Acute Pain Management: New agents (IV Acetaminophen, Liposomal Bupivacaine), Opioid Safety and the Role of Pharmacogenetics

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OBJECTIVES

• Discuss the use of new acute pain management agents
• Discuss key aspects of opioid safety and the role of pharmacogenetics

Multimodal Approach

Acetaminophen

Liposomal bupivacaine

OPIOID-RELATED ADVERSE EFFECTS FOLLOWING ORTHOPEDIC SURGERY

- Retrospective review, urban teaching hospital
- 402 patients who underwent spine (fusion, laminectomy), hip (TKA), knee (TKA) or shoulder surgery
- Primary outcome: length of stay following surgery
- 70% received PCA for 1 – 2 days post-op, then oral opioids
  - Mean oral morphine equivalent
    - 60 mg/day
    - 275 mg over entire post-op course

RESULTS

- 54% experienced at least one adverse effect (AE)
- Rate declined with each post-op day, closely following decline in opioid use
- Constipation, confusion and emesis were significantly associated with increased LOS
- Impact of number of AEs on LOS
  - One AE: no effect
  - Two AEs: 15% increase
  - Three AEs: 40% increase
  - Four AEs: 82% increase
IV ACETAMINOPHEN

- Available in Europe since 2002
- Approved by FDA in November 2010 for:
  - Mild to moderate pain
  - Moderate to severe acute pain with an opioid
  - Reduction of fever

CENTRAL MECHANISM OF ACTION

IV ACETAMINOPHEN PHARMACOKINETICS

Less variability in plasma concentration with IV route (vs. oral & rectal)

Earlier and higher peak plasma and CSF concentrations with IV route

EFFICACY

- Studied in:
  - Adults: abdominal, orthopedic, tonsillectomy, dental surgery
  - Pediatrics: tonsillectomy, adenoidectomy, dental surgery, inguinal hernia repair
- In general, IV acetaminophen:
  - Improved pain relief
  - Reduced opioid consumption by about 20%, although reduced opioid requirements and/or opioid-related adverse effects are not consistently demonstrated

SINGLE DOSE

- 33 studies (N=3,896)
  - 712 paracetamol, 1,431 propacetamol, 1,048 placebo, 705 active comparator (opioid or NSAID)
  - Intervention was given:
    - Shortly before or after end of surgery or
    - After patient reported moderate-severe pain
- Results
  - At least 50% pain relief over 4 hours
    - Par/propacetamol superior to placebo (NNT = 4)
  - Opioid requirements
    - Paracetamol propacetamol pts required 30% less opioid over 4 hours and 16% over 6 hours compared with placebo
    - No difference in adverse effects, except fewer GI disorders with paracetamol (11%, 5/46) vs. opioids (42%, 19/45)
  - No head-to-head studies of IV paracetamol vs. active comparator

SAFETY

- Decreased glutathione stores in:
  - Starvation, malnutrition, fasting
  - Liver steatosis
- Risk increases with:
  - Concurrent CYP inducers (alcohol, antiepileptic drugs)
  - Elderly patient in poor health
  - Patients ≥ 80 yrs old have 1.3 – 1.5 fold greater exposure to metabolites
  - Physical status is associated with capacity of liver to eliminate APAP
NSAID use was associated with an increased risk of death/recurrent MI at the beginning of treatment and it persisted throughout treatment

Rofecoxib: ↑ risk after 1 week
Celecoxib: ↑ risk after 14 – 30 days
Ibuprofen: ↑ risk after 1 week
Diclofenac: ↑ risk at beginning & throughout tx
Naproxen: not associated with ↑ risk

Authors’ conclusion: “there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe”

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ACETAMINOPHEN vs. NSAID vs. COX-2

- Mixed treatment comparison (network meta-analysis)
- Excluded trials with drugs no longer on the market (valdecoxib, rofecoxib) and studies published by S. Rueben
- 60 trials; PCA morphine for ≥24 hrs after major surgery
- Outcomes
  - Morphine consumption in first 24 hrs post-op, N, V, sedation
  - Respiratory depression, urinary retention, pruritus, bowel dysfunction, dizziness
- Results
  - All drugs significantly reduced morphine consumption
  - Little difference between drugs in reducing morphine consumption or adverse effects
  - Incidence of surgical bleeding (N=895): 2.4% NSAID group vs. 0.4% placebo group

ACETAMINOPHEN + NSAID

- 21 studies (N=1909)
- Combo vs. acetaminophen alone
  - Combo patients had lower pain scores, lower supplemental analgesics or better globally assessed pain relief in 17/20 (85%) of studies
- Combo vs. NSAID alone
  - Combo patients had lower pain scores, lower supplemental analgesics or better globally assessed pain relief in 9/14 (64%) of studies
- No evidence of increased adverse effects with combo vs. single drug
  - Incidence of NV significantly higher in some studies for single drug alone, likely due to increased rescue morphine
  - In 4/5 (80%) negative studies, mean pain scores in control group were ≤30/100 mm

