Anesthetic Considerations for Patients with Chronic Pain

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Disclosures

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What are the issues?

1. What are the common pain medications employed in chronic pain patients?
2. Are there important pharmacogenetic considerations?
3. Is the chronic pain patient predisposed to increased postoperative pain?
4. In general, how should postoperative pain be managed?
5. How should postoperative opioids, in either the opioid tolerant or opioid abusing patient, be managed?
Perioperative Management of Chronic Pain Patient

What are the common pain medications employed in chronic pain patients and what are their anesthetic implications?
Preoperative Management: Common Drugs

- **NSAID’s**
- **Opioids including tramadol**
- **Psychotropic:**
  - TCA’s: amitriptyline/nortriptyline
  - SSRI’s: Fluoxetine, paroxetine, sertraline, citalopram, escitalopram
  - SNRI’s: Duloxetine, venlafaxine
  - MAOI’s: Uncommon
- **Anticonvulsants:** gabapentin, pregabalin, valproic acid, topiramate
- **Benzodiazepines**
- **α-2 Agonists:** Clonidine
Perioperative Bleeding

- NSAID’s
- Valproic Acid (CYP2C9/10 effect of valproate) leads to increased effects of NSAID’s and warfarin
- NSAID’s and SSRI’s (inhibit serotonin reuptake of platelets)
- Warfarin and SSRI’s/SNRI’s (decrease warfarin metabolism)
- Topiramate and Warfarin (Lowers warfarin metabolism via CYP3A4)
MAO Inhibitors

- No TCA’s for at least 14 days
- No SSRI’s for 14 days or 35 days for fluoxetine
- Fentanyl and meperidine can cause serotonin syndrome
Perioperative Management of Chronic Pain Patient

Are there important pharmacogenetic considerations?
Table 2

<table>
<thead>
<tr>
<th>Genotype frequency (%)</th>
<th>Demand in first 24 h</th>
<th>Demand in second 24 h</th>
<th>Demand in first 48 h</th>
<th>Dose in first 24 h</th>
<th>Dose in first 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>62</td>
<td>24.3 (15.4)</td>
<td>9.5 (9.4)</td>
<td>39.0 (24.7)</td>
<td>16.0 (8.0)</td>
</tr>
<tr>
<td>GG</td>
<td>11</td>
<td>36.1 (15.2)</td>
<td>18.3 (14.9)</td>
<td>57.8 (24.7)</td>
<td>22.3 (10.0)</td>
</tr>
<tr>
<td>AG</td>
<td>27</td>
<td>22.2 (14.6)</td>
<td>10.5 (8.5)</td>
<td>35.3 (23.3)</td>
<td>14.8 (7.1)</td>
</tr>
<tr>
<td>AA vs. GG</td>
<td>*P = 0.033</td>
<td>*P = 0.028</td>
<td>*P = 0.026</td>
<td>*P = 0.018</td>
<td>*P = 0.003</td>
</tr>
<tr>
<td>GG vs. AG</td>
<td>*P = 0.021</td>
<td>*P = 0.059</td>
<td>*P = 0.012</td>
<td>*P = 0.010</td>
<td>*P = 0.008</td>
</tr>
</tbody>
</table>

AA, wild-type homozygous; AG, mutant heterozygous; GG, mutant homozygous.
The morphine consumed doses are expressed as mean (standard deviation).
Demand is the dose that represents the number of times the patient pushed the release button of the patient-controlled analgesia device.
P-value for one-way analysis of variance (ANOVA) with post hoc tests (*P < 0.05).
Mu-receptor Polymorphism: A118G

Table 2: Analgesic endpoints compared between wild-type (AA) and A118G SNP mutations (AG/GG)

