Postoperative Pain Management: Economic Implications of Conventional Therapy and Evolving Role of Non-opioid Approaches

Presented as a Midday Symposium at the 46th ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 6, 2011
New Orleans, Louisiana

Planned and conducted by ASHP Advantage and supported by an educational grant from Cadence Pharmaceuticals
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AGENDA

11:30 a.m. – 11:40 a.m. Introductory Remarks
Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP

11:40 a.m. – 12:05 p.m. Economic Implications of Postoperative Pain Management
Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP

12:05 p.m. – 12:45 p.m. Multimodal Postoperative Pain Management: Focus on Non-opioid Injectable Analgesics
Leslie N. Schechter, Pharm.D.

12:45 p.m. – 1:20 p.m. Practice Tips for Incorporating Non-opioid Injectable Analgesics into Optimal Postoperative Pain Management
Wesley D. McMillian, Pharm.D., BCPS

1:20 p.m. – 1:30 p.m. Questions and Discussion
All Faculty

FACULTY

Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP
Activity Chair and Moderator
Associate Professor of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Pittsburgh, Pennsylvania

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Advanced Practice Pharmacist, Pain Management and Nutritional Support
Thomas Jefferson University Hospital
Clinical Assistant Professor
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**Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP**

Dr. Kane-Gill declares that she has received a research grant from Cumberland Pharmaceuticals Inc.

**Leslie N. Schechter, Pharm.D.**

Dr. Schechter declares that she has served as a consultant for Cadence Pharmaceuticals and Pacira Pharmaceuticals, Inc., and on the speakers bureau for Cadence Pharmaceuticals and Janssen Pharmaceuticals, Inc.

**Wesley D. McMillian, Pharm.D., BCPS**

Dr. McMillian declares that he has no relationships pertinent to this activity.

**Carla J. Brink, M.S., B.S.Pharm.**

Ms. Brink declares that she has no relationships pertinent to this activity.

**Susan R. Dombrowski, M.S., B.S.Pharm**

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
ACTIVITY OVERVIEW

In this activity, the economic implications of conventional postoperative analgesia and the evolving role of injectable non-opioid approaches for the management of postoperative pain will be reviewed. Several non-opioid analgesics in intravenous formulations have recently become available, and injectable local anesthetics continue to be investigated for postoperative analgesia. The availability of these injectable agents provide non-opioid options to combine with other therapies, as necessary, in a multimodal approach for the management of postoperative pain.

This activity will begin with a discussion of factors contributing to the economic burden of inadequate pain relief, such as readmissions and delirium, as well as the potential cost of adverse drug events associated with opioid use for postoperative analgesia. Non-opioid injectable options for postoperative analgesia will be reviewed, and practice tips related to their use from both clinical and institutional perspectives will be discussed.

Using an automated audience response system, faculty will engage participants in the decision-making process related to the management of postoperative pain in different clinical scenarios.

ACTIVITY OBJECTIVES

At the conclusion of this knowledge-based educational activity, participants should be able to

- Identify at least three economic consequences of inadequate control of postoperative pain.
- Discuss the economic impact of adverse drug events associated with opioids used to treat postoperative pain.
- Outline the benefits of using a multimodal approach for managing pain.
- Discuss the clinical implications of non-opioid injectable analgesics for managing postoperative pain.
- Identify at least two practice tips for improving the safe, effective, and cost-effective use of non-opioid injectable agents for patients with postoperative pain.
- Outline a plan for reviewing post-surgical order sets for use of the multimodal approach for managing pain.
CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 2.0 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity #204-000-11-447-L01P).

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Instructions for Processing CPE online at http://ce.ashp.org

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4. Click on the click here link to view sessions associated with the day of the activity. This activity was held on December 6, 2011.

5. Enter the session code that was announced during the activity (e.g., A11XXX and note that the letter is case sensitive), and select the number of hours equal to your participation in the activity.

6. Click submit to receive the attestation page.

7. Confirm your participation and click submit.

8. Complete the overall Midyear evaluation and click the finish button. You will then be able to view and print your transcript.

<table>
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<th>Activity Code</th>
<th>Session Code (announced during the live activity)</th>
<th>CPE credit hours</th>
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Postoperative Pain Management: Economic Implications of Conventional Therapy and Evolving Role of Non-opioid Approaches
Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP
Activity Chair and Moderator
Associate Professor of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Pittsburgh, Pennsylvania

Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP, is Associate Professor of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy in Pittsburgh, Pennsylvania. She also serves as Associate Professor for the Center for Pharmacoinformatics and Outcomes Research at the School of Pharmacy. In addition to her academic appointments, Dr. Kane-Gill is Critical Care Medication Safety Officer at the University of Pittsburgh Medical Center in the Department of Pharmacy.

Dr. Kane-Gill received her Bachelor of Science degree in pharmacy from Wayne State University in Detroit, Michigan. She completed a pharmacy practice residency accredited by the American Society of Health-System Pharmacists at West Virginia University Hospital in Morgantown, West Virginia, and earned a Doctor of Pharmacy degree from the University of Toledo in Toledo, Ohio. Dr. Kane-Gill then pursued her Master of Science degree in Pharmacy Administration with emphasis on Pharmacoeconomics and Health Outcomes at The Ohio State University in Columbus, and she completed a critical care fellowship at The Ohio State University.

Dr. Kane-Gill’s interests focus on health service research, including the assessment of economic, clinical, and quality outcomes for critically ill patients. Her goal is to identify effective approaches for the detection, prevention, and management of medication errors and adverse drug events as to improve quality of care and patient safety. Dr. Kane-Gill has served as principal investigator and co-investigator on several funded research grants in this area of study. Her work has been presented at several professional meetings, and she has published more than 60 articles and book chapters related to critical care and patient safety. Her endeavors include editing a recently published book on the use of high-risk intravenous medications in special patient populations.

Dr. Kane-Gill is an active member of the American College of Clinical Pharmacy (ACCP), Society of Critical Care Medicine (SCCM), and International Society for Pharmacoeconomics and Outcomes Research. She currently serves as the chair for the 2012 SCCM Congress. At the 2011 Annual Meeting of ACCP, Dr. Kane-Gill received the Critical Care Practice and Research Network (PRN) Research Award. She is a fellow in the American College of Critical Care Medicine and ACCP.
Economic Implications of Postoperative Pain Management

Sandra L. Kane-Gill, Pharm.D., M.S., FCCM, FCCP
Associate Professor of Pharmacy and Therapeutics
University of Pittsburgh School of Pharmacy
Pittsburgh, Pennsylvania

Challenges of Conducting Economic Analyses of Acute Pain Management

- Pain occurs in a wide variety of conditions
- Hard to separate costs associated with pain from the primary disease costs
- Only a few studies have documented the economics of acute pain management
- Currently no data on comparative cost-effectiveness of injectable analgesics

Health care costs due to inadequate postoperative pain control have been quantified for all of the following EXCEPT

a. Hospital readmissions
b. Emergency department visits
c. Development of delirium
d. Longer hospital length of stay
e. Productivity loss
Hospital and Pharmacy Costs in Joint Replacement Therapy

- One of the first studies to document postoperative drug costs in orthopedic surgery
- Stanford University database of patients following hip and knee surgery in 1999
- Hospital costs estimated using micro-costing methods
- Patients
  - 145 undergoing hip replacement
  - 121 undergoing knee replacement
  - 32 undergoing bilateral knee replacement


