Management of Acute Pain in the Opioid Tolerant Patient

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Objectives

- To understand clinical features of tolerance and opioid-induced hyperalgesia.
- To understand various misconceptions concerning acute pain management in opioid tolerant patient.
- To review opioid equianalgesia dosing.
- To design a perioperative pain management strategy for an opioid tolerant patient.
Introduction

♦ The number of patients being prescribed opioids on a long-term basis has exploded over the last decade.

♦ Opioid prescription for both cancer pain and non-cancer pain has increased significantly.

♦ While illicit use of heroin, morphine and methadone remains stable; oxycodone and hydrocodone abuse has increased by over 100%\(^1\).
Introduction

♦ As clinicians treating acute postoperative pain the opioid tolerant patient provides unique challenges.

♦ Our overall goals are to provide effective analgesia, prevent withdrawal and ensure continuity of long term care.
Greater than 4,995 apparent opioid-related deaths in Canada in 2018.

Compared to 3,005 apparent opioid-related deaths in 2016 and 3,996 in 2017.

The number of daily deaths related to opioids is between 11-13 deaths per day in Canada.

17 people per day are hospitalized daily for opioid poisoning.
115 people per day in the United States die after overdosing on opioids\textsuperscript{10}.

It is estimated that the total "economic burden" of prescription opioid misuse alone in the United States is $78.5 billion a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement\textsuperscript{10}.

USA prescribes 50 times more opioids than the rest of the world combined excluding Canada which is the second highest prescriber\textsuperscript{11}.
Pain Statistics

- Prevalence of chronic pain in Canadians ages 12-44 years ranges about 10% (1.5 million people).\(^\text{12}\)

- Some studies estimate that 15-30% children are affected\(^\text{12}\)

- Institute of Medicine in USA estimates that about 100 million adults suffer from chronic pain\(^\text{13}\)

- Cost to society is huge, American Institute of Medicine estimates $560-$635 billion a year\(^\text{13}\).
Pain Management

♦ Pain Education for both MDs and DOs ranges between 1-31 hours in a 3-4 year period\textsuperscript{14}.

♦ In Canada, veterinarians get 5 times more pain education than physicians (16h vs 87h)\textsuperscript{15}.

♦ Practice models both in USA and Canada hinder proper pain assessment and management.

♦ Insurance reimbursement for nonpharmacological treatment is poor.
Pain Management

- Postoperative pain continues to be poorly managed throughout the western world.

- More than 80% of patients who undergo surgical procedures experience acute postoperative pain and approximately 75% of those with postoperative pain report the severity as moderate, severe, or extreme\(^{17}\).

- Alarm et al\(^{16}\) demonstrated patients who receive opioid prescriptions within 7 days of their surgery have a 44% increased chance to be still on opioids one year later.
Perioperative Surgical Home for Patients with Chronic Pain

♦ Patient-centered approach to surgical patients

♦ Emphasis is on process standardization, evidence-based clinical care pathways, and coordinated and integrated care.

♦ Similar to the process for enhanced recovery from surgery with attention being placed on the whole surgical journey of the patient.

♦ Care starts at the decision of surgery and continues 3-6 months after discharge.
Stress

“We wanted to make the stress test as realistic as possible.”
Presurgery Reduction of Opioids

♦ Chronic opioid patients have longer hospital stays and more complications than patients who are not on opioids

♦ A multidisciplinary approach to care can reduce opioid intake in chronic opioid patients.

♦ Reduction of opioids and use of nonpharmaceutical modalities can improve the patient’s surgical journey
Fig. 1. The perioperative surgical home for the patient with chronic pain.

Khan, T and Manion S. Perioperative Surgical Home for the patient with Chronic Pain. Anesthesiology Clin 36:281-294;2018
Key Points Preoperatively

1. Is this patient an opioid user or abuser?
2. Obtain detailed history of type of opioid or other agent, duration of use and timing of the last dose.
3. Recognize signs and symptoms of overuse and withdrawal.
4. Identify populations at risk
5. Obtain comprehensive assessment including history, physical examination and review diagnostic studies.
6. Evaluate common comorbidities in opioid tolerant patients.
7. Consider possible coexisting psychiatric disorders
8. Avoid prejudices and assure patients
9. Keep in mind patients’ fears
10. Plan perioperative pain management
Opioid weaning and pain management in postsurgical patients at the Toronto General Hospital Transitional Pain Service

- 251 high-risk TPS patients divided preoperatively as opioid naïve or opioid experienced.

