Inpatient pain management is a necessary skill set for all physicians, but it is particularly important for hospitalists working in the inpatient setting. Pain is so pervasive in the hospital setting that it is sometimes referred to as “the fifth vital sign,” and a failure to manage pain has important implications not only for hospitalists, but also for the hospitals where they practice. Hospitalists play a critical role not only in comanaging postoperative patients, but they also manage a wide range of conditions in which pain is prevalent, from pancreatitis to small bowel obstructions to sickle-cell disease.

While opioid monotherapy has long been the primary approach to pain management in the inpatient setting, the medical literature has documented numerous significant negative effects of opiate and analgesic use in hospital-based practice. These negative effects include opioid addiction, gastrointestinal issues such as nausea and vomiting, constipation and ileus, and serious complications such as respiratory depression and sedation, which increase the risk of respiratory failure, aspiration, decreased mobility, and falls.1

Research also indicates that current pain management strategies often fail to adequately control patient pain. One study found that more than 80% of U.S. patients who have surgery report significant postoperative pain.2 Data from another study indicate that fewer than half of postoperative patients report receiving adequate pain relief.3

An alternative approach to pain management that has been gaining traction among physicians is a multimodal analgesia strategy that incorporates not only opioids, but other classes of analgesics.4, 5, 6 By incorporating different classes of analgesic agents with unique pharmacologic and physiologic actions, physicians can prescribe smaller doses of each agent, a strategy that helps reduce the potential for drug-related adverse events.6

One element in such a multimodal approach to pain management is OFIRMEV®, an intravenous (IV) formulation of acetaminophen. IV acetaminophen was approved by the FDA in November 2010 for the management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever.7

While IV acetaminophen is relatively new in the U.S., the same formulation of IV acetaminophen has been available in Europe since 2002 and was widely used in more than 60 countries before reaching the U.S. market. As a result, a large body of literature exists supporting the role of IV acetaminophen in the management of acute pain while reducing opioid use. This special report examines data regarding the use of IV acetaminophen, including its efficacy in controlling pain; its ability to reduce not only the use of opioids, but also adverse effects such as post-operative nausea and vomiting; and its effects on length of stay and patient satisfaction.

Efficacy of IV acetaminophen

Compared to oral acetaminophen, IV acetaminophen achieves a rapid elevation in plasma concentration and higher peak levels.8 The IV form achieves plasma levels rarely achieved by similar oral doses of acetaminophen and produces 75% higher central nervous system (CNS) bioavailability compared to the oral form.8 The analgesic effect peaks within one hour and lasts for four to six hours.7

The efficacy of pain management therapies is of great interest to hospitalists for a variety of reasons. As comanagers of postoperative patients, hospitalists are routinely faced with a variety of complications of pain management that include nausea and vomiting, respiratory depression, ileus, and constipation. In addition, studies have shown that postoperative pain is associated with poor outcomes, such as increased time to ambulation, longer lengths of stay9 and increased rates of complications.
such as venous thromboembolism. Reducing length of stay in postoperative patients is a major goal of many hospitalists, so any alternative to opioids that can help accelerate discharge is welcome.

Clinical evidence demonstrates that IV acetaminophen has good utility to treat inpatient postsurgical pain, even following total joint arthroplasty, which is often associated with high pain scores. Results from a 2005 study by Sinatra et al. demonstrate that IV acetaminophen produces good quality analgesia even in this moderate-to-severe pain model, reducing the consumption of opioids and improving patient satisfaction. In that study, 101 postoperative orthopedic surgery patients were given either 1000 mg of IV acetaminophen or placebo every six hours for 24 hours. Patients were allowed to use a patient-controlled analgesia (PCA) pump with morphine for rescue analgesia if their pain was inadequately controlled. Overall, there was a 33% decrease over 24 hours in the use of morphine among patients who received IV acetaminophen. An expanded analysis of those data also found that the sum of pain intensity over 24 hours highly favored IV acetaminophen.

In another widely-cited 2010 study by Wininger and colleagues, 244 patients who had undergone abdominal laparoscopic surgery were divided into four groups and given either 1000 mg of IV acetaminophen every six hours, 650 mg of IV acetaminophen every four hours, 100 mL of IV placebo every six hours, or 65 mL of IV placebo every four hours. When researchers compared differences in pain intensity, they found that patients receiving IV acetaminophen reported significantly better scores. Results showed that while both 1000 mg of IV acetaminophen every six hours and 650 mg every four hours were effective, only the 1000 mg dose produced a statistically significant difference in time to meaningful pain relief and total pain relief when compared to the placebo group.

