabalin, acetaminophen, celecoxib) used significantly less opioids than those who received standard analgesia (IV ketorolac followed by oral oxycodone + acetaminophen [P < 0.01]).

h, hour; mg, milligram; PCA, patient-controlled analgesia.

morphine-related side effects.[85] In this meta-analysis, which included oral and IV acetaminophen formulations, all nonopioid analgesics could be described as opioid sparing.

In a recent meta-analysis of acetaminophen and selective and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) for the postsurgical reduction of opioid-associated side effects (n = 694 patients, six trials) found all had morphine-sparing effects with no clear advantage to any of the NSAIDs, COX-2 inhibitors, or acetaminophen.[86] Another meta-analysis (n = 1,464, 16 studies) of IV acetaminophen for acute postsurgical analgesia found it to be effective across a variety of surgical procedures.[87] The studies included in this analysis were too heterogeneous to permit a formal meta-analysis pooling of results.

Studies of IV Propacetamol

Intravenous propacetamol is not available in the United States and is being replaced in the European Union by IV paracetamol (IV acetaminophen). Although it is increasingly falling into disuse, studies evaluating its safety and efficacy may be useful to clinicians and are reviewed briefly here.

In a study of 550 patients undergoing a variety of surgeries, patients were randomized to receive IV propacetamol (2 g of propacetamol yielding 1 g acetaminophen) or saline over 15 minutes, with first dose administered at skin closure in the operating room and dosing continuing (2 g propacetamol every 6 hours).[88] IV morphine was administered in the postanesthesia care unit (PACU) based on a visual analog scale (VAS) score of ≥ 30 mm; patients were asked to rate pain intensity at least once every 15 minutes. When morphine was required, it was administered every 5 minutes in 3 mg increments (2 mg in patients whose weight was < 60 kg). After IV morphine titration, patients received subcutaneous morphine every 4 hours, starting as early as 2 hours following titration in the PACU or ward. The IV propacetamol group consumed significantly less morphine than the control group (21 vs. 14.5 mg, $P < 0.001$) but there was no significant difference in morphine-related side effects (42% vs. 46%). Morphine-induced side effects in this study were ventilator depression (respiration rate below 10 bpm and/or need for naloxone), nausea and vomiting, pruritus, retention of urine requiring drainage, bronchospasm, cutaneous rash, or other allergic events. Rates of nausea and vomiting, the most frequently reported morphine-related side effect, were 34% vs. 39%, respectively, for the acetaminophen vs. control groups. The morphine-sparing effects of fixed-dose acetaminophen combination drugs varied inversely with the intensity of the patient's postsurgical pain. For example, the morphine-sparing effect of IV propacetamol was 37% in patients with *moderate* postsurgical pain, but 18% in those with *severe* postsurgical pain. In patients with moderate levels of postsurgical pain, the acetaminophen combination increased the number of patients who required no morphine at all, reduced the initial pain VAS score, improved pain relief, and increased patient satisfaction. However, the acetaminophen combination failed to confer these same benefits on patients with *severe* postsurgical pain.

In a study of 97 orthopedic surgery patients, propacetamol 2 g (yielding 1 g acetaminophen) reduced morphine consumption by 43% over 24 hours compared to placebo, such that 8 g IV propacetamol (yielding 4 g acetaminophen) saved 8 mg morphine.[81] The rate of opioid-associated adverse events was similar in both groups.

A study of 42 spinal fusion patients administered postoperative morphine found those administered IV propacetamol consumed 46% less morphine in 72 hours than similar patients who received only morphine.[57] Patients were randomized to receive an IV infusion of either propacetamol 2 g (equivalent to 1 g acetaminophen) or placebo every 6 hours for 72 hours, commencing 30 minutes before the end of the surgical procedure.

In the PACU, patients received IV morphine 1 to 2 mg in bolus doses every 10 minutes until the patients were able to use a PCA system, with which they could administer a bolus dose of 0.01 mg/kg of morphine with a 10-minute lockout period and maximum dose of 0.15 mg/kg every 4 hours. In the first 8 hours after surgery, there were no significant differences in morphine consumption between the IV propacetamol and the control groups, but over the course of the study, the IV propacetamol patients consumed significantly less morphine (60.3 ± 20.5 mg vs. 112.2 ± 39.1 mg, $P < 0.001$). Pain scores were measured by VAS and were similar between groups except at 40 and 56 hours, when pain was significantly less in the IV propacetamol group ($P < 0.01$ and $P < 0.05$, respectively). Sedation was rated as mild for both groups but was significantly less in the IV propacetamol group vs. placebo at day 3 ($P < 0.05$).

