Naloxone Adult Medication Profile

AREAS APPLICABLE

All Monash Health clinical areas where opioids are used in the care and treatment of patients.

Opioid overdose can potentially occur anywhere and naloxone is available on every medication imprest.

EXCLUSIONS

This medication profile is not applicable to Community Mental Health Sites. These sites must refer to Standing Order - Naloxone

Intranasal Naloxone formulation is not covered by this medication profile.

This medication profile does not relate to Naloxone to take home for patients who are discharged from the Emergency Department.

INDICATIONS APPROVED AT MONASH HEALTH

- Complete or partial reversal of opioid intoxication or overdose, especially with respiratory depression or sedation.
- Relief of opioid-related pruritus (itch).

MEDICATION CLASS

- Opioid Antagonist

CONTRAINDICATIONS

- Hypersensitivity to naloxone (rare).

PRECAUTIONS

- **Naloxone therapy is not a replacement for supportive care in opioid toxicity/overdose. Death is the result of failure to breathe. It is vital to support patient's airway and ventilation while preparing naloxone and assessing response to treatment.**
- **Consult Monash Toxicology if uncertain about naloxone dosing or need for an infusion.**
- Patients requiring Naloxone infusion must be located in a High Dependency Unit
- Acute opioid withdrawal syndrome can be precipitated in opioid-dependent patients.
    - Response to naloxone would be titrated using smaller incremental bolus doses in opioid-dependant individuals.
- Analgesic effects of opioids are reversed by naloxone.
- Opioids with a high affinity for mu receptors (e.g., buprenorphine and carfentanil) may require larger doses of naloxone or naloxone infusion to reverse toxicity.
- Naloxone will not reverse respiratory depression caused by non-opioid medications.
- Naloxone will also antagonise the effects of other non-opioid mu-receptor agonists, such as tramadol and tapentadol.
- Rapid complete reversal of opioid toxicity may rarely be associated with myocardial infarction or ventricular arrhythmias in those with pre-existing cardiovascular disease or those receiving cardio toxic medications. These effects may be the result of sympathetic excess from rapid opioid toxicity reversal or possibly from prior hypoxia resulting from the overdose.
- The duration of action of naloxone is shorter than most opioid analgesic agents. Re-sedation often occurs and may require administration of repeated intermittent doses or a continuous infusion, particularly when used to reverse the effects of sustained release formulations.

ACTION

- Pure opioid antagonist, preventing or reversing the effects of opioid medications including respiratory depression, sedation and hypotension.
- Naloxone is a competitive antagonist primarily at mu, but also kappa and sigma opioid receptors.
- Naloxone has a much higher affinity for opioid receptors than most opioid analgesic agents.

PHARMACOKINETICS

- Low oral and sub-lingual bioavailability.
- Onset of action after intravenous (IV) injection is 1- 2 minutes.
- Onset of action after intramuscular (IM) is 5-6 minutes.
- Naloxone has a short duration of action. The half-life is approximately 1 hour (range 20-90 min) after IV dosing.
- The liver rapidly metabolises naloxone, and metabolites are excreted in the urine.
- The duration of action of naloxone is shorter than most opioid analgesic agents. Re-sedation often occurs and may require administration of repeated intermittent doses or a continuous infusion.

PRESENTATION

- Naloxone hydrochloride 400 microg / 1 mL ampoule.

STORAGE

- Store ampoules below 25 °C. Protect from light. Do not freeze.
- Infusion solution to be used within 24 hours.

DOSING

Bolus dosing

- **Naloxone therapy is not a replacement for supportive care in opioid toxicity/overdose. Death is the result of failure to breathe. It is vital to support patient's airway and ventilation while preparing naloxone and assessing response to treatment.**
- IV injection
  - Preferred route of administration in a hospital setting and is suitable for use in ALL areas.
  - Can be via central or peripheral line.
  - Dose can be repeated every two minutes.
  - Can be used both undiluted and diluted (in Sodium Chloride 0.9% or Glucose 5%).
- Intra-osseous injection
  - Suitable if IV route not available.
- IM Injection
  - Suitable if IV route not available. [Usually in the pre-hospital setting.]
  - Initial dose is larger: 800 microg.
  - Inject into the upper arm or thigh. Can be injected through clothing.
  - Dose can be repeated every five minutes.
  - Duration of effect may be longer than after IV bolus administration.

