Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP
MGH/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

Session Title: Opioid Alternatives for Treatment of Acute Pain

Tramadol

Tramadol has a reputation for being a safe, non-opioid alternative to opioids. Nothing could be further from the truth. Several blogs have published about the dangers of tramadol:

- Tramadol: When to Avoid It from Academic Life in EM
- Three Reasons Not to Prescribe Tramadol from EM PharmD
- Hypoglycemia: Another Adverse Effect Associated with Tramadol from Poison Review

Tramadol is an opioid, a synthetic one that is now schedule IV according to the DEA.

Problems with Tramadol

- It may not work very well (Sachs 2005)
    - Osteoarthritis-related pain: modestly effective in placebo-controlled trials (Cepeda 2006)
    - Neuropathic pain: efficacy comparable to gabapentin, TCAs, & carbamazepine (Hollingshead 2006)
    - Emergency Department
        - Musculoskeletal: Inferior to hydrocodone/APAP (Turturro 1998)
        - Ankle sprain: tramadol/APAP equivalent to hydrocodone/APAP (Hewitt 2007)
- Seizure risk
    - Previous studies have been unable to confirm an increased seizure risk with therapeutic doses of tramadol (Seizure Risk Associated with Tramadol Use from EM PharmD blog). However, a newer study refutes that premise. (Asadi 2015)
        - 22% of first-seizure patients had recent tramadol use!
        - Mean total tramadol dose in last 24 hours (reported): 140 mg
        - Duration of tramadol use less than 10 days: 84.5%
        - Seizure within 6 hours of tramadol consumption: 74%
        - This was a retrospective study without laboratory confirmation of tramadol intake
- Serotonin syndrome risk (Sansone 2009)
- Hypoglycemic risk (Fournier 2015)
- Erratic metabolism (Leppert 2011)
- Abuse/dependence/withdrawal risk (Senay 2003)
- Potential interaction with warfarin (Hosono 2017)

It behooves us not to think of tramadol as a safer alternative to opioids. (Young 2013) It is an opioid after all, and it comes with significant adverse effects.

Ketorolac (NSAID) Dose Ceiling

For acute pain, parenteral ketorolac is generally administered as 30 mg IV or 60 mg IM. Dr. Chris Bond (@socbmobem) has written about the 'ceiling effect' of NSAIDS. The question is: are we using too much ketorolac without getting additional pain benefit? A recent randomized, double-blind trial from Dr. Sergey Motov's group (@painfreeED) addresses this question. (Motov 2017)

Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP
MGH/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

What they did: 240 patients with acute pain in a 711-bed urban community teaching hospital ED were randomized to receive 10 mg, 15 mg, or 30 mg of IV ketorolac as a single-dose.

- Age 18 to 65 years
- Acute flank, abdominal, musculoskeletal, or headache pain with an intensity of 5 or greater on a standard 0 to 10 numeric rating scale
- Patients who would routinely be treated with IV ketorolac
- Pain scores, vital signs, and adverse effects were recorded at baseline and 15, 30, 60, 90, and 120 minutes
- Subjects still desiring pain medication 30 min after study drug administration were offered IV morphine 0.1 mg/kg as a rescue

Outcome: Reduction in numeric rating scale pain score at 30 minutes from medication administration.

What they found

1. No difference in reduction of pain scores between the groups
    - 10 mg – 7.7 to 5.2
    - 15 mg – 7.5 to 5.1
    - 30 mg – 7.8 to 4.8
2. No differences between the groups with respect to use of rescue morphine analgesia at any time
3. No clinically concerning changes in vital signs and no clinically significant adverse effects related to the study medication at any dose

Limitations: No placebo group and the box plot (Figure 2) revealed wide variability in all of the treatment arms

Implications for Clinical Practice

- A well-conducted study demonstrated no pain score reduction difference for various doses of IV ketorolac
- Doses of 10 mg or 15 mg are just as effective as 30 mg (or 60 mg) and should be used preferentially over higher doses (Reuben 1998, Staquet 1989, Minotti 1998, Brown 1990)
- Higher doses can cause more adverse effects, especially if more than one dose is administered (Quan 1994, Corelli 1993, Gallagher 1995, Dordoni 1994)

Ketamine

Early RCT's did not find an overall advantage of sub-dissociative ketamine for acute pain relief in the ED. (Sin 2015) A 2015 prospective, randomized, double-blind trial compared subdissociative ketamine to morphine for acute pain in the ED. (Motov 2015)

What they did

- 45 patients received IV ketamine 0.3 mg/kg (mean baseline pain score 8.6)
- 45 patients received IV morphine 0.1 mg/kg (mean baseline pain score 8.5)
- Source of pain was abdominal for ~70% in each group
- Exclusion criteria was pretty standard

What they found

- Pain score at 30 minutes: 4.1 for ketamine vs. 3.9 for morphine ($p = 0.97$)
- No difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes

- No serious adverse events occurred in either group
- Increased minor adverse effects in ketamine group at 15 minutes post-drug administration

Application to clinical practice

1. In an effort to reduce opioid use in the ED, low-dose ketamine may be a reasonable alternative to opioids for acute analgesia.
2. State/institution nursing regulations govern who can administer IV ketamine.
3. What to prescribe on discharge? Lead author Dr. Motov recommends a "pain syndrome targeted" approach with "patient-specific opioid and non-opioid analgesics."