<table>
<thead>
<tr>
<th></th>
<th>AA (n=72)</th>
<th>AG/GG (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (over 25 min) (µg)</td>
<td>4060 (3030)</td>
<td>6271 (4677)</td>
<td>0.009</td>
</tr>
<tr>
<td>Dose (over 25 min)/wt (µg kg⁻¹)</td>
<td>51.4 (37.3)</td>
<td>75.4 (44.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dose (over 25 min)/wt/RIP (µg kg⁻¹ kV⁻¹)</td>
<td>0.0011 (0.0009)</td>
<td>0.0017 (0.001)</td>
<td>0.002</td>
</tr>
<tr>
<td>Boluses attempted (over 25 min)</td>
<td>3.4 (3.4)</td>
<td>7.2 (5.9)</td>
<td>0.015</td>
</tr>
<tr>
<td>Boluses successful (over 25 min)</td>
<td>1.9 (1.0)</td>
<td>3.4 (2.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Boluses failed (over 25 min)</td>
<td>1.5 (2.9)</td>
<td>3.8 (4.6)</td>
<td>0.042</td>
</tr>
<tr>
<td>Mean plasma alfentanil concentration (over 25 min) (ng ml⁻¹)</td>
<td>139 (68)</td>
<td>177 (82)</td>
<td>0.034</td>
</tr>
<tr>
<td>Mean VAS pain score (over 25 min) (0–100)</td>
<td>2.1 (1.6)</td>
<td>3.2 (1.9)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Significance of A118G SNP

 Might G118G homozygotes be less sensitive to the analgesic effects of mu-opioids?

 Might G118G homozygotes have reduced nausea and vomiting with opioids?
Pharmacogenetic Interactions

- UGT (Uridine glycosyl transferase):
  - morphine*(active M-6-G)
  - hydromorphone*(HM-3-G, neuroexcitatory)

There are essentially no clinically relevant interactions with other drugs used in chronic pain patients.

Metabolites, however, require normal renal function for clearance.

* primary metabolic pathway
Pharmacogenetic Interactions

Hepatic P450 Alleles:

- **3A4**: fentanyl*, methadone*, morphine, hydromorphone, hydrocodone, midazolam
- **2D6**: codeine*, tramadol*, oxycodone*, hydrocodone*, methadone, fluoxitene*(also other SSRI’S), duloxetine*, amitriptyline*
- **2C9**: NSAID’s*, sertraline*
- **2C19**: diazepam*

Inhibitors:

- **2C9/19**: fluoxitene
- **2D6**: SSRI’s(strong to weak), duloxetine(moderate)
- **3A4**: fluoxitene and sertraline(weak)

* primary metabolic pathway
Pharmacogenetic Interactions

Hepatic P450 Alleles:

- 3A4: fentanyl*, methadone*, morphine, hydromorphone, hydrocodone, midazolam

Inhibitors:

- Fluoxetine and sertraline (weak)
- Up to 40% more active in women v. men

* primary metabolic pathway
Pharmacogenetic Interactions

Hepatic P450 Alleles:

- **2C9**: NSAID’s*, sertraline*
- **2C19**: diazepam*

Inhibitors:

- **2C9/19**: fluoxitene
- **2C9*3**: Allele slow NSAID metabolism
- **2C19*G681A**: Allele slow diazepam metabolism

* primary metabolic pathway
Pharmacogenetic Interactions

Hepatic P450 Alleles:

- **2D6**: codeine*, tramadol*, oxycodone*, hydrocodone*, methadone, fluoxetine*(also other SSRI’S), duloxetine*, amitriptyline*

Inhibitors:

- Many drugs compete for **2D6**;
- 2-8% of population has reduced or absent **2D6**;
- Codeine is only true prodrug; needs conversion to morphine;
- Oxycodone and hydrocodone are analgesic but metabolize to oxymorphone and hydromorphone, both more potent;
- SSRI’s(strong to weak), duloxetine(moderate);
- Methadone (minor pathway) can accumulate.

*primary metabolic pathway
Perioperative Management of Chronic Pain Patient

How should postoperative pain be managed in patients with chronic pain?
Postoperative Pain Management

- Continue various psychotropic medications as soon as patients are able to take them!!
- AVOID tramadol, codeine, methadone in 2D6 blockade
- Adjust dosing as needed for oxycodone and hydrocodone in 2D6 blockade
- Administration of fluoxetine can lead to NSAID toxicity (or improved analgesia!)
- SSRI’s can lead to delayed metabolism of intraoperative opioids
- Women may need higher doses of commonly used analgesics (more 3A4), even though they are more tolerant of pain,
Preoperative Neuromodulation

Is there a role for preoperative administration of gabapentin?
Perioperative Gabapentin

Figure 1. Postoperative Pain scores. Data are shown as mean (SD).