Results

- 6 months postoperative, pain and function were significantly improved.
- Opioid-naïve and opioid-experienced patients reduced consumption by 69% and 44%, respectively.
- 46% and 26% weaned completely.
- Consumption at hospital discharge predicted weaning in opioid-naïve patients.
- Pain catastrophizing, neuropathy, and recreational drug use predicted weaning in opioid-experienced patients.

Conclusions

- The TPS enabled almost half of opioid-naïve patients and one in four opioid-experienced patients to wean. The TPS successfully targets perioperative opioid use in complex pain patients.
Psychological Consequences

- Addiction
  - A primary, chronic neurobiological disorder characterized by particular patterns of behavioral and physiological adaptation.

- Dependence
  - A neuro-pharmaceutical disorder characterized by neuronal adaptation and plasticity.
Physiological Consequences²

♦ Tolerance
  ♦ Diminished analgesic effects from a given dose of opioid.
  ♦ Related to duration of opioid exposure, daily opioid consumption and receptor association/disassociation kinetics.

♦ US FDA defines an opioid-tolerant patient as a patient receiving 7+ days of 60 mg oral morphine per day or equianalgesic dose of any other opioid.
Tolerance

- **Innate tolerance**
  - Preexisting insensitivity which is genetically determined

- **Pharmacokinetic tolerance**
  - Changes in distribution and metabolism of the drug

- **Learned tolerance**
  - Reduction in the effects of the drug due to compensatory mechanisms that are learned

- **Pharmacodynamic tolerance**
  - Neuroadaptive changes that take place after long-term exposure
Opioid Induced Hyperaglasia$^1, 2$

- Paradoxical effect in which patients display increasing sensitivity to painful and non-painful stimuli.

- Mechanism not understood but may involve glutaminergic activation, altered opioid intracellular signaling involving G protein-coupled receptor switching, activation of substance P and neurokinin 1 receptors and spinal dynorphins, and activation of Toll-like receptors and glial cells.

- Bottom line is reduction of dose is required.
Misconceptions

True or false

- The baseline chronic opioid will provide acute pain relief?
- Acute use of opioids postoperatively may result in addiction relapse?
- Postoperatively the addition of opioid analgesia on top of the baseline chronic opioid may cause CNS and respiratory depression?
- In opioid tolerant patients postoperative pain may be reported high in order to manipulate to receive opioid medications because of addiction not pain?
The baseline chronic opioid will provide acute pain relief?

- False
  - Analgesic properties of opioid for addiction vs. analgesia is different. Methadone or Buprenorphine for analgesia is 4-8 hr vs. opioid suppression of withdrawal is 24-48 hr.
  - Opioid Tolerance
  - Opioid-induced Hyperalgesia
Acute use of opioids postoperatively may result in addiction relapse?

- False
  - No evidence that exposure to opioid analgesics in presence of acute pain increases rates of relapse
  - Relapse prevention theories suggest that poorly treated pain may trigger relapse vs. adequate analgesia
Postoperatively the addition of opioid analgesia on top of the baseline chronic opioid may cause CNS and respiratory depression?

- False
  - No evidence.
  - Tolerance to respiratory and CNS depression occurs rapidly and reliably.
  - Acute pain may act as natural antagonist to opioid-associated respiratory and CNS depression.
In opioid tolerant patients postoperative pain may be reported high in order to manipulate to receive opioid medications because of addiction not pain?

- False
  - Subjective reporting is difficult to interpret in this population.
  - Must relate subjective measures to preoperative baseline.
  - Use of objective measures is more accurate
    - eg ability to breath, cough, mobilize and physiological measures such as respiratory rate, sedation, heart rate and blood pressure.
  - Patients with unrelieved pain will exhibit drug-seeking behaviors, but there may be a medical reason just as in the opioid naïve population.
### Table 4 Equianalgesic doses of opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Approximate oral equianalgesic dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (reference drug)*</td>
<td>30 mg</td>
<td>2–3 h</td>
<td>8–12 h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>Tramadol*</td>
<td>150 mg</td>
<td>1–2 h</td>
<td>8–12 h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>Codeine (with APAP)</td>
<td>200 mg</td>
<td>30–60 min</td>
<td>4–8 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Oxycodone*</td>
<td>20 mg</td>
<td>1–2 h</td>
<td>6–10 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Tapentadol*</td>
<td>100 mg</td>
<td>1–2 h</td>
<td>8–12 h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>Hydromorphone*</td>
<td>7.5 mg</td>
<td>12–14 h</td>
<td>20–24 h</td>
<td>8–16 h</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 mg</td>
<td>30–45 min</td>
<td>4–6 h</td>
<td>2–3 h</td>
</tr>
<tr>
<td>Hydrocodone (with APAP, ASA, or ibuprofen)</td>
<td>30 mg</td>
<td>15–30 min</td>
<td>4–8 h</td>
<td>2–3 h</td>
</tr>
</tbody>
</table>