A follow up study asked the question of how best to administer the 0.3 mg/kg IV ketamine dose while minimizing the risk of adverse effects. (Motov 2017)

What They Did

- Prospective, randomized, double-blind, double-dummy trial comparing safety and analgesic efficacy of IV low-dose ketamine given as a push dose (over 5 minutes) versus given as a short infusion mixed in 100 mL 0.9% sodium chloride (over 15 minutes)
- Pain scores, vital signs, and adverse effects were recorded at baseline, 5, 15, 30, 60, 90, and 120 minutes
- Overall rates and specific severity levels of side effects were recorded in accordance with the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA)
- Patients < 46 kg or > 115 kg were excluded.

What They Found

- 24 patients were enrolled in each group
- At 5 min:
    - Median severity of feeling of unreality was 3.0 on SERSDA scale for the IV push group versus 0.0 for the short infusion group ($p = 0.001$).
    - Median sedation on RASS scale was greater in IV push group −2.0 versus 0.0 in short infusion group ($p = 0.01$).
- Decrease in mean pain scores from baseline to 15 min was similar across groups.
- No difference between groups for changes in vital signs or need for rescue medication.

Application to Clinical Practice

- If you're using low-dose ketamine for acute pain in the ED, or developing guidelines for its use, administer it in 100 mL over 15 minutes.
- A second study utilized this same approach with positive results (Sin 2017).

Final Thoughts on Ketamine

1. While most of the studies have been performed in the ED, there is no clinical reason it could not be used in other areas.
2. After receiving ketamine, patients still may need patient-specific opioid and/or non-opioid analgesics for short-term outpatient management.
3. Even short courses of opioid therapy are associated with dependence, with 6% of patients still filling opioid prescriptions a year after their initial prescription (3% at 2 years). (Shah 2017)
4. The American Academy of Emergency Medicine (AAEM) has a Clinical Practice Statement on the Role for Intravenous Sub-Dissociative-Dose Ketamine Administered as an Adjunct to Opioids or as a Single Agent for Acute Pain Management in the ED

Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP
MGH/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

5. Intranasal ketamine may also be an option in pediatric and select adult patient populations (Shimonovich 2016, Farnia 2017, Rech 2017, Graudins 2015)

Lidocaine

- Both topical and IV lidocaine have been studied for a wide variety of pain conditions. (Golzari 2014)
- "Lidocaine is an amide-type local anaesthetic that exerts its pharmacological action through the block of sodium channels in neural tissues, thereby interrupting neuronal transmission." (Eipe 2016)
    - Exact mechanism by which IV lidocaine provides systemic analgesia remains largely unknown.
- Early clinical evidence came from its use in chronic neuropathic pain
- More recently, lidocaine has been studied for renal colic, headache, post-surgery, post-herpetic neuralgia, and others
- In acute pain, IV lidocaine demonstrates analgesic, anti-hyperalgesic, and anti-inflammatory properties.
    - May also reduce sensitivity/activity of spinal cord neurons and decrease NMDA receptor-mediated post-synaptic depolarization
- IV dose is 1-2 mg/kg as an initial bolus followed by a continuous infusion of 0.5–3 mg/kg/hr
- Safe and effective in older adults (Daykin 2017)
- IV and IN lidocaine has not been successful in all studies, respectively (Tanen 2014, Avcu 2017)
- For renal colic specifically, IV lidocaine seems to be more effective than morphine, although no studies have compared it to NSAIDS, the standard of care (Best Evidence Topics' analysis, Firouzian 2016, Soleimanpour 2012)
- Lidocaine patches are a great option for many patients (Castro 2017)
    - In the U.S., the 5% patches are prescription-only and quite expensive
    - 4% patches are available OTC and are much cheaper

Sample Acute/Chronic Back Pain Management Protocol (radiculopathies, sciatica, intractable muscle spasms)

Oral/Topical Regimen
Ibuprofen 400-800 mg
Acetaminophen 500-1000mg
Lidocaine patch-5% no more than 2 patches per 12h

Parenteral Regimen
IV Ketamine infusion: 0.3 mg/kg bolus over 15 min, 0.15-0.25 mg/kg/hr infusion with titration q30 min by 5 mg
IV Lidocaine (preservative-free): 1.5 mg/kg over 10 min (Max 200 mg)
IV Ketorolac (only if cannot tolerate po) 10-15 mg

If no improvement-admit for observation
IV Ketamine: 0.3 mg/kg bolus over 15 min, 0.15-0.25 mg/kg/hr infusion with titration q30 min (no more than 24h)
IV Lidocaine: 2.5 mg/kg/hr (100 mg IV bolus over 20 min, if no side effects, start infusion at 2.5 mg/kg/hr)

Other Options

- Discussion of topical analgesics (eg, diclofenac gel, eugenol, capsaicin) from Emergency Physicians Monthly
- Other: trigger point injections (Robbins 2014, Staal 2009, Scott 2009, Liu 2015), nitrous oxide, music (Chai 2017)