IV Acetaminophen (IV Paracetamol)

Forty major surgery patients were randomized to receive every 6 hours over the first 24 hours following surgery either IV meperidine with 100 mL saline or IV meperidine with acetaminophen 1 g.[78] The Behavioral Pain Scale (BPS) assessed pain scores before extubation, and a VAS measured pain after extubation. When either BPS or VAS ≥ 4, 1 mg/kg IV meperidine was administered (both groups). At 24 hours, the BPS and VAS scores were significantly lower in the acetaminophen–meperidine group compared to the meperidine monotherapy group ($P < 0.05$). The IV acetaminophen–meperidine group consumed significantly less postoperative meperidine (76.75 ± 18.2 mg vs. 198 ± 66.4 mg, $P < 0.01$) and had significantly shorter times to extubation (64.3 ± 40.6 min vs. 204.5 ± 112.7 min, $P < 0.01$). The IV acetaminophen–meperidine patients also had significantly lower rates of postoperative nausea and vomiting (PONV) and sedation compared to the meperidine-only group ($P < 0.05$). Other postoperative side effects, such as respiratory depression and need for re-intubation did not occur in either group. Pruritus was reported in one patient in the meperidine-only group.

A study of 124 adult women undergoing robot-assisted thyroidectomy were randomized in a double-blind study to receive IV acetaminophen 1 g or placebo (saline) infused over 15 minutes 1 hour prior to anesthetic induction and then at intervals of 6 hours over the next 24 hours.[89] IV acetaminophen patients had significantly less pain at 1, 3, 6, and 24 hours after surgery than the control group. Fentanyl and NSAIDs were offered as rescue medication based on the patient's reported VAS pain score (NSAIDs given at pain level ≥ 4, fentanyl at ≥ 7). Significantly fewer IV acetaminophen patients required any rescue mediation (9.5% vs. 65.6%, $P < 0.001$) and significantly fewer took fentanyl (3.2% vs. 29.5%, $P = 0.0016$). Significantly fewer IV acetaminophen patients experienced postoperative nausea (22.2% vs. 44.3%, $P = 0.021$) and PONV (6.3% vs. 21.3%, $P = 0.015$).

A significantly reduced rate of PONV was observed in 40 major surgery patients randomized to receive IV meperidine and saline or IV acetaminophen plus meperidine every 6 hours in the first 24 hours following surgery (eight patients vs. one patient, respectively, $P < 0.05$).[78] This study also found that combination therapy with IV acetaminophen and meperidine significantly reduced postoperative meperidine consumption.

A study of 40 patients undergoing lumbar laminectomy or discectomy found that IV acetaminophen 1 g significantly reduced postoperative vomiting ($P = 0.027$) compared to a saline placebo, but did not significantly reduce morphine consumption ($P > 0.05$).[90] Other morphine-related side effects (nausea, dizziness, headache, drowsiness, and hypotension) were similar in both groups. IV acetaminophen patients had significantly lower pain scores at rest and on movement at 12, 18, and 24 hours after surgery, as measured on a VAS. IV acetaminophen patients significantly more often rated their pain management as excellent compared to placebo patients (45% vs. 5%, $P < 0.05$).

Intravenous acetaminophen during laparoscopic cholecystectomy followed by oral acetaminophen in the first seven recovery days was evaluated in 160 patients randomized to one of four treatment groups.[91] Group 1 received parecoxib 40 mg IV during surgery followed by oral valdecoxib 40 mg during recovery (7 days). Group 2 received 1 g IV acetaminophen and then 1 g oral acetaminophen per day for 7 days. Group 3 received the same regimen as Group 1 with the addition of 10 mg IV dexamethasone delivered intraoperatively. Group 4 received the same treatment as Group 2 but with the addition of 10 mg IV dexamethasone intraoperatively. Pain intensity measured on a VAS showed no significant differences among groups. Significantly more parecoxib patients (groups 1 and 3) required rescue medication (oxyoconde 0.05 mg/kg) on the first day after surgery than the acetaminophen patients ($P < 0.001$).