A separate study of ICU patients following major abdominal or pelvic surgery found that at 24 hours, patients who received IV acetaminophen with IV meperidine had better pain scale and visual analog scores than patients who received IV normal saline with IV meperidine. Patients receiving IV acetaminophen also experienced a decrease in extubation time, and had lower scores for postoperative nausea/vomiting and sedation. The authors concluded intravenous acetaminophen reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in the ICU.

In addition, IV acetaminophen monotherapy appears to have good utility in less painful procedures as well. In a study of adults undergoing tonsillectomy, patients given IV acetaminophen received fewer opioids, and 71% of patients receiving IV acetaminophen required no rescue analgesics. Patients given IV acetaminophen experienced less pain, and they were less likely to report insufficient pain relief.

And in a study of patients who had undergone endoscopic thyroidectomy, researchers found that subjects who received IV acetaminophen reported significantly lower postoperative pain scores than the control group, and fewer of those patients needed rescue analgesics. Postoperative nausea and vomiting were more frequent in the control group, but other side effects such as sedation, confusion, and pruritus were similar in both groups.

Optimizing postoperative pain management is an important goal for hospitalists involved in the management of surgical patients. Specifically, the careful use of effective pain management therapies may lead to reduced postoperative complications and, ultimately, reduced morbidity and health care costs.

**Data from nonsurgical patients**

While much of the literature examines the use of IV acetaminophen in postoperative patients, the drug also has been researched in several nonsurgical models. Many of these studies pertain to pain in patients presenting to the emergency department (ED), which is another area where hospitalists serving as consultants or staffing observation units are likely to encounter acute pain.

A study of 55 patients that compared IV acetaminophen 1000 mg to IV morphine 10 mg in treating acute traumatic limb pain in the ED found equivalent analgesic effect between the two therapies at all time intervals. Although no differences in time to first use of rescue medication were observed, patients given morphine experienced significantly more adverse reactions. Similarly, two

<table>
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<th>IV ACETAMINOPHEN DOSING INFORMATION*</th>
<th>Q4</th>
<th>Q6</th>
<th>Max. single dose</th>
<th>Max. total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults/adolescents ≥13 years old and ≥50 kg</td>
<td>650 mg</td>
<td>1,000 mg</td>
<td>1,000 mg</td>
<td>4,000 mg</td>
</tr>
<tr>
<td>Adults/adolescents ≥13 years old and &lt;50 kg</td>
<td>12.5 mg</td>
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<td>15 mg/kg (up to 750 mg)</td>
<td>75 mg/kg (up to 3750 mg)</td>
</tr>
<tr>
<td>Children 2-12 years old</td>
<td>12.5 mg</td>
<td>15.5 mg/kg</td>
<td>15 mg/kg</td>
<td>75 mg/kg</td>
</tr>
</tbody>
</table>

* See reference 7 (OFIRMEV® [acetaminophen] injection Prescribing Information).
Thus, more effective pain control of patients in the ED might reduce length of stay in the ED or, more importantly, prevent an unnecessary admission.

Opioid reduction
Because opioids are associated with adverse drug events that not only affect patient care but also increase costs, there has been a call for physicians to embrace a multimodal pain approach whenever possible to minimize the use of opioids. The American Society of Anesthesiologists (ASA) has strongly recommended the use of multimodal analgesia whenever possible to reduce reliance on opioids in the perioperative setting. Guidelines issued by the ASA’s Task Force on Acute Pain Management state that, unless contraindicated, patients should receive an “around-the-clock regimen” of therapies that include acetaminophen. Unlike opioids, acetaminophen does not produce sedation, respiratory depression, or ileus and constipation, and it is not associated with a risk of substance abuse or misuse.

By introducing IV acetaminophen into pain management regimens, researchers have been able to reduce opioid consumption in postsurgical patients in the ICU. In the previously mentioned 2010 study in the ICU in patients undergoing major abdominal or pelvic surgery, patients given 1000 mg of IV acetaminophen Q6h needed 61% less opioids than the control group. In the 2005 Sinatra study, patients who had undergone total hip or total knee replacement surgery receiving IV acetaminophen 1000 mg every 6 hours reduced morphine consumption by 48% over 6 hours and 33% over 24 hours. Two other studies examining total hip arthroplasty patients similarly found that total consumption of morphine dropped by 53% and 63%. Minimizing opioid use means decreasing the risk of sedation. For hospitalists, however, particularly those treating postoperative patients, decreasing opioid use also means increasing the ability of patients to participate in their care plans. Patients can be more active in rehabilitation and wound management, better follow instructions, and more fully comprehend patient education efforts. Being pain-free is important, but if patients are oversedated, their participation in their care may be impaired or limited.

