Multimodal Postoperative Pain Management

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Objectives

• Do we have a problem with pain management?
• Discuss the burden of opioid-based therapy
• HCAHPS and the new paradigm in patient care
• Discuss the basis of multimodal analgesia
• What are the outcomes?

Acute Postop Pain Continues to be Undermanaged

Moderate Pain
Mild Pain
++ Opioids
+++ Opioids

STEP 1
STEP 2
STEP 3

Potential Consequences of Unrelieved Acute Pain

Opioids have historically been the foundation for acute pain management

In a 2012 research database of 1,665,418 inpatients, 72% of the inpatients who were treated with IV analgesia received IV opioid monotherapy.

Data from the hospital research database maintained by the Premiere Health Alliance. July 17, 2013.
### Postsurgical Side Effects

**Up to Two Weeks**

![Graph showing side effects](image1)

- **Anesthesiology.** Anesth Analg 2003; 97:534-40
- **n=222** (patients receiving pain medication)

### Hospital Discharge Associated with Recovery of GI Function

![Graph showing hospital discharge](image2)

**Am J Surg 2006; 191: 315-319**

### Balancing the Imperative

**The harder we push with opioids, the greater the degree of side effects.**

- Nausea/Vomiting
- Sedation/Respiratory Depression
- Constipation/Ileus

### Importance of Balancing Pain Management with Risk of Adverse Side Effects

**Most post-surgical patients chose less pain relief than increased/more severe side effects** (N=50)

![Graph showing side effects](image3)

**Dr. Jessop 2004 025:67-68**

### Importance of Balancing Pain Management with Risk of Adverse Events

- Following orthopedic surgery in 402 patients who received opioids, a significant linear relationship was found between the number of adverse events per patient and increased length of stay
- The strength of the association increased as the number of adverse events increased
- The findings from this retrospective study reinforce the need to balance pain management with risk of adverse events

### Outcomes: Cost and Length of Stay (LOS) related to Opioid Related Adverse Drug Events (ORADE)

**Unadjusted Outcomes for all surgical procedures**

<table>
<thead>
<tr>
<th>ADVERSE DRUG EVENT</th>
<th>COST ($0)</th>
<th>LENGTH OF STAY (LOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>No ADE</em></td>
<td>$22,871</td>
<td>9.0</td>
</tr>
<tr>
<td><em>ADE</em></td>
<td>$12,835</td>
<td>4.2</td>
</tr>
</tbody>
</table>

**†** *P<0.0001

### Additional Notes

- Open colectomy, laparoscopic colectomy, laparoscopic cholecystectomy, total abdominal hysterectomy, and hip replacement
HCAHPS as an Indicator for Patient Experience of Care

- Local, regional, or national patient satisfaction data are now being reported via Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS, also known as CAHPS® hospital survey)\(^1\)
- As part of the Affordable Care Act 2010, the Centers for Medicare and Medicaid (CMS) have established hospital reimbursement based on HCAHPS scores\(^2\)
  - Started on October 1, 2012
  - Publicly available data
  - Data delay: 6-9 months behind

Some Basics on HCAHPS

- CMS, along with Agency for Healthcare Research and Quality (AHRQ) developed HCAHPS.
- Has 32 questions along 8 domains.
- Administered to random sample of adult patients across all medical conditions between 48 hours and 6 weeks after discharge.
- Survey not restricted to Medicare beneficiaries.
- All short-term, acute care, non-specialty hospitals were invited to participate. Over 4,000 hospitals nationwide participate in this survey.
- Goal is to have 300 completed surveys turned in per year per hospital.
- Data obtainable at: [www.medicare.gov/hospitalcompare/search.html](http://www.medicare.gov/hospitalcompare/search.html)

Patient Domain Weighting

<table>
<thead>
<tr>
<th>Domain</th>
<th>FY2013 Value-Based</th>
<th>FY2014 Value-Based</th>
<th>FY2015 Value-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Process of Care</td>
<td>75%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Pain Management</td>
<td>75%</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Staff Responsiveness</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Facility Safety</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Overall Experience</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

