IV Naloxone Infusion: A Forgotten Gem

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Disclosure

We have no potential conflicts of interest to report.

Our opinions do not necessarily reflect the opinions of Cedars-Sinai Medical Center
Learning Objectives

▪ Identify the benefits of low dose IV naloxone

▪ Discuss the evidence supporting the use of low dose IV naloxone to prevent and reverse several opioid induced side effects

▪ Discuss the mechanism of action of low dose IV naloxone

Debunking Myths

A SPIKE IN OVERDOSES HAS MADE THIS DRUG A COMMON LIFESAVER AS IT REVERSES THE EFFECTS OF OPIOIDS
Background about Naloxone

• Well known for reversal of opioid-induced respiratory depression BUT rarely used for prevention or treatment of opioid induced side effects.

• EVIDENCE

• Side effects affecting hospital LOS: opioid-induced
  ➢ Pruritus
  ➢ N/V
  ➢ Ileus
  ➢ Urinary retention
  ➢ Hyperalgesia

• Cedars-Sinai Medical Center experience

Naloxone Overview

• Naloxone
  ➢ μ-opioid receptor antagonist
  ➢ Low doses of naloxone can selectively eliminate adverse effects of opioids WITHOUT compromising analgesia (Cepeda et al., 2002).

• FDA approved indications
  ➢ Approved to reverse opioid overdose

• Clinical pharmacology
  ➢ Suggested doses of 0.1 to 2 mg intravenously repeated every 2 to 3 min as needed. WARNING
  ➢ Elimination half-life for adults: 30 to 81 min with renal excretion.
Warning against large doses of IV naloxone

- Withdrawal in the presence of physical opioid dependence
- Drug interaction with clonidine (HTN)
- Pulmonary edema, hepatotoxicity, cardiac dysrhythmia, hypertension, hypotension, and ventricular fibrillation *(NALOXONE CAN KILL!)*

Naloxone - Titration protocol

- 0.04 mg IV q 1 minute prn RR <15 if 6-8 years old or RR<12 if >8 years old
- May repeat up to maximum dose of 0.8mg
- O₂ by facemask
Low dose IV Naloxone
Mechanism of action

- G-Proteins between opioid and mu receptor
- Gi-Proteins induce analgesia and respiratory depression
- Gs-Proteins induce opioid tolerance and hyperalgesia

Literature Review: Earliest evidence

- First published data on continuous infusion of naloxone + morphine PCA
- 60 pts ASA1, 2, or 3 for TAH
- Naloxone at 0.25 (low dose) vs 1 mcg/kg/hr (high dose) vs NS
- Both naloxone doses were equally effective in reducing the incidence of nausea, vomiting, and pruritus compared with placebo (P<0.05)
- Cumulative morphine use was the lowest in the low-dose group compared with the placebo and high-dose groups at 24 h (P < 0.05)
Opioid-Induced Pruritus, Nausea

- Prospective, double-blind, RCT
- N=46 postop patients 14+/-2.5 years on MSO4 PCA
- NS vs naloxone at 0.25 mcg/Kg/hr “piggy-backed” into same IV
- Pruritus: 77% vs 20% (p<0.05); Nausea: 70% vs 35% (p<0.05)
- No differences in MSO4 consumption, pain at rest and with coughing

Opioid-Induced Pruritus

- Meta analysis of 8 RCTs
- N=800 patients (424 in naloxone group, 376 in NS grp)
- Outcomes: incidence of pruritus, opioid consumption, VAS pain scores, nausea, vomiting, sedation
- Decrease in pruritus and nausea. NO increase in pain scores
Opioid-Induced Pruritus, Nausea/V (2)

- Dose escalation study in 59 pediatric patients
- Min naloxone dose at which pts successfully Rx’d (<10% side effect rate) was 1mcg/kg/hr
- More effective in preventing pruritus than N/V
- “Piggy-Backed” IV naloxone infusion

Opioid-Induced Pruritus (Prophylaxis)

