UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Dexmedetomidine for Opioid-Induced Hyperalgesia (OIH)

Background:

Opioid-induced hyperalgesia (OIH) is a paradoxical increase in pain perception after opioid administration and there are no reliable ways to treat or prevent it. One proposed mechanism is an increase in NMDA currents in the dorsal horn. However, NMDA antagonists have not lived up to their potential in treating OIH (see Part 1) and other analgesics are being studied. The descending noradrenergic pathway from the locus coeruleus in the brainstem to the neurons of the dorsal horn is thought to reduce spinal transmission of pain. In fact, upregulation of this natural inhibitory system is part of the proposed analgesic mechanism of TCAs, SNRIs and gabapentanoids. Dexmedetomidine is a highly selective alpha2 adrenergic agonist used for sedation that has gained popularity among our anesthesiologists and critical care colleagues for having less respiratory depression compared to other sedatives and as part of multimodal analgesic plan. A 2012 meta-analysis found RCT evidence that alpha2 adrenergic agonists decrease postoperative pain intensity and morphine consumption but failed to find a single randomized placebo-controlled trial of the effect of perioperative dexmedetomidine on hyperalgesia. In 2021, an RCT was published with new data for this important question.

Importance:

Palliative care patients are at risk for OIH. Due to the infrequent nature and lack of standard definition and measurement of OIH, prospective, high-quality evidence in palliative care populations is unlikely to be available in the near future. Palliative care providers may be able to extrapolate data from other specialties/studies for treatment of OIH.

The Literature:

Anesth Analg. 2021 Feb 1;132(2):320-328.

Effects of an Intraoperative Intravenous Bolus Dose of Dexmedetomidine on Remifentanil Induced Postinfusion Hyperalgesia in Patients Undergoing Thyroidectomy: A Double-Blind Randomized Controlled Trial

Objective: to determine whether an intraoperative bolus of dexmedetomidine (dex) alleviates OIH in patients undergoing thyroidectomy under remifentanil-based general anesthesia

Methods: RCT; normal saline vs low-dose dexmedetomidine 0.2 μg/kg vs high-dose dexmedetomidine 0.5 μg/kg

Outcomes:

- Mechanical pain thresholds preoperatively via electronic von Frey device, 30 minutes, 6 hours, 24 hours, and 48 hours after surgery
- Postoperative pain scores
- Incidence of receiving rescue analgesics

Results (N = 90; mean age ~40)

- The pain thresholds around the skin incision were significantly higher in both low dose dex and high dose dex groups compared to placebo 30 minutes and 6 hours after surgery
- The incidence of hyperalgesia around the skin incision was lower with high dose dex than placebo 30 minutes and 6 hours after surgery
- Postoperative pain scores and the incidence of rescue analgesic demand were not different

Conclusion:

- An intraoperative bolus of dexmedetomidine alleviates OIH in patients undergoing thyroidectomy under remifentanil-based general anesthesia

Zhonghua Yi Xue Za Zhi. 2013 Jan 1;93(1):44-7.

Effect of dexmedetomidine in acute postoperative pain relief is independent of suppressing the hyperalgesia induced by remifentanil

(Unable to obtain full text in English through UPMC/Pitt librarian– summary below based on abstract only)

Objective: To explore the effect of dexmedetomidine in acute postoperative pain and remifentanil-induced hyperalgesia in patients undergoing elective abdominal surgery under general anesthesia

Methods: (N=120)

- Not placebo controlled

Outcomes:

- postoperative mechanical pain threshold
- pain visual analog scale (VAS) score
- morphine consumption

Results:

- Dexmedetomidine reduced postoperative morphine consumption significantly, and increased Ramsay scores, but had no effect on mechanical hyperalgesia.

Conclusion:

- Dexmedetomidine can alleviate acute postoperative pain effectively, but the effect is not dependent on inhibiting remifentanil-induced hyperalgesia

Bottom Line:

- Mouse models suggest multiple neuronal mechanisms are involved in the development of OIH, including NMDA and descending inhibition from the noradrenergic system. However, OIH is difficult to study in humans
- Research of OIH in humans has largely come from anesthesia literature because the most consistently associated opioid - remifentanil - is commonly used for procedural analgesia or sedation
- There has been only one rigorous RCT of dexmedetomidine for OIH in humans which found benefit in *preventing* the development of OIH
- Extrapolation of these results in our palliative care population should be done with caution given potential for mechanistic difference in OIH in surgical population and lack of evidence for *treatment* of OIH
- In cases of severe, refractory OIH that requires intervention, dexmedetomidine may be reasonable to try based on data from surgical patients although this finding needs further replication and validation. Barriers remain such as expense, provider comfort and knowledge and need for ICU level monitoring.

CLINICAL PEARL: Data for dexmedetomidine to *prevent* OIH is mixed in surgical populations