Hospital and Pharmacy Cost per Patient Undergoing Joint Replacement Surgery

<table>
<thead>
<tr>
<th></th>
<th>Total Hospital Cost ($)</th>
<th>Total Pharmacy Cost ($)</th>
<th>Approximate Cost of Analgesics ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip replacement</td>
<td>18,024</td>
<td>560</td>
<td>180</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>16,484</td>
<td>595</td>
<td>164</td>
</tr>
<tr>
<td>Bilateral knee replacement</td>
<td>28,559</td>
<td>922</td>
<td>286</td>
</tr>
</tbody>
</table>

- Pharmacy and operating room costs were 3.3% and 60% of total costs, respectively
- 2010 costs are approximately 30% higher than 1999


Clinical Consequences and Economics of Pain Management

- Continued pain can result in readmissions
- Pain and opioid use associated with development of delirium in critically ill patients
- Difficult to implement early mobilization efforts when patients in ICU experience pain
- Continued pain has negative effect on quality of life
- Adverse events associated with pharmacologic treatment

ICU = intensive care unit
Cost of Readmissions after Same-Day Surgery

- Retrospective analysis of same-day surgery in patients at University of Pittsburgh Medical Center during 1999
- Evaluated patients returning to ED or hospital on non-elective basis within 7-30 days
- Data for 313 patients obtained from chart review
- Financial data consisted of hospital charges – 2010 charges approximately 30% higher than 1999

ED = emergency department


Reasons for Readmissions after Same-day Surgeries

- Approximately 40% of readmissions attributed to pain underwent orthopedic surgeries

ADE = adverse drug event
N/V = nausea/vomiting


Cost Implications of Inadequate Pain Control after Ambulatory Surgery

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>All pain admissions</td>
<td>117</td>
<td>1,869</td>
<td>2,422</td>
</tr>
<tr>
<td>and readmissions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED visits</td>
<td>109</td>
<td>986</td>
<td>1,278</td>
</tr>
<tr>
<td>Inpatient admissions</td>
<td>8</td>
<td>13,902</td>
<td>16,966</td>
</tr>
<tr>
<td>and readmissions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes ED visits
Cumulative charges of 303 patients amount to $2.4 million (in 1999 dollars)

Clinical Consequences and Economics of Delirium

During the ICU/Hospital Stay

- Increased mortality
- Longer time on ventilator
- 3 times greater reintubation rate
- Average 10 additional days in hospital
- Higher costs of care
  ICU $9,000
  Hospital $14,800

After Hospital Discharge

- Increased mortality
- Development of dementia
- Long-term cognitive impairment
- Requirement for care in chronic care facility
- Decreased functional status at 6 months


Association of Pain and Opioid Use with Delirium

- Total of 541 patients undergoing hip surgery from one NY hospital prospectively assessed for delirium
- Confusion Assessment Method (CAM) performed daily until discharge
- Numerous potential risk factors, including pain-related variables, collected
- Multiple logistic regression performed


Results: Pain and Opioid Use

- 16% developed delirium after admission
- Independent risk factors for delirium
  - Severe pain before delirium (RR 9.0 [1.8-45.2])
  - < 10 mg i.v. morphine equivalent per day (RR 25.2 [1.3-493.3])
  - Administering meperidine (RR 2.6 [0.4-15.8])
- Additional support from 2008 study
  - Severe pain requiring opioid treatment is independent risk factor for postoperative delirium


RR = relative risk

Clinical Consequences and Quality of Life

- 411 cognitively intact elderly patients with hip fractures assessed for pain control
- Immediate outcomes of patient with higher pain scores
  - Longer length of stay (LOS) ($p = 0.03$)
  - Less likely to be ambulating on postoperative day 3 ($p = 0.002$)
- Long-term outcomes of patients with higher pain scores
  - Lower locomotion scores at 6 months ($p = 0.02$)


Cost Implications of Opioid-associated ADEs

- Clinical findings of opioid ADEs have been well described for many years
- Few studies have estimated costs from adverse effects associated with their use
- Minimizing dose or eliminating opioids is one approach to reduce these costs

What is the approximate additional cost of an inpatient episode of opioid-induced nausea and vomiting?

a. $200
b. $500
c. $800
d. $1100
e. $1500
Cost of Opioid-associated ADEs

• Retrospective matched cohort study in one hospital, 1998-2003
• 40,368 surgical patients receiving opioids
• Computer-based trigger of possible ADE
• 741 (1.8%) opioid-related ADEs
• Most common ADEs
  – Nausea/vomiting (50%)
  – Itching/rash (34%)
  – Mental status changes (17%)
  – Bradypnea (16.7%)


Cost of Opioid-associated ADE (2003 dollars)

• Median increase in total hospital cost $568
  – Would result in additional $421,000 for 741 patients
• Type of surgery and increased costs
  – OB-GYN $541
  – Orthopedic $862
• 10% increase in LOS (0.6 days)
• Odds ratio (OR) of factors associated with ADE
  – >10 mg parenteral morphine-equivalent dose OR 1.3
  – Orthopedic surgery OR 1.7
  – OB-GYN surgery OR 2.7


Opioid-related ADEs
Increase LOS and Cost

• Postsurgical patients in Premier database
  – Colectomy, cholecystectomy, hysterectomy, hip replacement
• 26.5% had ICD-9 code for ADE
• 42,469 cases matched to 127,325 controls
• LOS 1.1 days longer
• Additional cost $1640
• More apt to be outlier for LOS and cost

Costs of Managing Nausea, Vomiting, and Constipation (NVC) from Analgesics

- Retrospective analysis of Premier database
- 434,000 patients received an order for opioid or non-opioid analgesic (NSAID or COX-2 inhibitor)
- Use of drugs for nausea, vomiting, or constipation within 14 days of first analgesic order

NSAID = nonsteroidal anti-inflammatory drug
COX-2 = cyclooxygenase-2

Results: Managing NVC from Analgesia

- 55% received drugs for NVC
  - 50% for nausea or vomiting
  - 12% for constipation
  - 4% for NVC

<table>
<thead>
<tr>
<th>Description of Analgesia</th>
<th>Increase in Treatment Costs in Patients with NVC ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>756</td>
</tr>
<tr>
<td>Injectable opioids</td>
<td>232</td>
</tr>
<tr>
<td>Injectable non-opioids</td>
<td>868</td>
</tr>
<tr>
<td>Oral non-opioids</td>
<td>1464</td>
</tr>
<tr>
<td>Oral opioids</td>
<td>2223</td>
</tr>
</tbody>
</table>

*Each category was significantly different from patients without NVC at p < 0.00001.