- Double blind RCT. N=92 pediatric patient who received infusion of naloxone, opioid, and saline ADMIXTURE.
- No decrease the incidence or severity of opioid induced pruritus (OIP)
- HOWEVER pruritus was only 4% among pts w/ COI vs. 40% among pts with a PCA (naloxone mixed with opioid) (P < 0.001)
- SEPARATE administration of naloxone may be the more effective strategy for prevention of OIP.
PONV Prophylaxis
*Barrons & Woods, Pharmacotherapy. 2017 May;37(5):546-554*

- Meta-analysis of 9 RCTs
- N=946 adult and pediatric patients
- Naloxone gtt and PCA opioid/nalox ADMIXTURE (x6)
- Decreased PON but NOT for vomiting. Decreased PONV in naloxone gtt trials (x 3) at 0.05-1 mcg/kg/hr.

Postop morphine consumption

- Prospective, randomized, double-blind, controlled study
- N=90 pts (35-55 yrs) for TAH
- Naloxone 1 ng/kg (?) (loading)+infusion at **0.25 mcg/kg/hr**
- ↓ MSO4 during 1st 24 hrs (P<0.001), ↓ severity of N/V 1st 20 hrs (P<0.001), ↓ # pts received ondansetron
- No diff in pain at rest and coughing between groups
Opioid-Induced Urinary Retention

- Prospective randomized but not blind
- N=97 ortho surg pts with MSO4 PCA
- 0.1 mg IV naloxone q4h vs none
  - # voids/hr: 0.34 +/- 0.13 vs 0.26 +/- 0.11, (P=0.001)
  - Bladder scan vol/hr: 12 +/- 9.2 vs 20 +/- 22, (P=0.008)
  - % pts catheterized: 11.5% vs 24.4%, (P=0.048)
  - No diff. in pain scores a v p naloxone: 4.34 v 4.28 (P=0.509)

Opioid-Induced Urinary Retention (2)

- Double-blind RCT
- N=13 healthy male volunteers received IV infusion of remifentanil, then a single i.v. dose of study medication: methylnaltrexone 0.3mg/kg, naloxone 0.01mg/kg, or NS
  - 7/7 voiding in naloxone grp VS 0/6 in NS grp
- Naloxone produced a >50% decrease in bladder volume at first urge to void in 5/7 sessions, compared with methylnaltrexone (2/12), Placebo (0/6) (P=0.008)
Opioid-Induced Ileus


- Prospective, RCT, double-blind, single-center study
- N=72 patients undergoing open colorectal surgery
- Remifentanil: 1) Low dose  
  2) Large dose  
  3) Large dose+naloxone (0.25 mcg/kg/hr)
- Faster return of bowel function w naloxone (P < 0.05), LOS 8 vs 12 days (P < 0.001)

Opioid-Induced Hyperalgesia

Koo, CH et al, Br J Anaesth. 2017 Dec 1;119(6):1161-1168

- Prospective, double-blind, single center, RCT
- N=91 pts for thyroid surgery; 3 groups
  1) High remifentanil
  2) High remifentanil with naloxone (0.05 mcg/kg/hr)
  3) Low remifentanil
- Significantly reduced peri-incisional hyperalgesia in grp 2. No effect on postoperative pain
Summary

- 0.25 – 1 mcg/kg/hr for pruritus, nausea, vomiting, ileus
- Reversal of analgesia begins at 1 mcg/kg/hr
- Opioid-naloxone admixtures are ineffective
- Separate IV lines or “Piggy-Back”
- For urinary retention: 100 mcg IVP +/- infusion
- Analgesic effect of IV naloxone infusion?
- Reversal of hyperalgesia at 0.05 mcg/kg/hr?