HCAHPS Measures: There is Room to Improve Pain Management

<table>
<thead>
<tr>
<th>Measures</th>
<th>FY2013 Value-Based</th>
<th>FY2014 Value-Based</th>
<th>FY2015 Value-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication with Nurses</td>
<td>75.18%</td>
<td>85.70%</td>
<td></td>
</tr>
<tr>
<td>Communication with Doctors</td>
<td>79.43%</td>
<td>88.97%</td>
<td></td>
</tr>
<tr>
<td>Responsiveness of Hospital/Staff</td>
<td>61.82%</td>
<td>77.59%</td>
<td></td>
</tr>
<tr>
<td>Chain Management</td>
<td>58.57%</td>
<td>77.99%</td>
<td></td>
</tr>
<tr>
<td>Communication About Medications</td>
<td>59.18%</td>
<td>79.44%</td>
<td></td>
</tr>
<tr>
<td>Cleanliness and Quietness of Hospital Environment</td>
<td>62.88%</td>
<td>77.64%</td>
<td></td>
</tr>
<tr>
<td>Discharge Information</td>
<td>81.57%</td>
<td>89.29%</td>
<td></td>
</tr>
<tr>
<td>Overall Rating of Hospital</td>
<td>86.11%</td>
<td>89.29%</td>
<td></td>
</tr>
</tbody>
</table>

All short-term, acute care, non-specialty hospitals were invited to participate. Over 4,000 hospitals nationwide participate in this survey.

Goal is to have 300 completed surveys turned in per year per hospital.

Data obtainable at: [www.medicare.gov/hospitalcompare/search.html](http://www.medicare.gov/hospitalcompare/search.html)
HCAHPS QUESTIONS ON PAIN MANAGEMENT

12. During this hospital stay, did you need medicine for pain?
- □ Yes
- □ No

13. During this hospital stay, how often was your pain well controlled?
- □ Never
- □ Sometimes
- □ Usually
- □ Always

14. During this hospital stay, how often did the hospital staff do everything they could to help you with your pain?
- □ Never
- □ Sometimes
- □ Usually
- □ Always

CORRELATION OF PAIN MANAGEMENT AND HCAHPS COMPONENTS

A high level of pain management is strongly correlated with HCAHPS patient care measures and global satisfaction.

<table>
<thead>
<tr>
<th>HCAHPS Component</th>
<th>Coefficient of Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good communication with doctors</td>
<td>0.89</td>
</tr>
<tr>
<td>Good communication with nurses</td>
<td>0.89</td>
</tr>
<tr>
<td>Good communication about medicines</td>
<td>0.89</td>
</tr>
<tr>
<td>Good nursing service</td>
<td>0.84</td>
</tr>
<tr>
<td>Global satisfaction with hospital</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Multimodal Analgesia

Using a combination of varying agents that work on **two** different sites to achieve better pain management and to minimize opioid related side effects:

- Local anesthetics
- Opioids
- NSAIDs
- Acetaminophen
- Anticonvulsants
Types of Non-Opioid Based Multimodal Pain Treatment Medications

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Oxycodone</th>
<th>Cyclizine</th>
<th>Gallopentin</th>
<th>Oximemazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Anesthetics</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NSIAID</td>
<td>Ketamine</td>
<td>Diclofenac</td>
<td>Ketorolac</td>
<td>Nimesulide</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note: The above list agents are some of the more commonly employed medications used in the perioperative management of acute pain and is not meant to be a comprehensive list of all the available analgesic agents.

Reviews of systematic literature search support the use of multimodal analgesia in clinical practice.

Objectives

To determine which class of non-opioid analgesics – paracetamol, NSAIDS, or COX-2 inhibitors – is the most effective at reducing IV morphine consumption and associated adverse effects when used as part of multimodal analgesia following surgery.