Postoperative Patients and Respiratory Depression

- Risk factors (examples)
  - Age
  - Obesity
  - Obstructive sleep apnea
  - Opioid-naïve patient requiring short period of high dose opioids (10 mg in PACU)
  - Opioid-tolerant patient receiving more than usual dose
- 32 patients with critical respiratory event over 6 yr
  - 26 events and 3 deaths occurred within the first 24 hours of opioid therapy (high risk period)
- Cost of an ICU day $4000
  - Incremental cost of mechanical ventilation $1500

PACU = post-anesthesia care unit
What is the approximate additional inpatient cost of primary postoperative ileus?

a. $2500  
b. $5000  
c. $7500  
d. $10000

Influence of IV Opioid Use on Postoperative Ileus (POI)

- 8.6% incidence of POI in patients with colorectal surgery
- Significant risk factors for POI
  - Hydromorphone dose of 2 mg or more ($p = 0.034$)
  - Open surgical technique ($p = 0.045$)
  - More days of IV narcotic therapy ($p = 0.003$)


Costs of Postoperative Ileus

- Retrospective review of 186 colectomy patients from one hospital, July 2007 – June 2008
- Primary ileus defined as > 3 episodes of emesis in 24 hours, and return to NPO status and/or insertion of nasogastric tube
- Secondary ileus defined as an intraabdominal complication
- 24% had ileus (84% primary)

POI: Clinical and Economic Results

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Primary Ileus</th>
<th>No Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (days)</td>
<td>8.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Duration of opioids (hours)</td>
<td>142</td>
<td>43</td>
</tr>
<tr>
<td>Hospital cost ($)</td>
<td>15,914</td>
<td>8316</td>
</tr>
<tr>
<td>Pharmacy cost ($)</td>
<td>2639</td>
<td>454</td>
</tr>
</tbody>
</table>

*Data reported as mean values


Pain Control May Be Attached to Your Bottom Line $$$

- Hospital care quality information from the consumer perspective
  - Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS)
    - Hospital-specific data
    - Public reporting
    - Enhance accountability and transparency
- Center for Medicare and Medicaid Services
  - HCAHPS will be used for value-based incentive calculations starting October 2012

HCAHPS: Hospital care quality information from the consumer perspective (URL in ref list).

Conclusion

- Higher total hospital costs generated from
  - Inadequately managed pain
  - ADEs from opioids
- Multimodal therapy that contributes to opioid dose reduction may reduce these costs
- Cost of treating pain extends beyond cost of the drug
  - Value-based incentive programs
- Cost-effectiveness studies needed
  - Including patient-reported outcomes
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SELECTED REFERENCES


Postoperative Pain Management: Economic Implications of Conventional Therapy and Evolving Role of Non-opioid Approaches

Postoperative Pain Management: Economic Implications of Conventional Therapy and Evolving Role of Non-opioid Approaches

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Leslie N. Schechter, Pharm.D., is Advanced Practice Pharmacist specializing in pain management and nutritional support at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania. She is also Clinical Assistant Professor at Philadelphia College of Pharmacy at the University of the Sciences and Adjunct Assistant Professor at Temple University School of Pharmacy in Philadelphia. She serves as a preceptor for Doctor of Pharmacy students at Jefferson School of Pharmacy.

At Thomas Jefferson University Hospital (TJUH), Dr. Schechter serves as Pharmacy Liaison for the Acute Pain Management Service (APMS) and is involved in APMS clinical trials. She also provides pharmacotherapy recommendations relating to pain management, conducts medication use reviews related to pharmaceutical pain management therapy, and is involved in the drug review process for formulary addition considerations for anesthesia and pain medications. Dr. Schechter is a member of the TJUH Pain Initiative, an interdisciplinary group that developed a booklet of pain management guidelines, which is updated periodically and distributed to all medical, surgical, nursing, and pharmacy staff.

Dr. Schechter earned her Bachelor of Science degree in pharmacy from the Virginia Commonwealth University’s Medical College of Virginia in Richmond and her Doctor of Pharmacy degree from Purdue University College of Pharmacy and Pharmaceutical Sciences in West Lafayette, Indiana. She completed a residency accredited by the American Society of Health-System Pharmacists (ASHP) at the Medical College of Virginia Hospitals.

Dr. Schechter is a member of ASHP and the American Society for Parenteral and Enteral Nutrition. She has contributed chapters to several textbooks on pain management, including *The Essence of Analgesia and Analgesics* (Cambridge University Press), *Handbook of Drug-Nutrient Interactions* (Humana Press), *Acute Pain Management*, 1st ed. (Cambridge University Press), and *Textbook of Regional Anesthesia and Acute Pain Management* (McGraw-Hill). She has also authored several articles related to pain management. She is frequently invited to speak on topics related to pain management for interdisciplinary health care audiences.
Multimodal Postoperative Pain Management: Focus on Non-opioid Injectable Analgesics
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Advanced Practice Pharmacist, Pain Management and Nutritional Support
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Clinical Assistant Professor
Philadelphia College of Pharmacy
University of the Sciences
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Pathophysiologic Changes from Acute Pain
- Injury with peripheral nociceptors stimulation
  - Release of intracellular hydrogen, potassium, bradykinin, serotonin, prostaglandins
- Bradykinin and prostaglandin stimulate release of substance P
  - Sensitizes additional nociceptors at sites adjacent to the injury


Pathophysiologic Changes from Acute Pain
- Neurohumoral alterations
  - Termed peripheral sensitization
  - Triple response
    - Increased blood flow (flare)
    - Tissue edema (wheat)
    - Sensitization of peripheral nociceptors (hyperalgesia)

Pathophysiologic Changes from Acute Pain

- **Neuroendocrine responses**
  - Stress response to injury characterized by
    - Increased secretion
      - Cortisol, glucagon, growth hormone, catecholamines
    - Inhibition of anabolic mediators
      - Insulin, testosterone
  - Mediating
    - Hyperglycemia
    - Negative nitrogen balance
    - Impaired immunocompetence
      - Decreased resistance to infection


Pathophysiologic Changes from Acute Pain

- **Sympathoadrenal activation**
  - Marked increases in epinephrine and norepinephrine
    - Elevation of heart rate and blood pressure
    - Diminution of regional blood flow
  - Increased sympathetic tone may become deleterious
    - High risk patients where myocardial activity and work of breathing may exceed the oxygen and metabolic supplies may result in myocardial ischemia
    - Impaired wound healing with diminished blood flow to injured tissue
    - Renal hypoperfusion - activation of renin-angiotensin-aldosterone axis
      - May increase platelet activation and accelerate coagulation


Enlarged slide on page 37
Severity of Acute Postoperative Pain: Link to Chronic Pain

• In first postoperative week, patients undergoing thoracotomy who developed chronic pain (n=78)* vs. those who did not (n=71) reported
  – Greater incidence of acute pain (p=0.002)
  – More severe acute pain (p=0.0001)
  – Greater total amount of time spent having pain (p=0.02)
• Incidence of progression to chronic pain increased with intensity of acute postoperative pain

*Chronic pain assessed 6 months to 3.5 years after surgery


Long-Term Consequences of Acute Pain: Potential for Progression to Chronic Pain

- Surgery or injury causes inflammation
  - Peripheral nociceptive fibers
- Transient activation
- Peripheral nociceptive fibers
- Sustained activation
- CNS neuroplasticity
- Structural remodeling
- Hyperactivity

- Multimodal Analgesia
  • Pain involves multiple mechanisms
  • Requires treatment using multimodal analgesic techniques
  • Generally involves the administration of opioid and non-opioid analgesics
    – Acting at different sites within the central and peripheral nervous systems
    – Goal is to improve analgesia with additive or synergistic effects and to diminish or eliminate adverse effects

Benefits of Multimodal Analgesia

- Reduced doses of each analgesic
- Improved pain relief secondary to synergistic or additive effects of particular agents
- Adverse effects of individual medications may be reduced
- Fewer analgesic gaps
- Outcomes of acute pain are improved

*Pain is complex and multifactorial, thus appropriate management requires a “balanced” therapeutic approach*


Multimodal Approach


**Injectable NSAIDs**

- Currently available products in the U.S. include ketorolac and ibuprofen
- Diclofenac injection received a complete response letter from FDA in October 2010
  - Issues related to manufacturing quality processes and particulates found in European products
  - Timing of resolution is uncertain
- Tenoxicam and parecoxib are available in Europe

