The Role of Intravenous Acetaminophen in Multimodal Pain Protocols for Perioperative Orthopedic Patients

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abstract

Multimodal pain management should be considered for all perioperative orthopedic patients. The goal of reducing the amount of perioperative opioid medication given may be achieved by using nonopioid medications, including intravenous acetaminophen. The site of action of acetaminophen is a variety of receptors in the central nervous system. When given intravenously, acetaminophen produces a much higher plasma concentration, which then leads to higher levels in the cerebrospinal fluid. The safety profile and relative lack of systemic adverse reactions make this an attractive analgesic for a wide variety of orthopedic surgical patients. Clinical studies have demonstrated the efficacy and safety of intravenous acetaminophen in elective total hip and knee arthroplasty, knee arthroscopy, lumbar spine surgery, and for acute traumatic limb pain.

Perioperative pain management should be an integral part of all surgical procedures performed by orthopedic surgeons. In the early postoperative period, acute pain is often undermanaged. In a 2003 study of adults who had a variety of surgical procedures, Apfelbaum et al[1] reported that more than 70% of patients experienced moderate to severe pain postoperatively and almost 25% of patients had adverse effects with pain medications. Today, there are still opportunities for improvement in patient satisfaction postoperatively. For orthopedic patients, poorly controlled postoperative pain may be associated with delay in ambulation, longer inpatient hospital stays, and decreased patient satisfaction.[2-5] In addition, long-term complications may occur from poorly controlled postoperative pain, such as limited range of motion and chronic pain syndrome.[4,5]

Historically, the usual treatment for postoperative pain in orthopedic patients has been oral or intravenous opioid medication. Unfortunately, these medications are frequently associated with multiple adverse reactions, especially nausea and vomiting, pruritis, ileus, and constipation. At routine doses in elderly patients and higher doses in other postoperative patients, opioid analgesics may be associated with respiratory depression, hypotension, dizziness, confusion, and even delirium. These complications usually delay patient mobilization with physical therapy, and increase length of hospital stay.[3-6]

In 2004, the American Society of Anesthesiologists task force published the first set of guidelines dealing with perioperative pain management, and strongly recommended the adoption of multimodal analgesia protocols for all surgical patients, including those undergoing orthopedic procedures.[7] Multimodal analgesia involves using different classes of medications or analgesics with different receptors, and other techniques, such as local injections, nerve blocks, and epidural infusions, in order to decrease the amount of opioid medication required postoperatively.[8-10] Unless contraindicated, they recommended the routine use of perioperative nonopioid medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], COX-2 inhibitors, and acetaminophen) in addition to regional anesthetic techniques.[7] In 2012, an updated set

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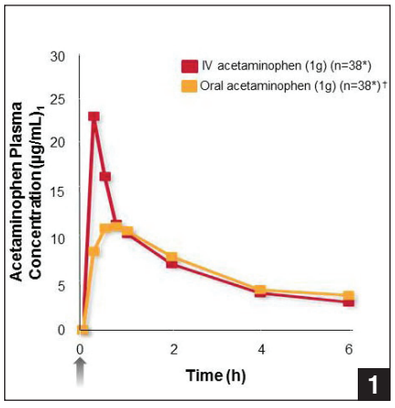

Figure 1: Mean plasma acetaminophen concentrations over 6 hours after intravenous (IV) and oral administration of 1000 mg in 38 test participants.

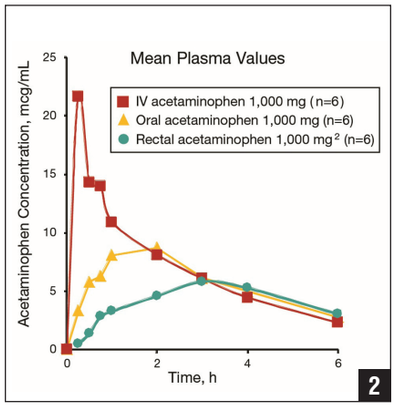

Figure 2: Mean acetaminophen plasma concentration over time in 6 test subjects after intravenous (IV), oral and rectal administration of 1000 mg. (Reprinted with permission from Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral or rectal acetaminophen. *Pain Pract.* 2012; 12:523-532.)