Methods:

Conducted systematic review of literature using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials between January 2003 and February 2009. Published and unpublished studies were eligible and no language restrictions were applied. The reference list of relevant systematic reviews were checked to identify relevant studies.

Conclusions:

- There was a decrease in 24-hour morphine consumption, compared to placebo, ranging from 6.3 mg to 10.9 mg, when paracetamol, NSAID, or COX-2 inhibitors were added to PCA morphine following surgery.
- No clinically significant advantage shown for one drug over the other.
- The benefits in terms of reduction of morphine-related adverse effects do not strongly favor one of the three non-opioid analgesics.

Methods:

Relevant studies were identified by searching electronic databases (PubMed, Embase, CINAHL, Cochrane Library, NHS Evidence) for RCTs evaluating combinations of systemic paracetamol and/or NSAIDS with systemic opioids for postoperative pain management in children. Titles and abstracts up to January 2012 were included in the search.

Conclusion:

This systematic review supports addition of NSAIDs and/or paracetamol to systemic opioid for perioperative pain management in children.

American Society of Anesthesiologists Survey Reveals Under Utilization of Multimodal Analgesia Among Anesthesia Providers

- ASA Annual Meeting 2011: Abstract 1178, presented October 18, 2011:
  - Multimodal therapy are used less than 25% of the time.
  - Most commonly used agents were NSAIDS, gabapentinoids, and acetaminophen.
  - The majority of surgical patients continue to experience moderate to severe pain. A single nonopioid is likely to be used as an adjunct rather than a primary treatment, and use of multimodal analgesia is uncommon. Surprisingly, even acetaminophen is not widely used, despite its safety profile. The use of multimodal therapy is not yet standard practice.

Comments by Jaime Baratta, MD, Jefferson University.
Letter to the Editor
Reader Stresses Use of Multimodal Analgesia to Decrease Risk of Opioid-Induced Respiratory Depression

• We are concerned that the focus to prevent opioid-induced respiratory depression (OIRD) is too heavily weighted on monitoring.
• We write this letter to remind our colleagues of the importance of multimodal treatment modalities to prevent OIRD.

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Clinical Instructor
Department of Anesthesia
Department of Anesthesia
Stanford University, School of Medicine
Stanford University, School of Medicine

Multimodal Analgesia: Rational Poly-Pharmacy

• Combining two or more analgesics with different mechanisms of actions along the pain pathway to provide analgesia
• Reduced dose of each analgesic
• Improved analgesia due to synergistic/additive effects
• Reduced severity of side effects of each drug

Opioids
Adjuvants:
acetaminophen,
NSAIDS,
gabapentinoids
LA, nerve blocks

Multiple Organizations Recommend a Non-Opioid Foundation to Multimodal Analgesia

Society Recommendations
American Society of Anesthesiologists (ASA)¹
American Society of Pain Management Nursing (ASPMN)²
American Society of PeriAnesthesia Nurses (ASPAN)³
American Geriatrics Society (AGS)⁴
Society for Critical Care Medicine (SCCM)⁵

Accrediting and Quality Organizations
The Joint Commission (JCI)⁶
Agency for Healthcare Research and Quality (AHRQ)⁷

Primary goal is reduction of opioid administration in order to minimize opioid-associated side effects.
• Avoids sedation, respiratory depression from excessive dosing.
• Decreases constipation, pruritus
• Avoids exacerbation of PDIV
   • Common cause of postop distress
   • Consumes additional resources: time, staff, supplies, unanticipated hospital admission
• Facilitates discharge from PACU and OPS

In my own words, opioids become second line agents
with around-the-clock adjuvants serving as the primary line drugs.