NSAIDs = nonsteroidal anti-inflammatory drugs

2 Hospira Inc. Form 10-K (URL in reference list).
Injectable NSAIDs

- Mechanism of action for non-selective NSAIDs
  - Inhibition of prostaglandin biosynthesis via non-selective inhibition of cyclo-oxygenase enzymes to decrease the conversion of arachidonic acid into prostaglandin endoperoxides, including thromboxane and prostacyclin

- Adverse effects for all products are similar
  - Gastrointestinal ulceration by inhibiting prostaglandins involved in protection of GI mucosa
  - Potential to prolong bleeding by inhibiting platelet thromboxane A₂ synthesis resulting in inhibition of platelet aggregation
  - Renal impairment by inhibiting renal prostaglandins

GI = gastrointestinal


Intravenous Ibuprofen

- RCT of 185 elective orthopedic surgeries
  - 800 mg IV ibuprofen every 6 hours (first dose pre-operatively)
    - 25.8% reduction in mean AUC-VAS assessed with movement (p<0.001)
    - 31.8% reduction in mean AUC-VAS assessed at rest (p<0.001)
    - 30.9% reduction in morphine use (p<0.001)
    - Similar adverse events
  - Pre- and postoperative administration of IV ibuprofen significantly reduce both pain and morphine consumption

RCT = randomized controlled trial
AUC-VAS = area under the curve visual analog scale

Intravenous Ibuprofen

- RCT of 406 patients undergoing single-site orthopedic or abdominal surgery
  - Study design
    - All patients received morphine patient-controlled analgesic (PCA)
    - Randomly assigned 1:1:1 ratio
      - Ibuprofen 400 mg IV every 6 hours
      - Ibuprofen 800 mg IV every 6 hours
      - Placebo IV every 6 hours
    - Received study drug at wound closure and every 6 hours for 48 hours
    - Continuation beyond 48 hours was permitted at discretion of investigator

Intravenous Ibuprofen

- Study results
  - 800 mg dose compared with placebo
    - Median morphine consumption significantly reduced by 26%
    - Significant reduction in pain at rest and with movement
    - Significantly fewer GI adverse effects, including nausea, vomiting, and constipation
  - 400 mg dose compared with placebo
    - Difference in morphine consumption compared to placebo not statistically significant
    - Significant reduction in pain at rest and with movement
    - Significantly fewer GI adverse effects, including nausea, vomiting, and constipation
  - No significant differences with respect to time to GI motility, time to ambulation, time to resumption of liquid and solid diet, or hospital length of stay


Injectable NSAIDs

- Studies have demonstrated that administration of intravenous NSAIDs will decrease opioid requirements and incidence of adverse events compared with opioids alone
- To date, there are no clinical trials on comparative efficacy between IV ibuprofen and IV or IM ketorolac
- Currently, duration of ibuprofen is not restricted
  - Only studied for up to 5 days
  - Use with caution for therapy > 5 days


M = intramuscular

Intravenous Acetaminophen (Paracetamol)

- Known outside the U.S. as paracetamol, acetaminophen is a non-opioid, non-NSAID analgesic and antipyretic
- 20-40% opioid dosage reduction across studies
- Component of multimodal analgesia
  - Alternative to oral and rectal acetaminophen
- Effective analgesia with low incidence of adverse events
  - Has not been shown to affect platelet function, increase surgical bleeding, or affect kidney function
- Approved by FDA in November 2010

Intravenous Acetaminophen (Paracetamol)

• Exact mechanism of action is unclear, but current evidence points to variety of central and peripheral mechanisms
  – Inhibition of centrally acting cyclooxygenase with very weak peripheral effects
    • Central effects may explain antipyretic effect
    • Minimal peripheral effects may be responsible for lack of gastric irritation and clotting abnormalities
  – Interactions with various neurotransmitters and modulators controlling pain processing and perception (serotonergic and cannabinoid systems)
• Contraindicated in patients with severe hepatic impairment


Pharmacokinetics of Intravenous vs. Oral Acetaminophen

38 healthy adult males randomly assigned to each group
n = number of patients with plasma concentrations measured

- Mean acetaminophen concentration over time: 6-hour dosing regimen (arrows)
- Mean maximum concentration up to 70% higher in intravenous than in oral acetaminophen

1Rapid release liquid oral acetaminophen
2Schutz RA et al. Presented at ASRA 32nd Annual Regional Meeting, Vancouver, Canada; 2007 Apr 19-22; Ofirmev injection prescribing information. 2010 Nov (URL in ref list).

Clinical Study in Orthopedic Surgery

• Randomized, double-blind, placebo-controlled multidose study in total hip or knee arthroplasty
• 7 U.S. centers, N=151 (n=101 excluding propacetamol* group)
• Patients with moderate to severe pain, 3 treatment groups
  – IV acetaminophen 1 g
  – IV propacetamol 2 g
  – Placebo
• Rescue medication: PCA morphine plus PRN bolus doses available
• Treatment initiated morning following surgery
• Endpoints measured at selected intervals
  – Pain intensity, pain relief, patient satisfaction, and morphine use

*Prodrug for paracetamol, not available in the U.S.
PRN = as needed

Clinical Study in Orthopedic Surgery: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IV Aetaminophen</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient satisfaction: good to excellent at 24 hr</td>
<td>40.8%</td>
<td>23.1%</td>
<td>0.0041</td>
</tr>
<tr>
<td>Median time to first use of rescue</td>
<td>3.0 hr</td>
<td>0.8 hr</td>
<td>0.0001</td>
</tr>
<tr>
<td>Morphine consumption over 24 hr</td>
<td>38.3 mg</td>
<td>57.4 mg</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\*Clinical benefit of reduced opioid consumption was not demonstrated
\* PCA = patient controlled analgesia

Clinical Study after Abdominal Laparoscopic Surgery

- Patients randomized to 4 groups
  - IV acetaminophen 1 g/100 mL every 6 hours for 24 hours
  - IV acetaminophen 650 mg/65 mL every 4 hours for 24 hours
  - Placebo 100 mL every 6 hours for 24 hours
  - Placebo 65 mL every 6 hours for 24 hours
- Open-label extension
- Rescue drug was limited to IV hydromorphone or morphine and oral limited to morphine or oxycodone


Clinical Study after Abdominal Laparoscopic Surgery

- Results
  - Both acetaminophen dosing regimens associated with significantly reduced sum of pain intensity differences over 24 hours (SPID24)
    - 1 g every 6 hours, \( p < 0.007 \)
    - 650 mg every 4 hours, \( p < 0.019 \)
  - Time to meaningful pain relief after first dose of study drug significantly shorter among subjects receiving acetaminophen 1 g compared with those receiving placebo 100 mL
  - Adverse effects across all treatment groups not statistically significant

**Serum Paracetamol Concentration with Rectal Administration**

- Paracetamol concentrations of 10 to 20 mcg/mL are associated with antipyretic activity
  - No formally defined concentrations for analgesia although consensus is that analgesic and antipyretic concentrations will be similar
- 10 volunteers, 4 occasions separated by at least 48 hours
- Each volunteer received increasing doses of rectal paracetamol starting with 15 mg/kg, rising by 10 mg/kg to a maximum of 45 mg/kg


**Serum Paracetamol Concentration with Rectal Administration: Results**

- Values not shown for 15 mg/kg dose (1.05 g in 70-kg person)
  - Failed to achieve median concentrations > 10 mcg/mL
- 25 mg/kg produced concentrations at lower end of therapeutic range for brief period of time
- 1-2 hour delay in achieving therapeutic concentrations
- Doses of 35 to 45 mg/kg, administered 2 hours before any desired effect are needed to achieve sustained concentrations within accepted therapeutic range

<table>
<thead>
<tr>
<th>Paracetamol Dose</th>
<th>Dose for 70-kg Person</th>
<th>Median Time above 10 mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg/kg</td>
<td>2.45 g</td>
<td>5.5 hr</td>
</tr>
<tr>
<td>45 mg/kg</td>
<td>3.15 g</td>
<td>6 hr</td>
</tr>
</tbody>
</table>


**Patient Case: MB**

- MB is a 76-year-old woman who is admitted for her 3rd knee revision. In the past, opioid administration has resulted in dementia.
- In the post-anesthesia care unit, she is experiencing severe nausea and vomiting. A wound VAC device has been placed on the knee incision secondary to excessive postoperative bleeding.
- Her postoperative pain regimen is fentanyl 10 mcg IVP q1hr for pain.