**Notes:** *PKs (pharmacokinetics) refer to slow release twice daily (BID) formulations. #PKs refer to once daily hydromorphone formulation.**

**Abbreviations:** APAP, acetaminophen; ASA, acetylsalicylic acid.

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**Buprenorphine**

- Partial µ-antagonist and kappa-antagonist with a high affinity for the receptor making it difficult to be displaced by other opioids.
- Doses for addiction 8-32 mg/day and for pain usually smaller doses TID
- Analgesic effects 4-8 hrs, withdrawal effects 24-48hrs.
- Estimated dose equivalent for sublingual buprenorphine 0.8 mg= 30 mg oral morphine=10 mg IV morphine
Strategies for Buprenorphine

♦ Minor Procedures
  ♦ Continue current buprenorphine consider increasing it by 25% or giving TID and maximize non-opioid treatments and use opioids.

♦ Major Procedures
  ♦ Stop 72 hrs. prior and start long acting morphine 24 hrs. later or if signs of withdrawal. Postoperatively, maximize non-opioid treatments and use opioids.
  ♦ Continue buprenorphine consider increasing it by 25% or giving TID and maximize non-opioid treatments and use opioids. Patient must be in monitored setting.
Naltrexone

- Opioid antagonist used for treatment in alcohol-dependent and opioid-dependent patients

- Oral naltrexone T1/2 is 4-13 hr but effects lasts 24-72 hour

- Injectable one month extended-release

- These patients are difficult and non-opioid stratagies need to be used.
Methadone

Conversion is more complex and depends on dosage\(^8\).

<table>
<thead>
<tr>
<th>Morphine oral dose</th>
<th>Morphine : methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100mg</td>
<td>3:1</td>
</tr>
<tr>
<td>101-300 mg</td>
<td>5:1</td>
</tr>
<tr>
<td>301-600 mg</td>
<td>10:1</td>
</tr>
<tr>
<td>601-800 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>801-1000mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Pain Physician 11:s133-S153, 2008
Methadone Management

♦ Continue regular dosing

♦ Consider divided doses to optimize analgesic effects

♦ If cannot give orally may give it SC or IM at approximately 2 to 1.5 ratio

♦ E.g. 80mg methadone PO equals 40-52mg sc or IM. Therefore give 10-13mg Q6H or 20-26mg Q8H
Principals of Management

♦ Preoperative Planning
  ♦ Assessment of opioid and non opioid intake.
  ♦ Where possible ensure regular daily dose taken - if not make sure equianalgesic loading dose given.
  ♦ Liaise with appropriate healthcare professionals.

♦ Preinduction
  ♦ Use regional, neuraxial and adjuncts where possible.
  ♦ Parental doses for induction opioid typically 25-50% higher.
Principals of Management

- Intraoperative
  - Replace usual opioids if long case
  - Titrate additional opioid to effect
  - Use non-opioid and adjunctive therapy
    - Ketamine, lidocaine, dexametatomadine infusions, gabapentinoids, clonidine, NSAIDs, acetaminophen, Cannabinoids, epidurals, and perineural catheters.

- Postoperatively
  - Replace usual opioids (if on methadone or buprenorphine consider dividing dose TID)
  - Maximize non-opioid agents, neuraxial or regional techniques and titrate additional opioids
Principals of Management

❖ Postoperative
  ❖ Remember neural axial opioids may not prevent withdrawal symptoms so systemic replacement must be given.
  ❖ Additional adjunctive therapy may be required including ketamine, lidocaine and dexmedetomidine infusions, NSAIDs, Tylenol, clonidine, benzodiazepines, and tricyclic antidepressants.
  ❖ Maximize use of regional techniques.
  ❖ Utilize nonpharmacologic techniques if possible - TENS and cognitive modalities.