Multimodal Approach to Postoperative Pain
Step 1: Mild Pain
Acetaminophen + NSAIDS + LA or blocks

Step 2: Moderate Pain
Low Doses of Opioids + Adjuvants

Step 3: Severe Pain
Higher Doses of Opioids + Adjuvants

Practice Guidelines for Acute Pain Management in the Perioperative Setting
An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management

• Whenever possible, a multimodal analgesic approach should be employed.
• A non-opioid treatment plan that includes local/regional anesthetic techniques, acetaminophen, or NSAIDS.
• Unless contraindicated, patients should receive around-the-clock regimen of acetaminophen or selective or nonselective NSAIDS.
• Opioids become the supplement treatment.
Multimodal Analgesia: Poly-Pharmacy That Makes Sense

- Reduces dose of each analgesic.
- Improves analgesia due to synergistic/additive effects.
- Reduces severity of side effects of each drug.

**NSAIDS**
- Acetaminophen
- Nerve blocks
- Gabapentinoids

**Classification of NSAIDS**

Nonselective COX Inhibitors:
- Salicylates: Aspirin
- Propionic Acid Derivatives: Ibuprofen, Ketoprofen
- Pyrrole-pyrrole Derivatives: Ketorolac
- Indole Derivatives: Sulindac, Indomethacin
- Pyrazolone Derivatives: Phenylbutazone
- Fenamic Acid Derivatives: Mefenamic Acid

Selective COX Inhibitors:
- Celecoxib

Preferential COX2-Selective Inhibitors:
- Celebrex in sulfa allergies.

Avoid COX-2 in high cardiac risk.

**Mechanism of Action of NSAIDs**

NSAIDS
- 1st line if no contraindications
- Can be combined with acetaminophen
- Mechanisms: blockage of COX enzymes → decreased PG synthesis
  - COX-2 → PG (pain, inflammation, fever)
  - COX-1 → PG (gastric protection, hemostasis)

Avoid/decrease dose in GI ulcerations, bleeding disorders, coagulopathies, renal dysfunction, allergies. Celebrex in sulfa allergies. Avoid COX-2 in high cardiac risk.

**COX Enzymes: Prostaglandin Effects**

<table>
<thead>
<tr>
<th>COX-1: Beneficial (Constitutive)</th>
<th>COX-2: Harmful (Inducible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Injury Site</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Brain</td>
<td>Modulates pain perception</td>
</tr>
<tr>
<td>Stomach</td>
<td>Protects mucosa</td>
</tr>
<tr>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Vasodilation</td>
</tr>
</tbody>
</table>

Acetaminophen

- Chemical name is N-acetyl-p-aminophenol.
- Para-acetylaminophenol = acetaminophen.
- Para-acetylaminophenol = Tylenol.
- Para-acetylaminophenol = paracetamol.
- Acetyl-para-aminophenol = APAP.

Acetaminophen

- Centrally acting analgesic, belonging to a family of analgesics called "aniline analgesics."¹
- Used for analgesia and anti-pyresis.¹
- Negligible anti-inflammatory and anti-rheumatic activities.²
- Following ingestion, relaxation, slight drowsiness, euphoria, or feeling of tranquility may be experienced.²

2. Behav Brain Res 2000; 121:177-186

Acetaminophen

- First synthesized in 1877 at Johns Hopkins University by Harmon Northrop Morse.¹ First used clinically in 1887³.
- Was not a popular medication until 1950s when identified as the active metabolite of two well-know analgesic and antipyretic prodrugs: acetanilide and phenacetin.²
- In 1955 phenacetin was withdrawn from the market due to nephrotoxicity. McNeil Laboratories in the USA marketed acetaminophen as Tylenol.²
- In 1956 marketed under the trade name Paranol in UK by Sterling Drugs.²
- In 1959 became available over the counter.²

¹. Ther Monatsch 1893; 7:577-587
². CNS Drug Reviews 2006; 12:25—275
³. Ther Monastsch 1983;7:577-587

How Does Acetaminophen Work?