VAC = vacuum-assisted closure
IVP = IV push
Although the choice and route of opioid may be optimized for MB, what would you recommend for multimodal therapy?

- Intramuscular ketorolac.
- Intravenous ibuprofen.
- Intravenous acetaminophen.
- Rectal acetaminophen.

**NMDA Receptor Antagonism: Ketamine as a Multimodal Agent**

- Renewed interest in enhancing postoperative analgesia
- Antagonist at the NMDA receptor
  - At low sub-anesthetic doses, exerts a specific NMDA blockade, modulating central sensitization induced by the incision and tissue damage
- Opioid-sparing effect with advantages in patients in whom high postoperative opioid consumption is anticipated (i.e., opioid-tolerant patient)


**Ketamine**

- Cochrane review included 2240 patients, 37 trials
  - Patient sample size small and heterogeneous
  - Variables
    - Timing of administration
    - Route (epidural and intravenous)
    - Dosage
    - Type of surgical procedure
- Subanesthetic doses of ketamine reduced
  - Postoperative pain intensity
  - Rescue analgesic consumption
    - PCA morphine consumption
  - Postoperative nausea and vomiting

Bell RF et al. Cochrane Database Syst Rev. 2006; CD004603.
Ketamine

- Systematic review of IV ketamine for postoperative analgesia, published studies from 1966-2010
  - 47 studies appropriate for evaluation
  - Randomized, double-blinded, placebo-controlled
  - Used IV ketamine to decrease postoperative pain
- Results
  - Reduction in total opioid consumption
  - Increase in time to first analgesic rescue dose
  - Greatest efficacy in thoracic, upper abdominal, and major orthopedic surgery
  - Majority of patients experienced lower pain scores
  - Hallucinations and nightmares more frequent with ketamine
  - No risk for increased sedation
  - Less postoperative nausea and vomiting when ketamine was efficacious for pain


Local Anesthetics

- Membrane stabilizers
  - Reversibly decrease the rate of depolarization and repolarization of excitable membranes, including nociceptors
  - Act primarily by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane
  - When the influx of sodium is interrupted, an action potential cannot arise, and signal conduction is inhibited

Local Anesthetic Techniques

- Wound and joint
  - Single injection
  - Catheters
- Peripheral nerve blocks
  - Single injection
  - Catheters
- Epidural
  - These techniques rarely provide complete analgesia but work best with multimodal analgesia and opioid rescue

Benefits of Continuous Peripheral Nerve Block (CPNB)

- Superior pain control over parenteral opioids
- Fewer opioid-related adverse effects
- Does not completely eliminate need for analgesic supplement (opioid)
- Improved sleep
- Improved rehabilitation
- Enhanced patient satisfaction


Ambulatory Continuous Brachial Blockade

- Study comparing efficacy of single injection interscalene brachial plexus blockade with CPNB
- Results for CPNB infusion of ropivacaine 0.2% at 10 mL/hr
  - Dramatic reduction in pain scores
  - 47% reduction in supplemental analgesics

Clinical pearl
- Consider the logistics of managing outpatient infusions


Wound Infiltration: Elastomeric Balloon Infusion Devices

- Device used for continuous wound infiltration with local anesthetic
- Approved by new products or value analysis committee within hospital organizations
- Local anesthetic is placed in device either in operating room (OR) or filled by pharmacy department in accordance with USP 797
- Requires mechanism to dispense and record administration of local anesthetic
- Requires physician, nurse, and pharmacy education
Elastomeric Balloon Infusion Devices

Elastomeric Balloon Infusion Devices: Clinical Trial

- RCT of 160 patients undergoing open nephrectomy
  - Patients received morphine PCA, ketorolac, and either saline placebo or 0.5% ropivacaine 4 mL/hr in elastomeric pump for 48 hours
- Results
  - Adverse effects for both groups similar
  - VAS pain scores, morphine consumption, time to bowel recovery, and mean length of hospitalization significantly reduced in active treatment group


Epidural Administration of Local Anesthetics

- Continuous infusion
  - Used for acute and chronic pain
  - Advantages
    - Permits concomitant use of local anesthetics and shorter-acting opioids
    - Eliminates need for repeated catheter injections, lowering risk for catheter contamination
    - Greater potency than systemic administration
  - Disadvantages
    - Potential for catheter migration and adverse effects
- Single injections

Pyati S et al. CNS Drugs. 2007; 21:185-211.
Multivesicular Liposome: DepoFoam®

- Particle suspension in isotonic aqueous solution
- 10 – 30 mm diameter
- Injected with fine-gauge needles
- Well tolerated
  - Phospholipids, triglycerides, cholesterol
- Release: 1 to 30 days
- Delivery: mcg to mg/day
- Water-soluble and solution-stable drugs


Liposomal Bupivacaine for Intradermal Administration

- Extended-release bupivacaine*
  - Bupivacaine is a short-acting local anesthetic with duration of action averaging 6 to 8 hours
- Bupivacaine extended-release liposome injection releases bupivacaine over several days
  - DepoFoam uses membrane components that are neutral and cleared by normal metabolic pathways
  - FDA approval October 28, 2011

*Pacira Pharmaceuticals, Inc.


Liposomal Bupivacaine for Intradermal Administration

- Clinical phase III trials demonstrated a sustained-release profile of bupivacaine 75 to 600 mg compared with placebo or bupivacaine 75 to 200 mg single injection
  - Included hemorrhoidectomy, herniorrhaphy, breast augmentation, bunionectomy, total knee arthroplasty, and cardiac surgery
- Clinical trials demonstrated
  - Reduction in pain scores
  - Reduction in opioid consumption
- Patients avoided opioids until later in their hospital stay
- No clinical trials comparing extended-release bupivacaine with CPNB

Patient Case: TC

- TC is a 56-year-old man who is admitted for his 2nd knee revision with flap.
- His current home medications include oxycodone extended release 120 mg every 8 hours (continued postoperatively) and oxycodone 30 mg every 4 hours prn.
- TC is given an epidural with local anesthetic and hydromorphone PCA. An epidural bolus and nursing PCA bolus have not improved his pain, still reported as 9 out of 10.