In 114 tonsillectomy patients (ranging in age from 16 to 50 years), adding 1 or 2 g of IV acetaminophen to IV ketoprofen 1 mg/kg did not significantly reduce pain compared to ketoprofen alone, but acetaminophen patients consumed less rescue analgesia (27% less in the 1 g acetaminophen group, $P = 0.023$ and 38% less in the 2 g group, $P = -0.002$).[92]

A randomized study of 87 patients undergoing elective breast surgery divided patients to receive 1 g IV acetaminophen or 1 g IV metamizol or placebo, all delivered 20 minutes before surgery and then 4, 10, and 16 hours after tend of the procedure.[93] No significant differences among groups was noted in rescue morphine consumption, but more IV acetaminophen patients did not receive any rescue medication compared to placebo patients (42% vs. 4%, respectively). IV acetaminophen patients ambulated significantly earlier than metamizol and placebo patients

(4.0 ± 0.2 hours vs. 4.6 ± 0.2 hours vs. 5.5 ± 1.0 hours, respectively, $P < 0.05$).

A randomized comparative study in 40 breast cancer surgery patients found that 1 g/100 mL IV acetaminophen was clinically equivalent to 1 g IV dipyrone (metamizol) for postoperative analgesia.[94] Patients in both groups received 1 g/100 mL: 30 minutes before arrival in the recovery area and then every 6 hours up to 24 hours postoperatively. There was no significant difference in opioid rescue medication consumption or pain scores.

In 76 abdominal hysterectomy patients randomized to receive IV acetaminophen 2 g or placebo 30 minutes before surgery under general anesthesia; postsurgical analgesia was treated with patient-controlled hydromorphone 0.2 mg bolus doses.[95] There was no significant difference between groups in pain scores but IV acetaminophen patients used 30% less rescue hydromorphone in the first 24 hours postoperatively ($P = 0.013$) and PONV was significantly reduced in the IV acetaminophen group compared to placebo ($P < 0.05$).

A double-blind study at 17 centers randomized adult laparoscopic abdominal surgery patients to receive 1,000 mg every 6 hours or 650 mg IV acetaminophen every 4 hours or placebo in the first 24 hours following surgery with rescue morphine available in a PCA system accessible to patients if pain intensity was moderate or severe (2 or 3 on a four-point scale of 0 to 3).[96] Both IV acetaminophen doses were associated with statistically significant pain relief compared to placebo. Time to meaningful pain relief (measured by stopwatch) was significantly shorter when the 1,000 mg IV acetaminophen group was compared to placebo (24.9 vs. 53.9 minutes, respectively, $P < 0.003$). No statistically significant differences in adverse events occurred among groups.

Other Studies of Note

In a study of 80 coronary artery bypass patients randomized to receive 1 g acetaminophen every 6 hours either IV or orally, no significant differences in postoperative analgesia were noted and the authors describe a "limited" opioid-sparing effect of IV acetaminophen vs. oral acetaminophen, in that although significantly smaller amounts of rescue opioids were consumed by the IV acetaminophen patients compared to the oral acetaminophen patients (17.4 ± 7.9 mg vs. 22.1 ± 8.6 mg, respectively, $P = 0.016$) this did not translate into a lower rate of PONV.[97] It may be noted here that PONV in cardiac bypass patients is a common problem and may be multifactorial in nature.

Tramadol and acetaminophen combinations have been shown to be effective in providing multimodal analgesia.[66,98] A formulation of low-dose tramadol and acetaminophen (tramadol 37.5 mg + acetaminophen 325 mg) has been shown to be as effective in providing pain relief as combination products of tramadol 75 mg and acetaminophen 650 mg and tramadol 100 mg and acetaminophen 1,000 mg, respectively.[99] Patients using the lower-dose formulation required less morphine in the first 12 hours following surgery than patients taking the higher-dose products.

In theory, reducing opioid consumption should result in reducing the occurrence of opioid-associated side effects, but those results are seen in only a few of these trials. There may be reasons that reduced opioid consumption does not always result in a measurable decrease in opioid-related adverse events. First, it is unlikely that small studies could record a sufficient number of opioid-related adverse events for reliable statistical analysis. Second, accurate recording and categorizing of adverse events is always challenging in that some adverse events may be subtle, transient, or overwhelmed by other factors and go unreported. Third, the method of statistical analysis and the duration of the observation period can also affect adverse event reporting.[100] Finally, there may be more interpatient variability in opioid consumption rates[34] than is presently appreciated. This would have the potential to obscure or exaggerate opioid-sparing benefits, particularly in smaller studies. Many of the studies evaluated here and in the literature allow for spontaneous reporting of adverse events rather than reporting of prespecified adverse events, which may provide more accurate results. More study is needed to determine to what extent opioid consumption must be reduced in order to reduce related adverse events.