Researchers Are Still Not Sure

1. Is a COX inhibitor (CNS >>>periphery) but sensitive to hydroperoxides.¹ Peroxide levels are low in the CNS but high in periphery especially at sites of inflammation.
2. Metabolite AM404 inhibits cellular reuptake of anandamide, an endocannabinoid.²
3. AM404 acts on Transient Receptor Potential (TRP) channels TRPV1 and TRPA1 in the brain and spinal cord, which play a central role in nociception.²,³
4. Acts on the serotonin (5HT) transmission in the CNS.²


ACETAMINOPHEN

- Double-blind psychological studies show that in addition to analgesia, acetaminophen blocks the mechanisms in the brain that make us worried or uneasy when faced with uncertainty.
- Participants (120 college students) who received Tylenol® felt less upset after conversations about death, social snubs, etc.
- Both physical pain and feelings of rejection are caused by activation in the dorsal anterior cingulate cortex.

Psychological Science 2013; 24:966
Oral Acetaminophen Absorption

- Absorption of acetaminophen occurs primarily along the small intestines by passive diffusion. The greatest amount takes place in the jejunum.  
- Rate of gastric emptying—not the trans mucosal transfer from the lumen of small bowel—is the rate-limiting step in absorption of acetaminophen.  
- Peak concentration of acetaminophen is reached 1-2 hours after oral ingestion.

Key Points

- Maximal analgesic and antipyretic activity occurs 1-2 hours after peak plasma levels.  
- Peak plasma concentration ($C_{\text{max}}$) achieved approximately: 
  - 25 minutes after 1 g IV  
  - 1-2 h after 1 g po  
  - 3.5-4.5 h after rectal route at both 20 mg/kg and 40 mg/kg  
- CSF levels lag behind plasma levels, with an equilibration half-time of 0.72-0.78 hours.  
- APAP should be given 1-2 h before anticipated pain or fever in children.

APAP Plasma and CSF Pharmacokinetics in Children

- Pediatric trauma patients who were ventilator dependent and had external ventricular drains placed for increased ICP management.
- Aim: determine the relationship of APAP between plasma and CSF pharmacokinetics in children.
- Given 40 mg/kg APAP elixir (250 mg/5 ml) via NG tube. Arterial and venous samples were obtained hourly for the 1st 4 hours, then q2h for the next 6 hours.
- Plasma to CSF standardization equilibration half-time of 0.78 h.
- Peak antipyretic lag behind maximum CSF concentration. Further time is required for paracetamol to act on receptors in both the spinal cord and the hypothalamus to exert an effect.

Conclusions:
- APAP should be given 1-2 h before anticipated pain or fever in children.
- Plasma concentrations between 0.08 and 0.13 mM were associated with an antipyretic effect.
Factors Affecting Oral APAP Absorption


Factors Affecting Oral APAP Absorption

Br J Anaesth. 1998; 60:24-27

Drug absorption from the small intestine in immediate postoperative patients

Br J Anaesth. 2006; 97:171-180

Pharmacokinetics of IV vs Oral Acetaminophen in Same Day Surgery


Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: a double-blind randomised controlled trial

Serum paracetamol concentrations in adult volunteers following rectal administration

Aim was to ascertain what dose of rectal paracetamol is needed in adults to achieve plasma paracetamol concentrations of 10-20 µg/ml.

- 10 volunteers received rectal paracetamol doses of 15, 25, 30, and 45 mg/kg
- Each took part in the study on 4 occasions, separated by 48 h.
- After self-administration of suppository, blood samples taken q 30 minutes for first 4 hours, then q hourly for the next 4 hours.

Limitation: lower limit of detection of plasma paracetamol was 10 µg/ml.