What would be the most appropriate addition to TC's pain management regimen?

a. IV ketorolac
b. Incisional administration of local anesthetic
c. IV ketamine
d. IV acetaminophen

Conclusion

- Advances in understanding the mechanisms of pain have led to improvements in the management of acute pain
- Improperly managed acute pain can trigger long-term plastic neuronal changes leading to chronic pain
- Multimodal therapy offers improvement in acute pain management and better clinical outcomes
- The optimal combination of adjuvant agents and understanding of dose-response relationships requires further investigation
Pathophysiologic Responses Associated with Trauma

SELECTED REFERENCES


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Clinical Assistant Professor of Surgery
University of Vermont College of Medicine
Burlington, Vermont

Wesley D. McMillian, Pharm.D., BCPS, is Clinical Pharmacy Manager at Fletcher Allen Health Care in Burlington, Vermont. He specializes in adult critical care and trauma. He is also Clinical Assistant Professor of Surgery at the University of Vermont College of Medicine in Burlington and Clinical Adjunct Assistant Professor of Pharmacy at Albany College of Pharmacy on both the Albany, New York, and Colchester, Vermont, campuses.

Dr. McMillian earned his Bachelor of Science degree in chemical engineering and Doctor of Pharmacy degree from Purdue University in West Lafayette, Indiana. He completed a postgraduate year 1 (PGY-1) residency at Boston Medical Center in Boston, Massachusetts, and a postgraduate year 2 (PGY-2) residency in critical care pharmacy at Fletcher Allen Health Care (FAHC) in Burlington, Vermont, both of which are accredited by the American Society of Health-System Pharmacists (ASHP). He is a board-certified pharmacotherapy specialist.

At FAHC, Dr. McMillian is the program director for the PGY-2 residency in critical care pharmacy. He practices in surgical and trauma intensive care at the only Level I Trauma Center in Vermont. As a member of the FAHC Pharmacy and Therapeutics Committee and Critical Care Committee, he is involved with reviewing new analgesics, as well as developing and revising sedation and analgesia guidelines for the intensive care units. Dr. McMillian orients all surgery, anesthesia, and critical care nursing interns on the prevention and treatment of pain and the use of multimodal therapies.

Dr. McMillian is a member of ASHP, American College of Clinical Pharmacy, and Society of Critical Care Medicine. His clinical research has focused on sepsis, antimicrobial pharmacodynamics, anticoagulation, and delirium in the intensive care unit. He has authored several publications and has given many invited lectures on sedation, analgesia, and delirium.
Practice Tips for Incorporating Non-opioid Injectable Analgesics into Optimal Postoperative Pain Management

Wesley D. McMillian, Pharm.D., BCPS
Clinical Pharmacy Manager
Fletcher Allen Health Care
Clinical Assistant Professor of Surgery
University of Vermont College of Medicine
Burlington, Vermont

What is the maximum daily dose of acetaminophen at your institution?

a. 4000 mg
b. 3000 mg
c. 2000 mg
d. Whatever the prescriber orders

Acetaminophen

- Almost 50% of all liver failure cases
  - Exceeded prescribed dose
  - Took more than 1 acetaminophen-containing product
    - > 600 over-the-counter products
  - Drank ethanol while taking acetaminophen

U.S. Food and Drug Administration (FDA). New steps aimed at cutting risk from acetaminophen. Updated 2011 Sept 9 (URL in ref list).
Acetaminophen: Coming Changes

- FDA action January 2011
  - 325 mg per tablet for prescription products
  - Boxed warning of severe liver injury
  - Phased in over 3 years
- McNeil action July 2011
  - Extra strength product maximum dose 3000 mg sometime in Fall 2011
  - Maximum daily dose for regular strength and other products to be reduced in 2012

Intravenous Acetaminophen

- FDA approved in November 2010
- Indications
  - Management of mild to moderate pain
  - Management of moderate to severe pain with adjunctive opioid analgesics
  - Reduction of fever
- Availability
  - 1000 mg/100 mL glass vial

Acetaminophen Doses < 1000 mg

- Create full dose in a separate container
  - Syringe
  - Intravenous bag
  - Glass bottle
- Once stopper is punctured, dose should be used within 6 hours
Where Does IV Acetaminophen Fit?

- Intraoperative administration
- Alternative to enteral and rectal acetaminophen
  - Lack of enteral access
  - Ileus
  - Profuse diarrhea or use of a fecal collection device
  - ? In hemodynamic instability
- Alternative to intravenous NSAIDs
  - Kidney dysfunction
  - High risk of postoperative bleeding

NSAIDs = nonsteroidal anti-inflammatory drugs

Does your anesthesia medication documentation record “speak” with your pharmacy system or medication administration record?

a. Yes
b. No
c. Unsure

IV Acetaminophen: Dosing and Administration

- Recommended dosage for adults and adolescents weighing ≥ 50 kg
  - 650 mg IVPB over 15 minutes every 4 hours
  - 1000 mg IVPB over 15 minutes every 6 hours
  - Maximum daily dose 4000 mg
- Recommended dosage for children ≥ 2 years and for adolescents and adults weighing < 50 kg
  - Administer via IV syringe pump over 15 minutes
  - 12.5 mg/kg every 4 hours
  - 15 mg/kg every 6 hours
  - Maximum single dose 750 mg
  - Maximum daily dose 3750 mg

IVPB = IV piggyback

Ofirmev injection prescribing information. 2010 Nov (URL in ref list).
IV Acetaminophen: Ensuring Safety

- Dosing
  - Organ function (liver function tests)
  - Discontinue all other acetaminophen sources
- Intravenous infusion rate
  - Expiration date and time
  - Use smart pump
  - Administer over 15 minutes
  - Concerns with hypotension
    - Associated with propacetamol and oral acetaminophen for treatment of fever in critically ill patients


IV Acetaminophen: How to Minimize Cost While Maintaining Effectiveness

- Reserve for patients who are nil per os (NPO) and nothing per rectum
- Automatic stop dates
- Pharmacist-run intravenous-to-oral conversion
- Dose rounding
  - Convert orders for 650 mg to 500 mg
  - Use single vial for 2 doses for every 4-hour regimen
  - Round up from 650 mg to 1000 mg, if clinically appropriate

Injectable NSAIDs: Indications

- Ketorolac tromethamine
  - For short-term (≤ 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level
- Ibuprofen
  - Mild to moderate pain
  - Moderate to severe pain as adjunct to opioids
  - Reduction of fever

Ketorolac tromethamine injection, USP, product insert. 2010 Mar (URL in ref list).
Caldolor (ibuprofen) injection, for IV use, prescribing information. 2009 Jun (URL in ref list).
Injectable NSAIDs: Administration

- Ketorolac tromethamine (IV and IM)
  - 15, 30, 60 mg/mL
  - Administer no faster than 15 seconds
- Ibuprofen (IV only)
  - 400 mg/4 mL, 800 mg/8 mL
  - Must dilute to 4 mg/mL or less
  - Infuse over a minimum of 30 minutes

Injectable NSAIDs: Dosing

<table>
<thead>
<tr>
<th>Ketorolac tromethamine</th>
<th>Ibuprofen injection*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>Pain</td>
</tr>
<tr>
<td>- 30 mg IV every 6 hours</td>
<td></td>
</tr>
<tr>
<td>- Max 120 mg per day</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years; &lt; 50 kg</td>
<td>Fever</td>
</tr>
<tr>
<td>- 15 mg IV every 6 hours</td>
<td></td>
</tr>
<tr>
<td>- Max 60 mg per day</td>
<td></td>
</tr>
<tr>
<td>Pediatric 2-16 years</td>
<td></td>
</tr>
<tr>
<td>- 0.5 mg/kg IV x 1</td>
<td></td>
</tr>
<tr>
<td>- Max 15 mg</td>
<td></td>
</tr>
</tbody>
</table>

*For adults ≥ 18 years old

NSAIDS: Ensuring Safety

- Intravenous ibuprofen not for age < 18 years
  - Injectable ketorolac < 2 years
- Caution in hypovolemia and elderly
- Black box warning
  - Cardiovascular risk
    - Hypertension and congestive heart failure
  - Gastrointestinal risk
- Assess organ function
- Limit duration of therapy
NSAIDS: Maximizing Cost Effectiveness

- Use ketorolac tromethamine
  - Roughly 1/30th the acquisition cost of intravenous ibuprofen
  - No compounding required
  - No head-to-head trials
- Establish pharmacist-run intravenous-to-oral conversion
- Limit ketorolac tromethamine and possibly ibuprofen to 5 days total

Acetaminophen or NSAID?