It has been suggested by Hahn and colleagues that IV acetaminophen has a ceiling dose of 5 mg/kg (corresponding to a serum concentration of 14 mg/L) for opioid-sparing effects in postsurgical analgesia.[30] Further study is warranted.

DOSING

The recommended dose of acetaminophen is a maximum of 4 g/day, even in alcoholic patients.[101,102] A higher initial dose of acetaminophen (for example, 2 g)

may provide better analgesic response. In a study of oral surgery patients (n = 132), patients who received oral acetaminophen 2 g had significantly greater pain relief than those who received oral acetaminophen 1 g or placebo ($P < 0.0001$) and pain relief remained significantly better from 30 minutes to 8 hours following surgery.[103] There was no difference in the rate of adverse events by group. The appropriate dosing regimen for IV acetaminophen for surgical pain remains to be clarified.

Fixed-dose combination analgesic products with acetaminophen offer the benefit of drug combinations selected for their complementary mechanisms along with convenience, which may encourage patient adherence.[104] Individual drug titration may be more appropriate to manage postsurgical pain in some cases, but can increase the complexity of drug administration.

In evaluating analgesics, the number needed to treat (NNT) provides a commonly used measure of relative strength in that it provides the number of patients one would need to treat in order to see equivalent effects (in drug comparisons).[67] The NNT typically is the NNT in order to achieve a 50% reduction in pain compared to another agent or placebo. An NNT value of 1 would mean that every patient treated with the active agent achieved at least a 50% reduction in pain while no patient in the comparator group did. While a low NNT number is desirable, typically values of 2 or 3 represent an effective therapy.[105]

The safety and efficacy of acetaminophen products have been thoroughly discussed in the literature, and there are data on NNT. See Table 3 for NNT data relating to comparisons of acetaminophen/codeine combination products. A bar chart illustrating NNT data for a variety of analgesics appears in Figure 3.

In a quantitative analysis of acetaminophen in postsurgical pain, the additional analgesic effect of 60 mg codeine added to acetaminophen (either 600–650 or 1,000 mg) was equivalent to having 12 additional patients in every 100 achieving at least 50% pain relief.[106] While quantitative conclusions were drawn from both surgical and oral surgical models, the NNTs associated with acetaminophen use in postdental and postsurgical pain were similar.[106]

Caution is advised when applying NNT results to specific procedures, in that the data on which NNT values are based come from a variety of studies and procedures, including both surgical and dental.[107]

RATIONALE FOR TRANSITION TO FIXED-DOSE ORAL COMBINATIONS

Good surgical outcomes may depend on safe and effective pain relief. Appropriate pain control allows for early mobilization and optimal recovery.[62,108] Multimechanistic postsurgical analgesic therapy may improve clinical outcomes and offer better analgesia than monomechanistic analgesia.[109] Multimechanistic

Table 3. Number Needed to Treat for Acetaminophen and Codeine Products Compared with Other Analgesics (All Products in This Table are Oral Formulations)

Analgesic Agent	Comparator	NNT	Range
Codeine 60 mg and acetaminophen 1,000 mg	Celecoxib 400 mg[127]	2.5	2.2–2.9
	Diclofenac 100 mg[128]	1.8	1.5–2.1
	Ibuprofen 400 mg[128]	2.7	2.5–3.0
	Oxycodone 10 mg + acetaminophen 650 mg[67]	2.6	2.0–3.5
	Tramadol 75 mg + acetaminophen 650 mg[67]	2.6	2.3–3.0
	Placebo[129]	2.2	1.7–2.9
Codeine 60 mg and acetaminophen 600 to 650 mg	Celecoxib 200 mg[127]	4.2	3.4–5.6
	Acetaminophen 1,000 mg[130]	3.6	3.2–4.1
	Aspirin 600 to 650 mg[131]	4.4	4.0–4.9
	Dextropropoxyphene HCl 65 mg + acetaminophen 650 mg[67]	4.4	3.5–5.6
	Placebo[106]	3.1	2.6–3.8
Codeine 60 mg and aspirin 650 mg	Placebo[132]	3.6	2.5–6.3
Acetaminophen 1,000 mg	Placebo[106]	3.6	3.0–4.4
Acetaminophen 600 to 650 mg	Placebo[106]	5.0	4.1–6.9
Tramadol 50 mg	Placebo[132]	7.1	4.6–18
Tramadol 100 mg	Placebo[132]	4.8	3.4–8.2
Tramadol 150 mg	Placebo[132]	2.4	2.0–3.1
Propoxyphene 100 mg and acetaminophen 650 mg	Placebo[132]	4.0	3.0–5.7
Oxycodone 15 mg	Placebo[133]	4.6	2.9–11
Oxycodone 10 mg and acetaminophen 650 mg	Placebo[133]	2.7	2.4–3.1

mg, milligram.