Perioperative Management of Chronic Pain Patient

Is the patient predisposed to increased postoperative pain?
Hyperalgesia in Chronic Pain Patients

- Patients on chronic opioids develop hyperalgesia to painful stimulation.
- Patients on chronic opioids develop tolerance to opioid therapy for increased
Perioperative Management of Chronic Pain Patient

How should we manage postoperative opioids in either the opioid tolerant or opioid-abusing patient?
## Chronic Opioid Use

<table>
<thead>
<tr>
<th>Chronic Pain Patient</th>
<th>Opioid-abusing Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate use of opioid</td>
<td>Out of control with opioids</td>
</tr>
<tr>
<td>Opioids improve quality of life</td>
<td>Opioids impair quality of life</td>
</tr>
<tr>
<td>Aware of side effects</td>
<td>Unconcerned of side effects</td>
</tr>
<tr>
<td>Follows treatment plan</td>
<td>Does not follow plan</td>
</tr>
<tr>
<td>Often has medications from prior prescriptions</td>
<td>Out of medications, loses prescriptions, drama</td>
</tr>
</tbody>
</table>

Mitra, S. and Sinatra, R., Anesthesiology 2004;101:212
Opioid Tolerant Patient

Preoperative administration of baseline opioid

- Oral or parenterally
- Consider addition of adjuvant analgesics (NSAID’s, gabapentin)
- If told to not take AM medications, load with equivalent dose of drug
- Continue implanted intrathecal pumps except consider reduction in baclofen
- Avoid mixed agonist/antagonists; they may precipitate withdrawal
Opioid Tolerant Patient

Intraoperative Management

- Consider use of lipophilic opioids to titrate to intraoperative responsiveness
- Doses will often be 30-100% greater than an opioid-naive patient
- Dosing can be guided by baseline opioid use converted into a 1 hour requirement
- Remember oral to parenteral opioid conversion guidelines
  - Morphine 3:1
  - Hydromorphone 4-5:1
  - Oxycodone 1:1 with morphine IV
- Consider reversal of neuromuscular blockade and then titrate opioid to response
Opioid Tolerant Patient

Postoperative Management

- Regional anesthesia is a great option
- For the extremely opioid tolerant patient, consider the use of neuraxial opioids
  - Conversions are roughly: 100:1 intrathecal; 10:1 epidural
  - Likely they will require supplemental oral or IV opioid to avoid withdrawal
  - Add local anesthetics to infusions
- PCA with basal equal to about 50%-100% of baseline hourly requirement; dose equal to 25-50% of baseline hourly requirement
- Early addition of methadone (Screen QTc) or another long-acting opioid
- Adjunctive use of NSAID’s, ketamine, or neuromodulating drugs (gabapentin)
Anesthetic Considerations for the Chronic Pain Patient

Patients with chronic pain challenge the pharmacologic knowledge-base of anesthesiologists.

Essentially no randomized controlled trials to guide evidence-based practice are available to aid in the perioperative management of these patients.

Nonetheless, integrating an understanding of the medications used to manage chronic pain with the postoperative analgesic needs of these patients leads to satisfactory perioperative care.
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sweisman@chw.org
## Perioperative Gabapentin

### Morphine equivalents used in mg/kg/time

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 0 Total</strong></td>
<td>.044 (0.017)</td>
<td>.064 (0.031)</td>
</tr>
<tr>
<td>Day 1 a.m.</td>
<td>.054 (0.023)</td>
<td>.062 (0.020)</td>
</tr>
<tr>
<td>Day 1 p.m.</td>
<td>.038 (0.013)</td>
<td>.048 (0.016)</td>
</tr>
<tr>
<td><strong>Day 1 Total</strong></td>
<td>.046 (0.016)</td>
<td>.055 (0.017)</td>
</tr>
<tr>
<td>Day 2 a.m.</td>
<td>.042 (0.017)</td>
<td>.055 (0.022)</td>
</tr>
<tr>
<td>Day 2 p.m.</td>
<td>.031 (0.018)</td>
<td>.040 (0.020)</td>
</tr>
<tr>
<td><strong>Day 2 Total</strong></td>
<td>.036 (0.016)</td>
<td>.047 (0.019)</td>
</tr>
<tr>
<td>Day 3 a.m.</td>
<td>.032 (0.015)</td>
<td>.037 (0.024)</td>
</tr>
<tr>
<td>Day 3 p.m.</td>
<td>.018 (0.016)</td>
<td>.024 (0.017)</td>
</tr>
<tr>
<td><strong>Day 3 Total</strong></td>
<td>.026 (0.014)</td>
<td>.030 (0.019)</td>
</tr>
</tbody>
</table>

**Key:** Bold results indicated significantly different results in mg/kg morphine equivalents consumed during day.