- Acetaminophen and NSAIDs are both analgesics and antipyretics
- NSAIDs are anti-inflammatory
- Acetaminophen does not prolong bleeding time
- No significant difference in analgesic efficacy for musculoskeletal or postoperative pain
- Selection depends on patient characteristics
- Combination of acetaminophen and NSAIDs

Ketamine Hydrochloride

- Indication and use
  - Sole anesthetic for diagnostic and surgical procedures not requiring muscle relaxation
  - Induction of anesthesia before administration of other general anesthetic agents
  - Supplement to low potency agents (i.e., nitrous oxide)
  - Anesthesia, short surgical procedures, and dressing changes in pediatrics
- Off-label
  - Prevention and treatment of acute pain

Ketamine Administration

- Intravenous
  - Pre-incisional
  - Post-incisional
  - Perioperative
  - In combination with or without morphine
  - Patient-controlled analgesia with or without morphine
- Epidural
  - Pre-incisional
  - Post-incisional
  - Perioperative
  - Patient-controlled epidural analgesia with morphine


IV Ketamine Dosing for Analgesia

- Pre-incisional dose
  - 0.15-1 mg/kg intravenous bolus
- Post-incisional dose
  - 0.05-1 mg/kg intravenous bolus
- Continuous infusion
  - 2-10 mcg/kg per minute +/- morphine
  - 0.1-0.5 mg/kg per hour +/- morphine
- Mix 500 mg in 100 mL normal saline or 5% dextrose in water


Epidural Ketamine Dosing for Analgesia

- Pre-incisional bolus dose
  - 0.25-0.5 mg/kg
- Post-incisional bolus dose
  - 0.25-1 mg/kg
- Continuous epidural infusion
  - 0.125-0.25 mg/kg per hour
  - 0.5 mg/hr + 0.5 mg/hr morphine

When Should You Use Ketamine?

• Patients at high risk of opioid-induced adverse events
  – Patients with COPD or OSA
• Patients with history of significant opioid use
  – Tolerance
  – Opioid-induced hyperalgesia

COPD= chronic obstructive pulmonary disease
OSA= obstructive sleep apnea

Opioid-Induced Hyperalgesia

• Hyperalgesia
  – Increased sensitivity to noxious stimuli
  – Mechanism not fully elucidated
    • Peripheral, spinal cord, central nervous system
    • Which neurotransmitters are involved?
    • Association with NMDA activation
  – Allodynia
    • Painful response to nonpainful stimuli

NMDA= N-methyl-D-aspartate


Opioid-induced Hyperalgesia

Does Ketamine Prevent Opioid-Induced Hyperalgesia?


Safety Measures: Ketamine

- Limited data in patients < 16 or > 65 years
- Caution in patients with uncontrolled hypertension
- Potential for emergence delirium
  - Rare in sub-anesthetic dosing
- Telemetry is unnecessary, especially if appropriate patients are selected
- Smart infusion pumps
- Acute (Anesthesia) Pain Service

Keys to Cost-effective Use of Ketamine

- Restrict to patients at highest risk of opioid adverse effects or on high doses of opioids before surgery
- Much of the associated cost may be attributed to provider fees if restricted to anesthesia
Continuous Peripheral Nerve Block (CPNB): Unknowns

• How does CPNB compare with single injection peripheral nerve block?
  – Less pain, earlier ambulation, greater patient satisfaction, earlier discharge, PACU bypass
  – Is it worth the additional effort (cost)?
• Failure rate of catheters
• Comprehensive cost analysis

PACU = post-anesthesia care unit

Concerns with Elastomeric Balloon Infusion Devices

• Preparation considerations
  – Filling devices in operating room versus pharmacy
  – Labeling of the device
• ISMP recommends safety improvements
  – Ensure proper education of hospital staff and the patient
  – Ensure pharmacy involvement
  – Pharmacy and nursing profiling of order
  – Identify medications that may be added to the device
  – Verify infusion rate and concentration
• Evaluate concomitant analgesic administration

Institute for Safe Medication Practices.

Liposomal Bupivacaine

• Indicated as a single-dose infiltration into the surgical site to produce post-surgical analgesia
• Available
  – 10 mL, 1.3% (13.3 mg/mL)
  – 20 mL, 1.3% (13.3 mg/mL)
• Contraindicated in obstetrical paracervical block anesthesia
  – Avoid the risks of fetal bradycardia and death

Exparel (bupivacaine liposome injectable suspension) prescribing information. 2011 Nov (URL in ref list).
Liposomal Bupivacaine: Ensuring Safety

- Not approved for use in patients < 18 years
- Only to be mixed in preservative-free normal saline
  - Free water will disrupt liposome particle
  - Not to be mixed with other medications
- Use only in 25-gauge or larger syringe
- Do not freeze
  - Has color indicator in label
- Use with caution in patients with hepatic or kidney insufficiency

Exparel (bupivacaine liposome injectable suspension) prescribing information. 2011 Nov (URL in ref list).

Liposomal Bupivacaine: Dosing

- Invert vial to re-suspend particles
- Wait at least 20 minutes after last lidocaine dose before administration
- Bunionectomy
  - 106 mg (8 mL): 7 mL into tissue and 1 mL subcutaneously
- Hemorrhoidectomy
  - 266 mg (20 mL): add to 10 mL saline and make six 5 mL aliquots for administration around anal sphincter
- Wait at least 96 hours before administration of other anesthetic products

Exparel (bupivacaine liposome injectable suspension) prescribing information. 2011 Nov (URL in ref list).

Developing a Plan of Attack
**Prevention of Pain...**

**Preoperative patient assessment**

- Past medical and social history
- Medications before admission
- Chemistry lab assessment

**Current pain medication use**

- Yes
- No

Assess if home pain regimen is contraindicated for planned procedure

Patient should take usual home dose

Intraoperative anesthesia and analgesia

Postoperative pain management

**Postoperative Analgesic Plan**

Review intraoperative analgesia

Initiate postoperative analgesia or adjust dose or interval of home analgesia

Was adequate pain relief obtained without untoward adverse effects?

- Yes
- No

Change drug, regimen, or route; add alternative therapy; or treat adverse effects

Optimize dose and/or interval

Follow up as needed

Educate on prevention

Provide discharge plan

Modified from U.S. Department of Veteran Affairs. 2002 Apr (URL in ref list).