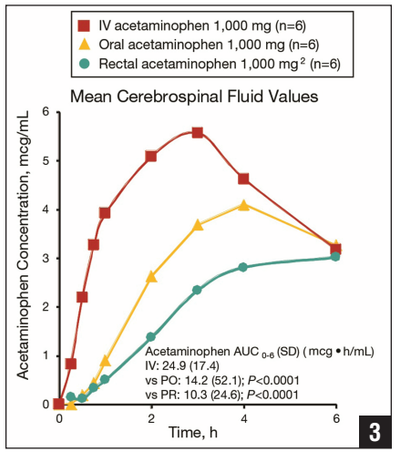

Figure 3: Mean cerebrospinal fluid acetaminophen concentration time-curves after intravenous (IV), oral and rectal administration of 1000 mg in same 6 test subjects. The area under the curve (AUC) is significantly greater after intravenous than oral (PO) and rectal (PR). (Reprinted with permission from Singla NK, Parulan C, Samson R, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral or rectal acetaminophen. *Pain Pract.* 2012; 12:523-532.)

of guidelines was published, with similar recommendations.[11] However, the 2012 guidelines stated that the dose and route of administration of NSAIDs and acetaminophen should be determined by the physician and based on individual patient differences, situations, and requirements.[11]

Intravenous Acetaminophen: Basic Science and Pharmacokinetics

Acetaminophen is a widely used nonopioid analgesic that has been available as an oral tablet or liquid, or as a rectal suppository for more than 4 decades in the United States. Since 2002, it has been available as an intravenous formulation and widely used in the United Kingdom and Europe. After the approval of the Food and Drug Administration (FDA) in November 2010, intravenous acetaminophen (OFIRMEV; Cadence Pharmaceuticals, San Diego, California) has been available in the United States and has been commercially available since January 2011. Intravenous acetaminophen is FDA approved for the management of mild to moderate perioperative pain alone; the management of moderate to severe pain with adjunctive opioid medication; and reduction of fever.

The site of action of the analgesic effect of acetaminophen is thought to be the central nervous system. Although the precise mechanism(s) of action of this central effect is not known, there are several theories as to its mechanism, including cannabinoid receptor agonist, serotoninergic bulbospinal pathways, cyclooxygenase-3 isoenzyme inhibition, and TRPV-1 agonist-mediating response to pain.[12,13] The antipyretic effect is thought to be mediated by the inhibition of prostaglandin synthesis within the hypothalamus.[14] The pharmacokinetics of intravenous acetaminophen have been described in several studies, and the serum therapeutic level required to produce an analgesic effect is 16 mcg/mL in adults and 10 mcg/mL in children.[15-20] Intravenous infusion of 1000 mg acetaminophen produces a rapid elevation in plasma concentrations and higher peak levels compared with oral acetaminophen (Figure 1).[15] In a study involving 8 doses every 6 hours in healthy volunteers, these pharmacokinetic differences continue with repeated doses.[15] With the use of intravenous acetaminophen, a clinical analgesic effect occurs within 15 minutes of administration, with a peak effect within 1 hour, and duration of effect of 4 to 6 hours. The pharmacokinetics has been compared to oral and rectal doses of acetaminophen (Figure 2).[16] The mean peak concentration after infusion of intravenous acetaminophen is 70% higher than the mean peak concentration seen with an equivalent oral dose. The median time to reach maximum plasma concentration (Tmax) for intravenous acetaminophen is 15 minutes, compared with the Tmax for the oral administration of 45 to 75 minutes and the Tmax for rectal administration of 3 to 4 hours. With the high plasma concentration, acetaminophen readily diffuses across the blood-brain barrier, with rapid and high levels in the cerebrospinal fluid.[16-18] There are significant differences in the peak and total amount of acetaminophen in the cerebrospinal fluid between intravenous acetaminophen compared with either the oral or rectal route of administration (Figure 3).[16] The half life of intravenous