Hospitalists treating postoperative patients also may see another benefit of a drug like IV acetaminophen. Postsurgical patients whose pain is better controlled, particularly those who have undergone abdominal surgery, can take deeper breaths and are less likely to develop atelectasis or pneumonia.

Reducing hospital-acquired conditions such as pneumonia is not only a laudable patient safety goal, but is one that has the attention of hospital administrators and hospitalists alike. Pay-ers like Medicare have stopped paying for hospital-acquired conditions such as pneumonia and pressure ulcers, giving both physicians and hospitals a financial incentive to prevent complications associated with pain management.

Postoperative nausea and vomiting
Postoperative nausea and vomiting are associated with increased morbidity, including aspiration, and may prolong recovery and, ultimately, length of stay. Therefore, minimizing postoperative nausea and vomiting is an important pain management goal in the postoperative setting.

While other strategies such as prokinetic agents and gastric pH modifying agents are used, the most important strategy to reduce the risk of aspiration is the prevention of vomiting. The use of narcotics, especially in narcotic-naive patients, is strongly associated with nausea and may lead to vomiting. Any opportunity to address the symptoms of pain while reducing exposure to

### IV ACETAMINOPHEN AND REDUCED OPIOID CONSUMPTION

| Morphine usage over 24 hours after total hip/knee replacement | Placebo | 57.4 mg | IV APAP | 38.3 mg | -33% difference |
| Meperidine use after major abdominal surgery | Placebo | 198 mg | IV APAP | 77 mg | -61% difference |
| Meperidine doses per group after adult tonsillectomy | Placebo | 82 doses | IV APAP | 18 doses | -78% difference |

1. See reference 11.
5. See reference 23.
agents that induce nausea will likely reduce the risk of vomiting and consequently reduce the risk of aspiration pneumonia. A formal study to address this has not been undertaken to date.

One study designed to examine postoperative nausea and vomiting found that a single dose of IV acetaminophen was superior to placebo in decreasing the incidence of nausea (14.6% vs. 33%) and vomiting (7.3% vs. 24.4%) during the first 24 hours after surgery. Researchers also found differences between the IV acetaminophen and control groups in the number of doses of analgesics required for rescue during that 24-hour period.24

In two other studies that examined postoperative nausea and vomiting, researchers found statistical differences between IV acetaminophen and placebo in both nausea and vomiting.25, 26 Several other studies have compared IV acetaminophen to meperidine, tramadol, and morphine. One found reductions in nausea at all points in the study, and a reduction in vomiting at the 30-minute timepoint when compared to tramadol alone.27 Another study showed differences between IV acetaminophen and morphine in the rates of nausea and vomiting.28

**Length of stay, patient satisfaction**

Hospitalists are very familiar with the importance of managing length of stay and reducing unnecessary health care costs. The diagnosis-related group (DRG) reimbursement model currently provides hospitals with a single fee for many conditions, regardless of the number of days the patient stays in the hospital. Therefore, length of stay is a metric that can have serious ramifications for a hospital’s finances.

The current system of reimbursement gives hospitals an incentive to achieve two goals regarding patients in pain. The first goal is to control patient pain more quickly, which allows patients to begin eating, ambulating, and preparing for discharge more quickly. The second goal is to minimize side effects of pain therapy. Data from a number of studies have examined the role of IV acetaminophen in achieving both these goals.

In a review of more than 350 patients who had undergone laparoscopic high anterior bowel resection, researchers compared PCA morphine to IV acetaminophen combined with morphine, as well as to IV acetaminophen combined with morphine plus a transverse abdominis plane block. Patients receiving IV acetaminophen resumed a normal diet in a median of 12 hours; patients receiving PCA morphine, by comparison, resumed a normal diet in a median of 36 hours. In this study, researchers also found that patients receiving IV acetaminophen had a hospital stay of three days compared to a median of five days for patients receiving PCA morphine.29

Several studies have examined the effect that IV acetaminophen can play in another important metric for hospitalists: patient satisfaction scores. In the previously mentioned 2005 Sinatra study of orthopedic patients, global satisfaction evaluations were higher after both the initial dose of IV acetaminophen and the dose given at 24 hours compared with those in a placebo group. In addition, at 24 hours, significantly more patients given IV acetaminophen rated their satisfaction as “good” or “excellent” (40.8%) compared to patients in the placebo group (23.1%).11 In the Wininger study of patients who underwent abdominal laparoscopy, patients who received IV acetaminophen gave significantly better satisfaction evaluations than subjects in the placebo group.13

Several other studies of IV acetaminophen in postsurgical pain patients similarly showed that patients reported significantly higher satisfaction ratings when given the therapy than patients in control groups.30, 31, 32, 33 Hospitalists know that patient satisfaction scores are increasingly important in today’s health care environment. Hospitals must collect and submit scores from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey to receive their full Medicare payment, and the Centers for Medicare & Medicaid Services (CMS) publishes patient satisfaction scores from the HCAHPS survey on its Hospital Compare Web site. Anything that hospitalists can do to improve patient satisfaction—and, as a result, optimize patient satisfaction scores and reimbursement—is welcome.