Br J Anaesth 2001; 87(4): 638-40

Combining Paracetamol (Acetaminophen) with Nonsteroidal Antiinflammatory Drugs: A Qualitative Systematic Review of Analgesic Efficacy for Acute Postoperative Pain

Giff K, S. Ong, PhD, A. Seppen, PhD, T. Phillip Lin, MD, F
and R. Chiocci, MD, F NURSE, FARMACIE, ANAESTHESIA, FRCA

20 RCTs involved 1852 patients, APAP+NSAID vs APAP alone
- 17 (85%) of these studies demonstrated:
  - With APAP/NSAID, mean decrease in pain intensity = 35%
  - mean decrease in need for supplemental analgesia = 39%
- 14 RCTs, 1129 patients, APAP+NSAID vs NSAID alone
- 9 (64%) of these studies demonstrated:
  - With APAP/NSAID, mean decrease in pain intensity = 38%
  - mean decrease in need for supplemental analgesia = 31%

Systemic review supports the use of a combination of APAP+NSAID.

Anesth Analg 2010 Apr; 110:1170


Does it make sense to add acetaminophen to a NSAID?

- Identified and reviewed RCTs in humans that specifically compared combination of APAP with various NSAIDS versus at least one of the constituent drugs.
- NSAIDS used were ibuprofen (n=6), diclofenac (n=8), ketoprofen (n=3), ketorolac (n=1), tenoxicam (n=1), ASA (n=1), and rofecoxib (n=1)
- Surgeries: orthopedic, ENT, dental, general, and GYN
- Stratified studies into 2 groups:
  - APAP+NSAID versus APAP or NSAIDS.

Anesth Analg 2010 Apr; 110:1170

Analysis 3.1. Comparison | Suppository 400 mg | paracetamol (1000 mg versus Suppository 400 mg. Dosette 1

Paracetamol 200 mg | 100 mg | 50 mg

Ropin 200 mg 250 mg 125 mg

Ropin 200 mg 250 mg 125 mg

Total 95% CI 216 140 416

95% confidence interval for difference

Gabapentinoids

**General:**
- Anticonvulsants.
- Effective in reducing immediate post op pain scores and opioid use.
- Likely effective in reducing emergence of chronic surgical pain.
- Side effects include sedation, dizziness, visual disturbances.

**Mechanism:**
- Pregabalin and Gabapentin.
  - Both bind to the α,β subunit of the presynaptic P/Q-type voltage gated calcium channels. Inhibit calcium-induced release of glutamate from activating pain-transmitting neurons.
  - May also exert an analgesic effect by activating the descending inhibitory noradrenergic pathway.

**Pharmacodynamics:**
- Gabapentin absorption is limited to a small portion of the duodenum while pregabalin is absorbed throughout the small intestine.
- Gabapentin absorption can be significantly impaired by antacids.
- Both are renally excreted without significant metabolism.
Comparing Pregabalin against Gabapentin

### Indication
- Pregabalin: DPN and PHN
- Gabapentin: PHN

### Mechanism of action
- Pregabalin: Selectively binds to the α2δ subunit in CNS tissues
- Gabapentin: Selectively binds to the α2δ subunit in CNS tissues

### Pharmacokinetic profile
- Pregabalin: Linear (plasma concentration increases disproportionately to dose)
- Gabapentin: Nonlinear (plasma concentration increases disproportionately to dose)

### Oral bioavailability
- Pregabalin: Oral absorption is variable
- Gabapentin: Absorption is variable, but not in the small intestine

### Dosing
- Pregabalin: BID or TID
- Gabapentin: TID

### Time to effective dose
- Pregabalin: 2 days (dose of 300 mg/d)
- Gabapentin: 2 days (titrate to allow mg/d)

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Recent Controlled Trials Supporting the use of Multimodal Analgesia in Clinical Practice

- Anesth Analg Clin 2012; 30:91-100
  - A good review article.
  - MMA compared to IV morphine alone, resulted in lower IV morphine requirements and better post-op recovery, and fewer side effects.
- Anesth Analg 2013; 117(3):677-685
  - MMA reduced epidural opioid consumption by 30% after cesarean delivery.
  - MMA reduced patient pain and morphine consumption after arthroscopic rotator cuff repair.
- J Arthroplasty 2014; 29:329-334
  - MMA compared to epidural PCA, resulted in decreased opioid consumption, better pain control, better satisfaction, and reduced nausea and emesis after orthopedic surgery.