Clinical Pharmacology & Toxicology Pearl of the Week

~ Naloxone ~

- ✓ First synthesized in 1960, naloxone is a competitive opioid antagonist at mu, kappa and delta receptors.
- ✓ It is most potent at the mu receptor (the receptor responsible for analgesia, sedation, miosis, euphoria, respiratory depression, and decreased GI motility).
- ✓ Naloxone can be administered via the intravenous, intramuscular, subcutaneous, intranasal, intraosseous, intralingual, nebulized or via endotracheal routes. Onset is fastest when given IL (30 seconds) and slowest when given IM (6 minutes).
- ✓ Duration of action is 20-90 minutes and elimination half-life is 60-90 minutes
- ✓ Indications for naloxone administration in patients with opioid-associated CNS depression include hypoventilation (respiratory rate < 12/min) and /or hypoxia (oxygen saturation < 90%).
- ✓ Naloxone has also been used in management of overdoses of non-opioids such as ethanol, clonidine, ACE inhibitors, and valproic acid. Mechanism of action may be due to reversal of endogenous opioid peptides at opioid receptors. Clinical improvement in these situations is neither as dramatic nor consistent as with opioids.

- ✓ **Dosing:**
  - Adult starting dose:
    - 0.4 mg IV/IM/IO/SQ for non-opioid dependent patients.
    - 0.04 mg IV/IM/IO/SQ for opioid-dependent patients.
  - If using the nebulized or endotracheal route, start with at least twice the recommended IV dose.
  - Repeat with escalating doses every 2-3 minutes as needed until reversal of hypoventilation is achieved, to a maximum of 12 mg.
  - The goal of naloxone reversal is adequate oxygenation and ventilation without requiring supplemental oxygen
  - In the opioid-dependent patient, rapid reversal of CNS depression should be avoided due to the risk of precipitating acute withdrawal.

  - Pediatric starting dose:
    - 0.1 mg/kg IV/IM/IO/SQ for non-opioid dependent patients
    - 0.001 mg/kg IV/IM/IO/SQ for opioid-dependent patients
  - If using the nebulized or endotracheal route, start with at least twice the recommended IV dose.
  - Repeat with escalating doses every 2-3 minutes as needed until reversal of hypoventilation is achieved, to a maximum of 12 mg.
  - The goal of naloxone reversal is adequate oxygenation and ventilation

without requiring supplemental oxygen.
    - In the opioid-dependent patient, rapid reversal of CNS depression should be avoided due to the risk of precipitating acute withdrawal.

- ✓ If there is no response after 12 mg naloxone, search for other causes of CNS depression.

- ✓ Repeat intermittent naloxone dosing or continuous naloxone infusion is often required as the duration of action of naloxone is 20-90 minutes compared with 24 hours for methadone.

    - If starting an infusion, the infusion should be started (in mg/hr) at two-thirds of the effective naloxone dose and titrated as needed. The effective dose of naloxone is the dose that resulted in improvement of hypoventilation and/or hypoxia.

    - If needed, give another bolus of one-half the effective naloxone dose 15 to 20 minutes after starting the continuous infusion.

- ✓ Naloxone may need to be continued for more than 24 hours post-exposure.

- ✓ Monitor the patient for at least 6 hours after naloxone is discontinued.

- ✓ Patients who remain symptom free after at least 6 hours post cessation of naloxone can be medically cleared from a toxicologic perspective.

- ✓ **Naloxone-associated acute opioid withdrawal:**
    - Naloxone can potentiate withdrawal in opioid-dependent patients. Opioid withdrawal is typically not life threatening but is extremely uncomfortable for the patient. In rare cases, acute lung injury may occur in the setting of precipitated opioid withdrawal, thus rapid reversal should be avoided.

    - Clinical features of opioid withdrawal include yawning, rhinorrhea, nausea, vomiting, diarrhea, lacrimation, piloerection, muscle aches, weakness, perspiration, anxiety, depression, dilated pupils, tremors, tachycardia, and hypertension. Seizures may be seen in neonatal opioid withdrawal.

    - If the patient develops withdrawal after a bolus dose of naloxone, allow the effects of the bolus to abate. Symptoms resolve over 1 hour as the naloxone inhibition of opioid receptors decreases.

- If the patient develops withdrawal during an infusion of naloxone, stop the infusion until the withdrawal symptoms abate, and restart the infusion at half the initial rate.

- In addition to adjusting the naloxone dosing, treatment of naloxone-associated opioid withdrawal may involve the following depending on the symptoms and the expected duration of withdrawal:
  - IV fluid boluses for volume depletion.
  - Antiemetics for nausea and vomiting.
  - Caution using ondansetron in patients with prolonged QTc.
  - A small dose of a short-acting opioid (e.g., fentanyl 25-50 mcg IV) may be sufficient to relieve withdrawal symptoms.
  - H2 blockers (e.g., ranitidine) for gastrointestinal reflux symptoms.
  - Clonidine 0.1-0.2 mg PO every 4 hours for control of autonomic symptoms (elevated HR and BP). Daily maximum of 1.2 mg.
  - Loperamide for diarrhea.
  - NSAIDS (e.g., ibuprofen) for myalgias.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, RAAPID, and Connect MD. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

Created: April 26, 2019

Reviewed: December 1, 2025