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DANISH POPULATION STUDY # 1

> 100,000 pts with first-time hospital admission for MI (1997 – 2006)
NSAID use was identified using pharmacy records
Risk of death and recurrent MI according to duration of NSAID treatment was estimated

DANISH POPULATION STUDY # 2

~ 500,000 healthy individuals, with 45% receiving at least one NSAID between 1997 and 2005
Estimated risk of stroke with use of NSAID from stroke data from hospitalization and death registries
Result: NSAID use was associated with an increased risk of stroke

<table>
<thead>
<tr>
<th>NSAID</th>
<th>HR (95% CI) for risk of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.28 (1.14 – 1.44)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.86 (1.58 – 2.19)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.61 (1.14 – 2.29)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.69 (1.11 – 2.36)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.35 (1.01 – 1.79)</td>
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LIPOSOMAL BUPIVACAINE
(EXPAREL®)

Infiltrate all tissue layers
Inject along length of site
(dilute with saline if more volume is needed)
Aspiration should not draw blood

PHARMACOKINETICS
(LIPOSOMAL BUPIVACAINE)

Bimodal Release
Small amount of extra-liposomal bupivacaine allows for fast (< 1 hr) onset, with a second peak from encapsulated bupivacaine in 12 – 36 hours
Systemic absorption depends on:
- Dose
- Vascularity of site
- Patient factors (e.g. cardiac, renal, hepatic dysfunction)

EFFICACY
- Pooled efficacy and safety data from 9 studies
  - Liposomal bupivacaine (≤ 266 mg, N = 505) vs. bupivacaine HCl (N = 406)
  - Inguinal hernia repair, TKA, hemorrhoidectomy, breast augmentation, bunionectomy
- Outcome measures
  - AUC of pain intensity scores (up to 72 hrs)
  - Time to first use of rescue opioid
  - Total amount (mg) of opioid used
  - Opioid-related adverse events
  - Overall adverse events
- Results
  - Longer time to first opioid use with liposomal bupivacaine
  - Lower mean pain score (through 72 hrs) with liposomal bupivacaine
  - Lower incidence of opioid-related adverse events
  - Less opioid use with liposomal bupivacaine
DEFINITELY A STEP IN THE RIGHT DIRECTION, BUT….  

Monitoring, toxicity, lipid rescue  

Dilution / injection technique  

Most appropriate surgical procedure  

OPIOIDS  

- For most patients, there is no difference in efficacy and minimal differences in adverse effects between opioids  
- Most respond to morphine but adverse effects may not allow adequate dose titration  
- Others do not achieve good analgesia despite dose escalation  
- Response to a medication depends upon pharmacokinetics (drug, concentration) and pharmacodynamics (relationship between concentration & effect)  
- Effects of age, renal / hepatic function, comorbidities, genetics  

CODEINE’S ANALGESIA & TOXICITY RELATED TO CYP2D6 PHARMACOGENETICS  

Morphine & Morphine-6-glucuronide are active analgesia and adverse effects (excessive sedation, respiratory depression)  

Some opioids are converted by CYP2D6 to an active metabolite (codeine, hydrocodone, oxycodone)  

Genetic variability in CYP2D6 gene  

<table>
<thead>
<tr>
<th>Allele Variant</th>
<th>Drug Metabolizing Phenotype</th>
<th>Incidence - Population</th>
<th>Incidence - Ethnic Groups</th>
</tr>
</thead>
</table>
| Two nonfunctioning alleles | Poor metabolizer (PM) | ~5 – 10% | African-American: 2 - 8%  
Asian: > 1%  
Caucasian: 5 – 10% |
| One reduced functioning allele | Intermediate metabolizer (IM) | ~2 – 11% | |
| At least one functional allele | Extensive metabolizer (EM) | ~77 – 92% | |
| Multiple copies of a functional allele | Ultrarapid metabolizer (UM) | ~1 – 2% | Asian: 1%  
Ethiopian: 28%  
Northern Europeans: 1 – 2%  
Southern Europeans: 10% |

2007 Product Label Change and FDA Public Health Advisory issued  

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PRECAUTIONS  

Ultra-rapid Metabolizers of Codeine  

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultrarapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.  

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August 2012 FDA Safety Communication  

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### PREEMPTIVE TRIPLE ANALGESIA

- 135 children undergoing tonsillectomy randomized to preemptive triple analgesia (rectal diclofenac, IV acetaminophen, IV tramadol) or placebo
- All patients received local infiltration of bupivacaine
- Primary outcome: pain control (through POD 3)

### QUESTIONS?