- Dosage
  - Reversal of opioid overdose (known or suspected)
    - Opioid naïve patients:
      - 200 microg intravenous boluses.
      - Repeat every 2 minutes until desired response, or up to a total of 2 mg.
      - Full reversal will not result in opioid withdrawal syndrome.
    - Opioid-dependent patients:
      - Stepwise increase in intravenous bolus dosing from initial dose of 40 microg, to 80 microg, then 120 microg every 2 minutes until desired response, or up to a total of 2 mg.
      - Full reversal may result in opioid withdrawal syndrome.
    - Consider infusion if repeated (3 or more) naloxone boluses have achieved a partial effect, or opioid effects re-emerge an hour after giving naloxone.
    - A continuous infusion will more likely be required after a positive response to bolus dosing for sustained-release (SR) opioid toxicity, long-acting opioid toxicity and intrathecal opioid dosing toxicity.
    - **Desired response**: patient responding to verbal commands, normal respiratory rate and depth, normal $ETCO_2$ or Pa/v CO_2, and resolution of respiratory acidaemia on blood gas analysis.
  - Post-op respiratory depression
    - 40 – 80 microg intravenous boluses.
    - Repeat every 2 minutes until desired response, or up to a total of 2 mg.
    - If no intravenous access, give 200 microg intramuscular bolus while obtaining intravenous access.
    - Consider infusion if repeated (3 or more) naloxone boluses have achieved a partial effect, or opioid effects re-emerge an hour after giving naloxone.
    - A continuous infusion will more likely be required after a positive response to bolus dosing for sustained-release (SR) opioid toxicity, long-acting opioid toxicity and intrathecal opioid dosing toxicity.
    - **Desired response:** patient responding to verbal commands, normal respiratory rate and depth, normal $ETCO_2$ or Pa/v CO_2, and resolution of respiratory acidaemia on blood gas analysis.
  - Treatment of opioid pruritis
    - 20-40 microg intravenous boluses.
    - Repeat every 5 minutes until the itch resolves.
    - [For post-partum patients on the maternity ward, administer 20-40 microg subcut, repeated every hour, until itch resolves.]
  - Dosing comments:
    - Effective dose is variable. Dose depends on the amount and type of opioid taken, and pre-existing opioid tolerance.
    - In opioid-dependent patients, aim to use the lowest dose required to reverse respiratory depression – start low and titrate.

        - Isolated heroin overdose rarely requires re-dosing after a naloxone bolus therapy. Re-sedation and requirement for additional bolus doses suggests the presence of a longer-acting opioid such as methadone, buprenorphine or sustained-release oral opioids.
        - Consider alternative non-opioid analgesic agents or consult APS for ongoing analgesic options.
    - **A lack of any response to a 2 mg total dose suggests, in most cases, non-opioid sedative agents are more than likely implicated in the intoxication. <u>Manage supportively.</u>**
        - *(Note: for some synthetic opioids, toxicity may respond to even higher total doses of naloxone – up to 10 mg. Continue to provide supportive care and discuss with Monash Toxicology).*
    - **Consult Monash Toxicology if uncertain about naloxone dosing or need for an infusion.**

IV Infusion

- Scope of IV infusion use:
    - Intensive Care Unit, Emergency Department and Theatres.
- Route:
    - Via central or peripheral line.
- Infusion:
    - Dilute 4mg (10 x 400 microg ampoules) in 90mL of solution, to a total volume of 100mL.
    - Compatible Solutions: Glucose 5%, Sodium chloride 0.9%
    - Final Concentration: 40 microg/mL
    - 1mL/hr = 40 microg/hr
- Dose Range:
    - The ***starting*** hourly rate of the infusion is two-thirds of the cumulative effective intravenous bolus dose.
        - E.g., if a patient required 200 microg + 200 microg + 200 microg = 600 microg total dose to achieve reversal of opioid toxidrome, the infusion starting rate will be 400 microg /hr.
    - Common Dose Range: 80 – 1000 microg/hr.
    - Corresponding Infusion Rate: 2-25 mL/hr.
    - Nb: If needing greater doses, other causes of sedation must be considered, and supportive care (e.g., invasive ventilation) may need to be instituted.
- Titration:
    - The initial infusion rate commonly needs reassessment and adjustment and often needs to be increased based upon clinical response.
    - This includes:
        - Serial assessment of level of consciousness / alertness (sedation scores).
        - Serial assessment of respiratory rate and depth, and blood gas pCO2.
        - Heart rate and blood pressure.
    - Adjustment of infusion rate:
        - If a patient is re-sedating despite the current naloxone infusion rate:

- Re-dose with bolus doses (80 microg repeat doses) until awake and ventilating normally.
- Increase infusion rate by 20%.
- Reassess response hourly.

- Ceasing infusion:
  - Weaning is not required.
  - Monitor the patient closely for 4 hours after cessation of the infusion for re-sedation.
    - If a patient is re-sedating following cessation of infusion:
      - Re-dose with bolus doses (80 microg repeat doses) until awake and ventilating normally.
      - Restart the infusion at previous rate.
      - Reassess response hourly.
  - Do not cease an infusion at night (2000 hrs – 0700 hrs).
- Monitoring
  - Naloxone infusion is not a substitute for continual vigilance.
  - Infusion must be administered in a HDU setting.
  - Monitor patient closely for clinical improvement with regular observations every 15 minutes:
    - