Perioperative Management of the Opioid Tolerant Patient

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NO CONFLICTS FOR THIS TALK

Got Tolerance?

Clinical Definition: Opioid Tolerance?

- Following repeated therapeutic doses of an opioid analgesic, there is a temporal loss of effectiveness.
- In order to reproduce the original analgesic response, larger doses must be administered.
No Clear Mechanistic Definition of “Opioid Tolerance”

- No Scientific Consensus
- Morphine and its derivatives do not promote desensitization and endocytosis ...while, paradoxically, the endogenous ligands do!
- Hypothesis: opioid receptor endocytosis and recycling serves a protective role in reducing the development of physiological tolerance. (Whistler, Gallo Center – UCSF).

Back to a clinical (FDA) definition: see the package insert

Current Analgesic Daily Dosage (mg/day)
60 mg oral morphine equiv. / day for at least 1 week.

- Oral morphine 60-134
- Oral OXYCODONE 30 – 67
- IV HYDROMORPHINE 1.5 - 3.4
- IV methadone 10 – 22

Recommended: fentanyl patch dose 25 mcg/hr
UCSF Pain Committee

Is the prevalence of opioid tolerance increasing?

The 2011 IOM report: as many as 100 million adults in the US report having a common chronic pain condition exceeding those affected by heart disease, cancer and diabetes.

257 million prescriptions for opioids were dispensed in 2009 a 48% increase compared with figures for 2000.

From 1998 to 2008 there was a 400% increase in substance abuse treatment program


U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.
Where do we turn to for answers?

Perhaps an earlier story can provide some perspective in the management of tolerance

Here Clint Eastwood searches for a cache of stolen gold against rivals ..the Bad (Lee Van Cleef), a ruthless bounty hunter and the Ugly (Eli Wallach), a bandit..

Though dubbed "the Good," Eastwood’s character is not much better than his opponents” – R T

Current Clinical Strategies

- Tell the patient to wean off all narcotics preoperatively
- Give the patient more of the same opioid ..a lot more?
- Opioid Rotation: Used in cancer pain ...post-op?
- Use of analgesic “adjuncts”: ketamine, alpha-2-agonists

“Which is the good ? are they all ‘bad’ or ‘ugly’

“Which clinical strategy is the ‘good’ strategy for these patients with opioid tolerance?

- 22 yo F with h/o AML with pain from Graft vs. Host disease
- 43 yo M with h/o recurrent Sickle Cell Crisis
- 58 yo F with failed s/f T9-sacrum A/P spinal fusion

………. are the choices all ‘bad’ or ‘ugly’ ?
Case 1 “Drowning in fentanyl”

- 22 yo F with h/o AML s/p bone marrow transplant.
  - Recurrent Disease
  - Graft vs. Host Disease
  - Intubated / Ventilated
  - Total body pain secondary to 80% skin & oral/GI breakdown
  - Intubated – wide awake c/o 10/10 pain

Result of.. “giving a lot more”

Fentanyl
(7000 ug/hr)
3.4 L / day !!!

Midazolam
20 mg/hr

Case 1

- Pt on escalating doses of fentanyl without adequate pain control
- Unable to tolerate continuous propofol infusion due hepatic dysfunction
- Renal Failure
- Over 2 week period a “give a lot more” rule is followed:

Initial Options

- Denial…can this be true?
- Yes..the patient is fluid overloaded and the hospital is running out of fentanyl
- Consider Opioid Rotation
- If primarily a volume issue, consider Sufentanil? Hospital says NO! too $$...
  “we’ll find more fentanyl”
Plan:
- Rotation with other potent opioid (ie: Dilaudid 10 mg/ml) & increase methadone

The Bad then the Ugly
- Attempt to replace fentanyl infusion with Dilaudid (10mg/cc) with goal of final rate of 140mg/hr (14cc/hr).
- Result: Patient did not tolerate switch, briefly on both Fentanyl 7000 ug/hr and Dilaudid 140 mg/hr. Realizing failure, dilaudid dc’d and fentanyl restarted in am
- Later ..she has tonic/clonic seizure.. but recovers
- What is our next step?

Ketamine: NMDA antagonist
- Low dose’ range significantly improves pain and hyperalgesia when used with opioid analgesics.
- Prevents and reverses opioid-induced tolerance in animals and humans.
  - Low dose-opioid sparing: 1-5 mcg/kg/min iv / sc
  - Moderate dose - analgesia: 0.1-0.3 mg / kg iv bolus
  - High dose: Dissociative anesthesia: 1-2 mg/kg iv bolus

Ketamine: “re-couples” opioid receptor function
- N-methyl-D-aspartic acid (NMDA) receptor antagonist
- Sub-anesthetic doses has been shown to reverse opioid induced tolerance in animals and humans.
- Based on case reports and a single controlled trial, ketamine infusions at ≤ 0.2mg / kg / hr (3-5 mcg/ kg min) with plasma levels of ~ 50 ng/ml had an opioid sparing effect and did not drive psychomimetic effects.
Low dose Ketamine (3 ug/kg/min)

Day # 24 = 21 ng/ml
Day # 28 = 77 ng/ml

"Reversal of Fentanyl-Induced Tolerance by administration of Small-Dose Ketamine" (Eilers et al., 2001. Anesth Analg 93 (1) p213-214)

NMDA Antagonists: Ketamine

When the effect of low-dose ketamine was studied in perioperative subgroups. Greater analgesic benefits were realized following major abdominal surgery and in certain spinal operations.

Oral Ketamine

Wide ranges in both oral dose and interval (oral dose ranges of (0.25-0.5 mg / kg) and interval dosing ranging from daily to every four hours).

Oral administration may result in briefly exceeding desired target plasma concentration resulting in side effects.

Recommend that just as low dose infusions of iv ketamine, use be restricted to physicians experienced in pain management.

Recommendation: Ketamine

Low - dose ketamine’s perioperative benefit is probably most pronounced when used in the setting of the opioid tolerant patient with concurrent inflammatory / neuropathic pain.
Ketamine: Implementation (UCSF Fact Sheet & Nursing Procedures)

HIGH DOSE KETAMINE INFUSION FOR THE TREATMENT OF SEVERE INTRACTABLE PAIN

We have defined “Low-dose” ketamine as: 1-5 mcg/kg/min

Providers: Low dose ketamine orders for severe intractable pain outside the ICU will only be written by a member of the Pain Service (Acute, Chronic, Pediatric) or member of the Palliative Care Team following consultation.

Case 2 “Analgesia gone wild”

43yo M with h/o sickle cell anemia c/o acute pain crisis for 1 day

PMH:
- Sickle cell anemia, dx age 2
- Bilateral AVN
- H/o multiple alloantibodies – transfusion blood must be of African decent
- HCV

Case 2

Drug allergies:
- Dilaudid, fentanyl, morphine, codeine → all cause stomach cramping, psychosis, violence, delirium

Home medications:
- Methadone 40mg PO BID
- Oxycodone 40mg PO Q2h PRN
- Ibuprofen 800mg PO Q8h PRN
- Diazepam 20mg PO BID
- Epo 40,000 units qMWF

In ED received:
- NS 2L
- Methadone 60mg IV x 3
- Oxycodone 120mg PO x 3
- Benadryl 50mg PO x 3

Inpatient regimen:
- Methadone 60mg IV Q4h ATC
- Diazepam 10mg IV Q4hr ATC
- Oxycodone 120mg PO Q4hr PRN
- Benadryl 50mg PO Q4h ATC with Methadone
Methadone to the rescue?

- Day 1
  - Methadone 240mg IV
  - Oxycodone 240mg

- Day 2
  - Methadone 640mg IV
  - Oxycodone 840mg
  - Valium 70mg

Pain score: 10/10

Case 2: Are we making progress?

- Day 3: Transferred to ICU on
  - Methadone 640mg IV
  - Oxycodone 1440mg
  - Valium 80mg
  - Poor pain control

Page from pharmacy:
“‘You will deplete the entire pharmacy of oxycodone in 3 days’ ……Then a page from the ICU
"Could you please come by the bedside now?"

Case 2

- ICU nurse had stepped away for a moment upon return, pt found by nurse to be unresponsive for 10 seconds
- Telemetry monitoring revealed the following rhythm:

Methadone and the ECG

- QTc prolongation leads to delayed repolarization.
- Abnormal repolarization leads to variable refractory periods that causes reentrant ventricular arrhythmias
- IV methadone (Dolophine) contains racemic methadone preserved with chlorobutanol that may synergize the QTc effect.

Pain. 2003;105(3):499-506
“Got Tolerance?”
- Day 5:
  - Methadone 440mg
  - Oxycodone 1440mg
  - Valium 60mg
  - Ibuprofen 2400mg
  - Demerol 600mg
  - Tylenol 3900mg
  - Marinol 10mg
  - Ketamine
  - $3 > 5 \text{mcg/kg/min}$

Methadone (let’s take a step back)
- History:
  - Synthetic opioid, developed before World War II
  - Approved by FDA 1947
  - NMDA Antagonist
    - $\mu$ receptor
    - (d): NMDA antagonist
    - NE and 5HT reuptake inhibition

Methadone: Bioavailability
- High uptake across all routes (oral, nasal)
  - Oral bioavailability (40-99%) stomach
  - Considered ‘Equipotent’ to Morphine in opioid naïve patients
  - Loading phase - unpredictable
  - Maximum analgesic effects:
    - IV = 15 min
    - Oral = 2 hours

Methadone: Distribution
- Primary factors in variability:
  - Differences in $V_d$ (alpha1-acid glycoprotein & tissue binding sites)
  - Opioid dependent patients may have 2X greater $V_d$.
  - Differences in type and level of CYP3A4
    - up to 30-50 fold!
Methadone: Metabolism & Elimination

- Hepatic metabolism dominates
- Both hepatic and intestinal CYP
- No active metabolites (ok in renal failure)
- Biphasic pattern of elimination

Because of the variability
Half-life ranges from 22-60 hr

Methadone: Common perioperative indications

No single approach

- To prevent withdrawal: the literature supports the use of 0.05 - 0.1 mg/kg iv. q 6 hours with increases of 0.05 mg/kg until symptoms of withdrawal subside

- Opioid rotation
  Requirements may be as low as 30% of the calculated equi-analgesics dose.

- Post-operative analgesia
  Caution: requires communication and monitoring

Got Tolerance?

Case 3 “Building a strategy”

- 58 yo F with failed back syndrome s/f T9-sacrum A/P spinal fusion
  - Persistent pain 6-8/10 worse with sitting
  - Progressive lower extremity radicular pain and sensory motor loss
  - Allergies: Morphine, Vanco, NSAIDS
  - Meds:
    • Methadone 60 mg po every 8 hours
    • Hydromorphone tablets 8-16 mg po every 2hr
    • Diazepam 10 mg po three time daily
    • Neurontin 200 mg po at bed time
Case 3: Caveats

What if ketamine is not available, we do not want to increase the methadone dose and opioid rotation is impractical perioperatively?

Building a Strategy

- Preop pain consult for opioid “super users”
- Intra-op > post-op planning
- Review opioid regiment to avoid withdrawal
- Consider Multimodal Therapies (non-opioid)
- Neuraxial analgesia / Periph. nerve infusions
- Early and continued use of adjunctive agents to reduce opioid requirements.
- If PCA opioids: SAFETY FIRST (Overdyk et al. 2007)

Clonidine-Dexmedetomidine

The systemic administration of α2 agonists also recruits a descending inhibitory noradrenergic effect at the dorsal horn.

Alpha-2 agonists: Clonidine - Dexmedetomidine

Alpha 2 receptor agonists: show promise as analgesic agents due to their synergistic effect with spinal opiates, lack of cross tolerance to opioids and efficacy in opioid tolerant patients.

They offer an alternative analgesic strategy under nerve injury conditions.

One of the few FDA medications approved for the treatment of opioid withdrawal

Score Card: Opioid Tolerance

- The patient weans off all narcotics 1 week prior to surgery = ugly
- Give the patient more of the same opioid... a lot more? = May start good but then bad > ugly
- Opioid Rotation: Used in cancer pain ... post-op?
  - be mindful of hepatic / renal fx = probably good
- Use of analgesic "adjuncts" such as ketamine, alpha-2-agonists = 'good'

Thank You