Table

Recommended Dosing of Intravenous Acetaminophen

Age Group	Dose Every 6 hours	Maximum Single Dose	Maximum Total Daily Dose of Acetaminophen (Any Route)
Adults and adolescents (≥13 years) weighing ≥50 kg	1000 mg	1000 mg	4000 mg over 24 hours
Adults and adolescents (≥13 years) weighing <50 kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)
Children (2 to 12 years)	15 mg/kg	15 mg/kg	75 mg/kg

acetaminophen in the cerebrospinal fluid is 3.2 hours.[19]

There are major differences in pharmacokinetics when comparing oral and intravenous acetaminophen in postoperative patients.[20] In a recent study, oral acetaminophen 1000 mg had median plasma concentrations under 12 mg/L at 30 minutes, whereas 1000 mg intravenous acetaminophen had median plasma concentrations of 19 mg/L at 30 minutes.[20] Given orally, rectally, or intravenously, acetaminophen is metabolized by the liver by 3 different enzymatic pathways—glucuronidation, sulfation, and oxidation. Approximately 3% to 5% is excreted by renal mechanisms. The possible hepatotoxicity of acetaminophen may be affected by the absorption of this drug given by the oral route, which may result in a high local concentration in the portohepatic circulation, the hepatic first pass effect.[21] Intravenous acetaminophen achieves rapid and high plasma concentrations while avoiding the hepatic first pass effect.[22] There is no evidence that hepatic toxicity is more or less frequent when acetaminophen is given intravenously rather than orally.

The recommended dosing of intravenous acetaminophen is fairly simple (Table). For adults and adolescents (≥13 years) weighing ≥50 kg, the dose is 1000 mg every 6 hours (maximum single dose) and a total maximum daily dose of acetaminophen (any route) is 4000 mg per 24 hours. This dose has generally been used for 24 to 48 hours postoperatively, but has been tested for as long as 7 days postoperatively. For adults and adolescents(≥13 years) weighing <50 kg, the dose is 15 mg/kg every 6 hours (maximum single dose is 750 mg) and a total maximum dose of 75 mg/kg (up to 3750 mg) in 24 hours. For children ages 2 to 12 years, the dose is 15 mg/kg and the maximum daily dose is 75 mg/kg. No adjustment in dosing is needed for obese or morbidly obese patients. However, when using intravenous acetaminophen with opioid analgesics, it is imperative that the clinician not prescribe opioid tablets that contain additional doses of oral acetaminophen. Intravenous acetaminophen may be advantageous for postoperative orthopedic patients, because it is not associated with the opioid adverse effects of altered mental status, increased respiratory depression and altered gastrointestinal motility, or NSAID-related adverse effects such as platelet dysfunction, bleeding, impaired renal function, and impaired bone formation and fracture healing. In a meta-analysis of studies involving intravenous acetaminophen in the postoperative setting, there were no statistically significant differences in the rate of adverse reactions or liver function test abnormalities, when comparing intravenous acetaminophen with placebo.[23]

CLINICAL STUDIES OF INTRAVENOUS ACETAMINOPHEN IN ORTHOPEDIC PATIENTS

There have been clinical studies of the efficacy of intravenous acetaminophen in total hip and total knee arthroplasty, acute limb trauma in the emergency department, lumbar spine surgery, and outpatient knee arthroscopy. In a multicenter, prospective randomized study of 101 total hip and total knee arthroplasties,[24] patients were given 1000 mg intravenous acetaminophen or placebo every 6 hours for 24 hours, starting on postoperative day 1. All patients had morphine available by a patient-controlled analgesia pump and additional doses of morphine if needed. Pain relief from 15 minutes to 6 hours was significantly better with intravenous acetaminophen compared with placebo. The median time to morphine rescue was 3 hours with intravenous acetaminophen compared with 0.8 hours with placebo. There was a significant reduction (33%) in morphine consumption over 24 hours with intravenous acetaminophen (38.3 mg) compared with placebo (57.4 mg). There were no differences in adverse reactions between the two groups.