❖ Discharge
  ❖ Must liaise with appropriate team member in the hospital and outside to ensure continuity of care.
Cannabis

♦ There is fairly good evidence that cannabis helps some types of chronic pain

♦ More patients will be coming to the OR who are using medicinal or recreational cannabis

♦ These patients do have higher opioid requirements and often have more severe postoperative and difficult to treat pain.
Smoking Cannabis effects on pain perception

- Clark et al. Effects of moderate and high dose of marihuana on thermal pain: A sensory theory decision analysis\textsuperscript{20}
  - 14 males 18-30
  - Washout period-smoking period-washout period
  - Smoked 2\% THC cigarettes (20mg)
  - Average smoked per week 3.7, 10.4, 14.5, 16.5
  - Verbal and physical responses to pain recorded.
Results

♦ Moderate smokers had an increased pain perception in both the smoking weeks and the post smoking weeks.

♦ Heavy smokers the pattern was not clear and there was no difference in pain perception.
Intrathecal Pump

♦ Continue infusions.
♦ Mindful of cautery near pump or catheter.
♦ Must know where catheter is for neuraxial techniques.
Neurostimulators

- Patient is to turn the device intensity down to zero then turn off devices
- Cautery must not arch across the IPG
- Monopolar cautery should be avoided. Use bipolar or plasma blade.
- Patient should contact their implanter once surgery done to have device interrogated.
- Neuraxial or regional techniques should be done with imaging to avoid damage of the electrodes.
Summary

- Acute pain management of opioid tolerant patients is a growing concern.
- There are psychological and physiological consequences in taking long-term opioids including addiction, dependence, tolerance and opioid hyperalgesia.
- Opioid tolerant patients require opioids and non-opioids postoperatively above baseline medications to adequately treat pain.
Summary

- Use equianalgesia conversion tables to calculate baseline opioid requirements.
- Use additional opioid medications to treat acute pain.
- Use all adjunctive therapies available.
- Liaise with other professionals in hospital and out of hospital to ensure continuity of care.
References

References

11. Ticks et al. Evidence-based nonpharmacologic strategies for comprehensive pain care: the consortium pain task force white paper. EXPLORE 14(3): 177-211, 2018


Case 1

♦ 72 year old male with chronic back pain comes in with a bowel obstruction and is NPO. Usually takes 150 mg long acting morphine BID.

♦ What is your plan?
Case 1

♦ Opioids
  ♦ Morphine 300 mg/24 hr. oral conversion 3:1 would equal 100 mg IV/24 hr.
  ♦ Due to incomplete cross tolerance 50-75% as a morphine infusion therefore 2-3 mg/hr. background infusion.
  ♦ PCA dose 50% of infusion = 1.5-2 mg/injection with standard lockout of 6 min. If patient has working epidural may not require PCA.

♦ Adjuncts
  ♦ Use adjuncts intra- and postoperatively
    ♦ Ketamine (up to 5 days) and lidocaine infusion (up to 24 hr.) and if not contraindicated NSAID and acetaminophen.

♦ Convert back to orals
  ♦ Convert IV opioids to oral; give 50% of oral equivalents as sustained release BID.
  ♦ In addition, the give 1/6-1/9 of calculated oral dose as PRNs every 4 hrs.
Case 2

- 54 year old IVDU on methadone maintenance 100 mg/day comes in for major surgical intervention and will be NPO for 2 days.

- What is your plan?
Case 2

♦ Opioid
  ♦ Oral conversion of methadone to morphine at dose of 100 mg is about 1:3 = 300 mg Oral morphine
  ♦ Oral morphine 300 mg converted to IV is 100 mg
  ♦ Give back 50-75% as a background infusion so 50-75 mg/24 hr.= 2-3 mg/hr. background infusion
  ♦ PCA dose 50% of background infusion with standard 6 min lockout.

♦ Adjuncts
  ♦ Epidural or perineural, ketamine, lidocaine, NSAIDs, benzodiazepines, gabapenaniods, TCA, and acetaminophen

♦ Convert to orals ASAP
Case 3

♦ You are working in the preadmission clinic and you see a 36 yr. old female coming for elective closure of an ileostomy on buprenorphine/naloxone 8mg every 2 days. Her surgery is scheduled for 1 week from today.

♦ What is your plan?
Case 3

- Continue on buprenorphine/naloxone
  - Place preoperative epidural and ensure working well.
  - Consider intraoperative lidocaine and ketamine
  - Maximize adjuncts

- Stop buprenorphine/naloxone 72 hrs. prior to surgery and give oral morphine sustained release
  - 8mg = approximately morphine 64 mg/24 hr. therefore 30 mg SR BID to start 24 hr. after last dose or if withdrawal symptoms. Admit preoperatively if necessary
  - Use same principals as in case 1.