Naloxone Use at Cedars-Sinai Med Ctr

Prophylactic or Treatment for Opioid Induced Side Effects

1. Pruritus
2. Nausea / Vomiting
3. Urinary Retention
4. Ileus
### CSMC Continuous Naloxone gtt orders

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>Opioid induced PRURITIS, NAUSEA, VOMITING</td>
<td>Starting dose at 0.25 mcg/kg/hr up to 0.5 mcg/kg/hr</td>
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<tr>
<td>Opioid induced ILEUS</td>
<td>Starting dose at 0.25 mcg/kg/hr up to 0.5 mcg/kg/hr</td>
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<td>(For use in high risk patients -- colorectal, spine, hepatobiliary patients or high dose opioid patients &gt;100 MEDD)</td>
</tr>
<tr>
<td>Opioid induced URINARY RETENTION</td>
<td>Starting dose at 0.35 mcg/kg/hr up to 0.5 mcg/kg/hr.</td>
</tr>
<tr>
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<td>(For use in patients receiving high dose opioid patients &gt;100 MEDD)</td>
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### January to June 2018 Naloxone gtt

**140 patients**

- 41% Male
- 59% Female

**Age Distribution**

<table>
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<tr>
<th>Age Group</th>
<th>Count</th>
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<tbody>
<tr>
<td>10 - 20</td>
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<td>71 - 80</td>
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<td>81 - 90</td>
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12/4/18
January to June 2018 Naloxone gtt

- Ileus 48%
- Multiple 15%
- N/V 19%
- Pruritus 11%
- Urinary Retention 7%

A Closer Look: Patient with nausea

79 year old F
POD#0, Closure of right chest wall wound with local flap advancement

Thoracic epidural fentanyl 2.5 mcg/ml +bupivacaine 0.1%

POD#1
Patient used 115.9 ml via PCEA; tramadol 75 mg in 24 hours

POD#2
Total PCEA used 201.4 ml; tramadol 75 mg in 24 hours.

POD#3
Patient still c/o nausea. Patient used ondansetron 24 mg in 24 hours. Started naloxone gtt 0.25 mcg/kg/hr for nausea

POD#4
Patient denies any nausea or vomiting. Did not use any ondansetron post initiation of naloxone gtt.

Patient was able to optimize oral pain regimen (tramadol and oxy IR)

Day 0
Day 1
Day 2
Day 3
Day 4
A Closer Look: Patient with pruritus

POD#0
40 year old F
POD#0, s/p exploratory laparotomy, total abdominal hysterectomy

POD#1
Patient used 76 ml via PCEA in 12 hours
Thoracic epidural fentanyl 5 mcg/ml + bupivacaine 0.125%
Started to c/o pruritis and received diphenhydramine 12.5 mg IV x1
Started naloxone gtt 0.25 mcg/kg/hr for pruritus

POD#2
Patient denies any pruritus.
Did not use any diphenhydramine post initiation of naloxone gtt.
Patient pain remained controlled via PCEA

Day 0
Day 1
Day 2

A Closer Look: Patient with urinary retention

POD#0
53 year old F
POD#0, s/p T3-4 and T10-11 laminectomy and CSF leak repair

POD#1
Pain service was consulted.
Patient currently on oxy IR and IV hydromorphone for pain.
Multimodal pain regimen ordered.
MEDD used 147 mg
MEDD used 112 mg

POD#2
Post operative pain controlled.
Patient c/o urinary retention (recent straight catheterization)
Naloxone 100 mcg IV push given

POD#3
Patient voided 200 ml yesterday.
Discharge home today.

POD#4

Day 0
Day 1
Day 2
Day 3
Day 4
A Closer Look: Patient with ileus

58 year old F admitted with severe abdominal pain 2/2 chronic constipation d/t opioid use

Multiple bowel regimen was ineffective.
Pt continue to c/o abdominal distention and constipation

Admission day 1

Pain service team consulted
Started naloxone gtt 0.25 mcg/kg/hr for opioid induced ileus

Day 2

Patient had three bowel movement since initiation of naloxone gtt.
Less abdominal distention
Decreased opioid consumption

Day 2

Future Directions

▪ Ongoing retrospective chart review for naloxone treatment outcomes.

▪ More proactive use of naloxone for prophylaxis

▪ Consider adding prevention or treatment of opioid induced hyperalgesia as an additional indication.
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