A randomized double blind study compared intravenous paracetamol (acetaminophen) and intravenous morphine for acute limb trauma in an urban United Kingdom emergency department.[25] There were 55 patients, between the ages of 16 and 65 years, with isolated limb trauma and a pain score of 7 or greater. Approximately half in each group had a fracture and the other half had soft tissue trauma. They received either 1000 mg intravenous paracetamol (acetaminophen) or 10 mg intravenous morphine. The outcome measures were: pain score measured on a visual analog scale; requirement for rescue analgesia; and frequency of adverse reactions. There was no significant difference in the rescue medication, but there were significantly more adverse

reactions in the morphine group. There were no significant differences between the groups in mean pain score and patient satisfaction.

A prospective, double-blind, randomized placebo-controlled study of intravenous acetaminophen (1000 mg every 6 hours for 24 hours) was performed in 40 patients undergoing lumbar laminectomy and discectomy.[26] Pain scores at rest and with movement were significantly lower with intravenous acetaminophen than with placebo at 12, 18, and 24 hours. Patients receiving intravenous acetaminophen had greater patient satisfaction with pain control (excellent rating 45% compared with 5%, $P<.05$) and decreased incidence of vomiting ($P<.05$). There was lower morphine consumption, but this was not statistically significant.

Finally, there was a randomized study of 84 patients undergoing outpatient knee arthroscopy (meniscectomy, loose bodies, wash-out, diagnostic), comparing pain score and adverse reactions between 1000 mg intravenous paracetamol (acetaminophen) and intravenous morphine (0.1 mg/kg) given prior to awakening from general anesthesia.[27] There was no difference in pain scores between those patients given the 2 medications, but there were more adverse reactions, dizziness, nausea, and vomiting, in the patients who received morphine. This study has important implications for discharge time from outpatient surgery centers.

Intravenous acetaminophen has possible advantages compared with intravenous opioid or NSAIDs analgesia in a variety of other orthopedic procedures, including hip fracture patients, adolescent scoliosis surgery, and pediatric hip surgery. Intravenous acetaminophen has no affect on gastrointestinal motility, platelet function and bleeding, renal function, or bone healing, and is not associated with confusion, respiratory depression, and ileus. In one study of total hip arthroplasty patients, the standard perioperative pain protocol included 6 doses of intravenous acetaminophen given over 36 hours.[28]

The author has used intravenous acetaminophen as part of a multimodal pain protocol for all total hip and total knee arthroplasties for the past 18 months. The medication is started intraoperatively, during wound closure for those patients having spinal anesthesia and at 1 hour prior to the end of the procedure for those patients who require general anesthesia. The timing is selected based upon the known pharmacokinetics of peak plasma level after administration of intravenous acetaminophen. An additional 4 doses are given every 6 hours. An oral opioid analgesic, oxycodone (not a combination medication with oral acetaminophen), is routinely administered at 3 hours after each dose of intravenous acetaminophen.

Conclusion

Multimodal pain protocols should be utilized in all orthopedic surgical procedures. The unique pharmacokinetics of intravenous acetaminophen provide some distinct advantages over other analgesics for the orthopedic patient. Studies have shown reduced opioid requirements after total hip and total knee arthroplasty, as well as a variety of other surgical procedures. The safety profile of intravenous acetaminophen is excellent and adverse reactions are similar to placebo. There may be opportunities and advantages for the use of intravenous acetaminophen in a wide variety of orthopedic surgical procedures, including spine surgery, pediatric surgery, and arthroscopy.

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