Intravenous Acetaminophen

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MOST PATIENTS WHO UNDERGO surgical procedures will experience acute postoperative pain. The use of multimodal analgesia, defined as the concurrent use of various analgesic drugs or techniques that target different mechanisms of analgesia, is recommended for the management of postoperative pain.[1] The goal of multimodal analgesia is to maximize the use of one or more scheduled (around the clock) nonopioid analgesics, as well as nonpharmacologic therapies, to minimize or eliminate the need for opioids and their often unacceptable adverse effects. The current recommendation (strong recommendation and high-quality evidence) is to provide acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in adults and children unless contraindicated.[1] An analgesic regimen that includes acetaminophen or an NSAID generally provides improved analgesia or less opioid consumption compared with an opioid alone.[2-4]

Oral Acetaminophen for Treating Postoperative Pain

Two authors independently reviewed 51 studies (approximately 5,700 patients) who received a single standard dose of oral acetaminophen or placebo to treat postoperative pain.[5] Effective analgesia, defined as at least 50% maximum pain relief over 4 to 6 hours, was achieved in about half of the patients who received acetaminophen compared with about 20% of patients who received placebo. The number needed to treat (NNT, defined as the number of patients who need to be treated for one patient to benefit compared with a control) after a single dose of acetaminophen ranged from 3.5 to 4.6 (500 mg NNT = 3.5 [95% confidence interval = 2.7 to 4.8]; 600 to 650 mg NNT = 4.6 [3.9 to 5.5]; and 975 to 100 mg NNT = 3.6 [3.4 to 4.0]). Note that analgesia was not greater (lower NNT) with acetaminophen doses higher than 500 mg.[5]

Intravenous Acetaminophen for *Preventing* Postoperative Pain

De Oliveira et al[6] reviewed 11 studies (740 patients) that evaluated a single dose of intravenous (IV) acetaminophen administered either before surgery begins or at the end of surgery versus control (no treatment) to prevent postoperative pain. Acetaminophen improved early (0 to 4 hours) pain control at rest and with movement, as well as reduced postoperative opioid consumption by approximately 10 mg IV morphine equivalents. Acetaminophen also reduced postoperative nausea/vomiting (PONV). The reduction in PONV was comparable to that seen after the administration of prophylactic dexamethasone[7] or metoclopramide[8] to patients undergoing general anesthesia for a surgical procedure.

Apfel et al[9] examined the effect of IV acetaminophen versus placebo on PONV in patients undergoing general anesthesia for a surgical procedure. The analysis included 30 studies (2,364 patients). When given prophylactically or before arrival to the postanesthesia care unit (PACU), IV acetaminophen reduced nausea at least as well as an antiemetic. However, when administered after the onset of pain, IV acetaminophen did not reduce nausea. The authors noted that the reduction in nausea correlated with the reduction of pain, not a reduction in opioid consumption. The authors postulated that acetaminophen reduces PONV either by providing effective analgesia (pain itself is thought to be a risk factor for PONV) or by a direct effect through increased anandamide levels (anandamide is a cannabinoid receptor agonist).[9]

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IV Acetaminophen for *Treating* Postoperative Pain

Two authors independently reviewed 75 studies (7,200 patients) in which patients received a single IV dose of acetaminophen or placebo to treat postoperative pain. Thirty-six percent of patients who received IV acetaminophen achieved at least 50% maximal pain relief over 4 hours (NNT = 5; 95% confidence interval = 3.7 to 5.6) compared with those who received placebo. Patients who received acetaminophen required 26% less opioid over 4 hours and 16% less over 6 hours than patients who received placebo. This reduction in opioid consumption, however, did not result in a relevant reduction of opioid adverse effects. The authors concluded that a single dose of IV acetaminophen provides about 4 hours of effective analgesia for 36% of patients experiencing postoperative pain.[10]

Apfel et al[11] analyzed pooled patient satisfaction data from five randomized placebo-controlled studies comparing 24 or 48 hours of postoperative IV acetaminophen versus placebo. At 24 hours, patients were essentially asked to rate their satisfaction with the study treatment as fair, good, or excellent. Patients who received IV acetaminophen were more than twice as likely to report excellent satisfaction than patients who received placebo (32.3% vs 15.9%, respectively). The results for patients who received IV acetaminophen reporting good satisfaction were similar. The last pain rating before asking patients to rate their satisfaction with the study treatment did not differ between the acetaminophen and placebo groups ($P = .904$). Although patients who received IV acetaminophen required less rescue opioid (mean 32.1 ± 30 mg for IV acetaminophen group vs 38.7 ± 34.8 mg for placebo group; $P = .01$), it is unclear if this difference is clinically relevant.

Perioperative Factors That Affect Absorption of Oral Medication

Acetaminophen has a high oral bioavailability and is absorbed by passive diffusion, primarily in the small intestine (duodenum and jejunum). The rate of gastric emptying determines the rate by which acetaminophen reaches the small intestine where it can be absorbed.[12] Kennedy and van Rij[13] investigated drug absorption in patients undergoing abdominal surgery (tumor resection of large bowel and abdominal aneurysm repair). Patients were administered four test substances, one of which was acetaminophen (1 g IV and 1.5 g oral syrup) before surgery and 2 days after surgery. There was no change in the maximum plasma concentration, area of under the curve, or other pharmacokinetic variables when IV acetaminophen was administered before versus after surgery; surgery had little to no effect on the pharmacokinetics of IV acetaminophen. When acetaminophen was administered orally before surgery, the maximum plasma concentration was significantly lower and the mean residence time increased after surgery versus before surgery. The lower maximum plasma concentration after surgery was attributed to the inhibitory effects of surgery on gastric emptying. However, the overall amount of acetaminophen absorbed over time (area under the curve) did not change. From the transit time portion of the study, the authors concluded that the small intestine begins to function normally approximately 6 hours after surgery. The authors concluded that absorption of acetaminophen and similar drugs from the small intestine after surgery is essentially unchanged from its preoperative capacity.

In addition to the surgery itself, concurrent administration of an opioid may have an effect on the absorption of oral acetaminophen. Administration of opioids has been shown to delay gastric emptying in the perioperative period.[14]

IV Versus Oral Acetaminophen

The use of the IV route for administration of a medication is widely recognized as appropriate when a patient is not able to tolerate the oral route or the oral route has not been effective. For acetaminophen, the IV route of administration has a faster onset of action and yields more predictable pharmacokinetic parameters.[15,16] On the other hand, there are risks associated with IV administration,[17] the cost of 1 g IV acetaminophen is approximately 500 times that of 1 g oral acetaminophen, and it is unclear if IV acetaminophen is more effective than oral administration for managing postoperative pain.

Jibril et al[18] conducted a systematic review of the literature to compare the efficacy, safety, and