**General Postoperative Pain Treatment Algorithm**

**Moderate to Severe Pain**
- Opioids + NSAID or Acetaminophen
- Adjuncts:
  - Local anesthetics or ketamine
  - Anticonvulsants
  - Steroids
  - Tricyclic antidepressants

**Mild to Moderate Pain**
- Opioid + NSAID or Acetaminophen
- Adjuncts:
  - Anticonvulsants
  - Steroids
  - Tricyclic antidepressants

**Mild Pain**
- Acetaminophen or NSAID

Use as a basic template for development and review of postoperative analgesia order sets or guidelines.
Patient Case: AJ

- AJ is a 57-year-old man, 5’10” 212 lb
- Past medical history (PMH)
  - Low back injury suffered years ago
  - No significant medical issues
- Past surgical history (PSH): “tonsillectomy as a kid”
- Social history: 4-5 beers per week
- Medications prior to admission
  - Oxycodone/acetaminophen 5 mg/325 mg 1 tab PO q6hr PRN
  - Ibuprofen 200 mg PO PRN
- Posterior spinal fusion (L4-S1)

Which of the following is the most appropriate postoperative analgesic regimen for AJ?

a. Fentanyl 100 mcg IV q1hr PRN plus ketorolac 30 mg IV q6hr
b. Morphine 5 mg IV q6hr plus morphine breakthrough plus acetaminophen 1 g IV q6hr PRN
c. Fentanyl 100 mcg IV q1hr PRN plus acetaminophen 650 mg PR q4hr PRN
d. Morphine 5 mg IV q4hr plus morphine breakthrough plus acetaminophen 1 g PO q6hr

PR = per rectum

Patient Case: AB

- AB is a 29-year-old woman admitted secondary to motor vehicle collision, 5’4” 120 lb
  - Multiple rib fractures with flail segment bilateral open tib/fib [type II left, type I right], grade III liver laceration
- PMH/PSH: unobtainable
- Mechanically ventilated in surgical ICU
- Norepinephrine 7 mcg/min goal mean arterial pressure of 60 mmHg

```
142 115 120
4.0 20 0.8 14 157
ALT/AST 404/383
```
Which of the following is the most appropriate postoperative analgesic regimen for AB?

a. Morphine 2 mg IV q2hr PRN plus acetaminophen 1 g IV q6hr
b. Fentanyl 25 mcg/hr IV continuous plus fentanyl breakthrough plus ketamine 0.2 mg/kg per hour
c. Morphine 2 mg/hr IV continuous plus morphine breakthrough plus ketamine 0.2 mg/kg per hour
d. Fentanyl 50 mcg q1hr PRN plus ketorolac 30 mg IV q6hr

Conclusion

• Patient selection is the key to the safe and effective use of injectable non-opioid analgesics for the treatment of postoperative pain
• Guidelines or protocols for postoperative analgesia should include multimodal therapies
• Medication-use evaluations should be conducted to assess appropriateness of patient selection and cost effectiveness of newer injectable analgesics
Prevention of Pain...

Preoperative patient assessment
- Past medical and social history
- Medications before admission
- Chemistry lab assessment

Current pain medication use
- Yes
- No

Assess if home pain regimen is contraindicated for planned procedure
- Patient should take usual home dose
- Intraoperative anesthesia and analgesia
- Postoperative pain management

Postoperative Analgesic Plan

Review intraoperative analgesia
- Initiate postoperative analgesia or adjust dose or interval of home analgesia

Was adequate pain relief obtained without untoward adverse effects?
- Yes
- No

Change drug, regimen, or route; add alternative therapy; or treat adverse effects
- Optimize dose and/or interval
- Follow up as needed
- Educate on prevention
- Provide discharge plan

Modified from U.S. Department of Veteran Affairs. 2002 Apr (URL in ref list).
**SELECTED REFERENCES**


Postoperative Pain Management: Economic Implications of Conventional Therapy and Evolving Role of Non-opioid Approaches

SELF–ASSESSMENT QUESTIONS

1. Health care costs due to inadequate postoperative pain control have been quantified for all of the following EXCEPT
   
a. Hospital readmissions.
   b. Emergency department visits.
   c. Development of delirium.
   d. Longer hospital length of stay.
   e. Productivity loss.

2. What is the approximate additional cost of an inpatient episode of opioid-induced nausea and vomiting?
   
a. $200.
   b. $500.
   c. $800.
   d. $1100.
   e. $1500.

3. What is the approximate additional inpatient cost of primary postoperative ileus?
   
a. $2500.
   b. $5000.
   c. $7500.
   d. $10000.

4. The multimodal analgesia approach to the management of acute postoperative pain generally results in all of the following EXCEPT
   
a. Reduced doses of each analgesic.
   b. Improved pain relief secondary to synergistic or additive effects of different medications.
   c. More analgesia gaps.
   d. Reduced severity of adverse effects of individual medications.

5. Which of the following statements best summarizes the outcomes of clinical trials involving the administration of intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) as part of a multimodal analgesic regimen compared with opioids alone?
   
a. Decreased opioid requirements and increased safety in patients with renal impairment, thrombocytopenia, or active gastrointestinal bleeding.
   b. Decreased opioid requirements and decreased incidence of adverse effects.
   c. No change or increased opioid consumption and increased incidence of adverse effects.
   d. No change in opioid consumption and more gastrointestinal adverse effects.
6. Which of the following statements best describes the role of intravenous acetaminophen for the management of postoperative pain?

a. Offers no advantages compared with intravenous NSAIDs and should be avoided in the postoperative period because it may increase the risk of postoperative bleeding.
b. Offers no advantage over rectal acetaminophen and should be reserved for patients with coagulopathies who cannot be administered rectal medications.
c. May be safely used in patients with severe liver impairment.
d. May be used as alternative to intravenous NSAIDs and as alternative for oral and rectal acetaminophen.

7. Which of the following statements best describes the role of injectable local anesthetic options in the management of postoperative pain?

a. Injectable local anesthetics usually eliminate need for analgesic supplement.
b. Single injection peripheral nerve blocks result in less pain, earlier ambulation, and greater patient satisfaction compared with continuous peripheral nerve blocks.
c. The use of elastomeric balloon infusion devices for local anesthetic administration requires physician, nurse, and pharmacist education and policy development for preparation and profile documentation.
d. Liposomal bupivacaine for intradermal administration has been shown to have equal efficacy to continuous peripheral nerve blocks.

8. Which of the following strategies can help promote effective use of intravenous acetaminophen for postoperative pain while minimizing cost?

a. Reserve for use in patients who are fluid restricted.
b. Institute automatic stop dates.
c. Round up all orders for 650 mg to 1000 mg.
d. Continue for only 24 hours after postsurgical patients begin drinking and eating.

9. Which of the following strategies can help promote the cost-effective use of ketamine for postoperative pain?

a. Restrict to patients at highest risk of opioid-induced adverse effects.
b. Restrict to patients taking low doses of opioids before surgery.
c. Restrict to patients who are in intensive care units.
d. Restrict to patients under the age of 60 years.
10. If the head of the pharmacy and therapeutics committee asked how to maximize the cost-effective use of injectable non-opioid products in the surgical intensive care unit, which of the following would be the most appropriate response?

a. Create a pharmacist-run intravenous-to-oral conversion protocol for acetaminophen and NSAIDs on patient discharge from the surgical intensive care unit.
b. Create a postoperative analgesia protocol and restrict ordering of all analgesics through an order set.
c. Implement a postoperative analgesia order set and a pharmacist-run intravenous-to-oral conversion for acetaminophen and NSAIDs.
d. Implement a postoperative analgesia order set and a pharmacist-run intravenous-to-oral conversion for acetaminophen and NSAIDs and complete a medication-use evaluation at one year post-implementation.

11. In developing and reviewing postoperative order sets, local anesthetics or ketamine should be considered to be an adjunct to opioids combined with a NSAID or acetaminophen for which of the following categories of pain?

a. Mild only.
b. Mild to moderate.
c. Moderate to severe.
d. Severe only.

Answers
1. e
2. c
3. c
4. b
5. b
6. d
7. c
8. b
9. a
10. d
11. c