It has been said that patient satisfaction equals patient experience, and this indeed is true. Patient experience in a hospital or health care system is defined to a large degree by patient satisfaction. In the postoperative environment, a key element of patient experience is pain management.

**Conclusion**

While opioid monotherapy is typically viewed as the gold standard of pain management, downsides such as addiction, ileus, and respiration issues are well-known and well-documented in the medical literature. As a result, a movement is underway toward a multimodal approach to pain management that incorporates nonopioid analgesics to not only better manage pain, but reduce the adverse effects of opioids.

An important component of this multimodal approach to pain management is IV acetaminophen. A wide body of research demonstrates that IV acetaminophen not only effectively manages patients’ pain but can help reduce the adverse effects of opioid use. +

**DISCLAIMER** This special report is a summary of publicly available information and is not designed to be a comprehensive clinical review of the subject. Today’s Hospitalist assumes no legal liability for the use of the material in this special report. Readers are directed to consult the primary data sources cited in this article for more information.
Case Study One

IV Acetaminophen for a Patient With Ileus on Parenteral Nutrition and Mechanical Ventilation

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A 61-year-old morbidly obese woman presented at the burn center with necrotizing fasciitis of the abdomen, which developed following a midline hernia repair and adnexal mass removal. Her case was complicated by multiorgan dysfunction, and she arrived septic, requiring pressor support and mechanical ventilation. The patient also had a history of asthma, hypertension, depression, and hypothyroidism.

When the patient arrived at the burn center, she was on total parenteral nutrition and very sick. Prior surgical intervention had resulted in paralytic ileus, resulting in prolonged nil-by-mouth status. For pain management, she required 10 mg intravenous (IV) methadone every 12 hours, a midazolam infusion of 4 mg/hr, and intermittent doses of morphine sulfate for breakthrough pain. Once the patient was medically stabilized, she required debridement, which necessitated a return to the operating room. Postoperatively, her Richmond Agitation-Sedation Scale (RASS) score was 4, indicating deep sedation, which further complicated her ileus.

Based on the above issues, the methadone and the midazolam drip were discontinued and replaced with 1000 mg IV acetaminophen every six hours; morphine was provided for breakthrough pain. No other sedatives or analgesics were given to the patient.

The patient’s variability in blood pressure improved, and enteral nutrition was initiated using a postpyloric tube. IV acetaminophen allowed the pain management team to promptly wean the patient from the ventilator as her narcotic requirement significantly decreased, resulting in greater respiratory drive.

Once the patient was taken off all narcotics and benzodiazepines, she showed a RASS score of 0, which indicated that she was calm and alert without any complaints of pain. She required morphine only during complex dressing changes, not for breakthrough pain. The patient reached enteral nutrition goals 48 hours after IV acetaminophen was initiated. At that point, parenteral nutrition was no longer required, and the patient encountered no further issues with ileus.

While the patient required additional surgical procedures involving abdominal wound debridement and negative pressure wound therapy, she needed no additional narcotics for the remainder of her hospitalization. IV acetaminophen was routinely continued for 32 days until her discharge.

Once the patient’s ileus resolved, her premorbid problems with mood disorder resurfaced. At that point, her RASS score vacillated between +1 and +2 secondary to anxiety. The burn center team prescribed up to 1 mg alprazolam every 6 hours and later added 60 mg/day duloxetine. The team was able to reduce her RASS score to 0 without adding any narcotics or analgesics.

A major concern in this case was the potential for drug retention of lipid-soluble drugs such as opioids and benzodiazepines because of the patient’s morbid obesity and associated disadvantageous pharmacokinetics. That could have potentially led to difficulty weaning from the ventilator and prolonged sedation. Drugs such as IV acetaminophen allow decreased reliance on opioid analgesics, thus potentially avoiding these kinds of issues.
Case Study Two

IV Acetaminophen for Renal Colic in the Emergency Department

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EMH Healthcare, Elyria, Ohio

A 59-year-old woman presented to the emergency department complaining of right flank pain radiating to the lower groin. The patient had been experiencing symptoms for three hours, and she rated her pain as severe, assigning it a score of 10 on a 10-point pain scale. Kidney stones were the suspected cause of the patient’s symptoms, and a CT study confirmed the presence of a 3-4 mm calcification in the proximal right ureter that was causing a moderate obstructive uropathy. When asked about drug allergies, the patient noted she was morphine-intolerant.