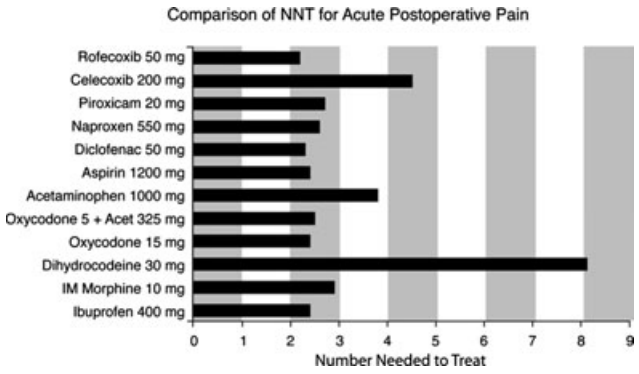

Figure 3. Number needed to treat (NNT) for a variety of analgesic products.[134] All products are oral formulations except as noted.

analgesic combinations are most effective when they activate multiple pain-inhibitory pathways and take advantage of the additive or synergistic effects of combined agents. This is the case of acetaminophen and opioids.

Oral fixed-dose acetaminophen combination drug products are familiar mainstays for effective postoperative pain relief. A few examples of commercially available oral acetaminophen and opioid combinations are hydrocodone and acetaminophen (Vicodin®; Abbott Labs, Chicago, IL, USA), oxycodone and acetaminophen (Percocet®; Endo Pharmaceuticals, Chadds Ford, PA, USA), tramadol and acetaminophen (Ultracet®; Johnson & Johnson, New Brunswick, NJ, USA; and Zaldiar®; Grünenthal GmbH, Stolberg, Germany) and propoxyphene and acetaminophen (Darvocet®; Eli Lilly, Indianapolis, IN, USA). For that reason, the use of IV acetaminophen in combination with an opioid for perioperative analgesia could be followed postoperatively by oral formulations of the same drugs, either in fixed-dose formulations (if available) or as loose dose products. Fixed-dose oral combination products offer convenience and possibly better compliance and optimal ratio. Oral acetaminophen tablets prescribed along with oral opioids provide versatility to meet the needs of individual patients.

The use of any postsurgical analgesic requires patient education, because patients will spend most if not all of their recovery period in a home rather than clinical setting. Whenever acetaminophen is prescribed or advised to a patient, the clinician must caution the patient not to exceed the recommended daily dose of 4 mg.[110] Since many consumers are unaware of the fact that acetaminophen is contained in many OTC medications,[111] excessive use of acetaminophen may occur accidentally, particularly if that patient takes OTC combination products, including, but not limited to headache, sinusitis, and cold remedies.[112]

ADVERSE EVENTS

In many controlled studies of acetaminophen, adverse events were not significantly different for acetaminophen vs. placebo.[103] A safety study of IV acetaminophen administered for up to 5 days in 213 adult surgical inpatients found the agent well tolerated.[113] At therapeutic dose ranges, IV acetaminophen has rarely been associated with hepatoxicity.[114] Overdoses of acetaminophen are associated with serious clinical consequences.

Propacetamol, the prodrug of acetaminophen, was associated with more injection site pain in a study of dental patients (n = 152) compared to IV acetaminophen (49% vs. 0%, respectively).[115]

CONCLUSION

Safe and effective postsurgical pain management is crucial to improved outcomes and patient satisfaction. Postsurgical pain involves multiple mechanisms and is best addressed by multimechanistic analgesia that targets the different mechanisms of pain. Combination therapy involving acetaminophen and opioids has been shown to be safe and effective in a variety of acute and chronic pain syndromes, including surgical pain. The use of IV acetaminophen and opioids in the perioperative period could transition to oral formulations of these same agents in the same proportions for postsurgical pain management. Fixed-dose or loose dose combinations could be used, as appropriate, to meet the individual patient's needs.

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