Before the patient was sent for imaging, she was given intravenous (IV) normal saline for rehydration and two medications for pain: 1,000 mg of IV acetaminophen and 30 mg of IV ketorolac. About two hours later, when reassessing her pain, the patient rated her pain as 5 on a 10-point scale and was given 1 mg of IV hydromorphone. Ninety minutes later, the patient rated her pain as 0 out of 10. The patient was discharged with an outpatient referral after a total door-to-door time of about six hours.

Inability to control pain and insufficient analgesia in the emergency room often leads to acute hospital admission. When adequate pain relief can be achieved and no complicating factors such as infection are present, patients can be managed conservatively as outpatients, eliminating the need for admission to the hospital.

Patients presenting with renal colic are not unusual in the emergency department, but this case serves as a useful example of the benefits of using nonnarcotics such as IV acetaminophen in treating acute pain. While this patient reported an allergy to morphine, this was not the primary reason that IV acetaminophen was ordered. My practice is to frequently order IV acetaminophen for patients presenting with renal colic and other conditions that involve intense pain for several reasons.

In the emergency department, patient comfort is one of the key components of quality and compassionate care, and a key goal of the emergency department staff is to make patients comfortable as quickly and safely as possible. Following treatment with IV acetaminophen and IV ketorolac and a small dose of IV hydromorphone, this patient left the emergency department reporting 0 out of 10 pain and a patient satisfaction score of 5 on a 5-point scale. In my practice, patients who receive IV acetaminophen tend to report improved patient satisfaction scores.

Patients who have received IV acetaminophen, either alone or in combination with other pain medications, have demonstrated a greater reduction in pain scores and are often less likely to require additional analgesia or repeat dosing. IV acetaminophen can also lead to a decreased length of stay in the emergency department or hospital, increased patient and nurse satisfaction, and a reduced need for opiates.

IV acetaminophen is associated with less bleeding risk than with NSAIDs and less respiratory depression or altered sensorium than opioids. Unlike opioids, IV acetaminophen is not associated with addiction or drug-seeking behavior, which can complicate a patient’s stay in the emergency department or hospital. IV acetaminophen has been a great addition to the pain management armamentarium of the emergency physician.
Case Study Three

IV acetaminophen for pain management in orthopedic surgery patients

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A man in his mid-50s living with chronic obstructive pulmonary disease (COPD) that required two liters of oxygen per minute had been regularly using a combination of acetaminophen and oxycodone for knee pain for more than a year. He was referred by his primary care physician to an orthopedic surgeon at a hospital where I worked previously. The patient was relatively young and debilitated by knee osteoarthritis. At the recommendation of the orthopedic surgeon, he underwent total knee arthroplasty.

Because of his COPD and longtime narcotic use, the anesthesiologist used a spinal anesthetic technique with intrathecal morphine during the surgery.

About 12 hours after surgery, the spinal anesthesia started to wear off and the patient complained of intense pain. Because of the risk of respiratory failure in patients with chronic pulmonary disorder who take morphine, the surgical team was hesitant to administer systemic opioids on top of the spinal narcotic. As a result, the patient was given 1000 mg IV acetaminophen and 30 mg IV ketorolac, and ice was applied to the affected knee.

The patient did very well through the night. IV acetaminophen 1000 mg was continued every six hours for a further 24 hours. The next morning, the patient was able to participate in physical therapy and did not experience any respiratory complications. The patient was successfully discharged on postoperative Day 2.

Without IV acetaminophen and ketorolac, the pain management approach taken for this patient would have been much different. He was in so much pain following surgery that systemic opioids would have been required despite the intraspinal morphine precautions. That may well have led to a delay in physical therapy and possible respiratory complications in this susceptible patient. And without IV acetaminophen, this patient may have required a more prolonged stay in hospital.

Due to the positive experience in this patient and in others, the hospital has now protocolized the use of IV acetaminophen for all orthopedic surgery patients. The first dose is administered about 30 minutes before the end of surgery and then continued every 6 hours for 24 hours.

These patients typically have their first physical therapy session the morning after surgery and then have a second session that afternoon. Many are able to have a third session on postoperative Day 2, and then are discharged home. Thus, patients who receive IV acetaminophen not only tend to use less opiates, but they are more likely to start physical therapy right away, which can lead to an earlier discharge.
IV Acetaminophen: The Hospitalist’s Perspective

References


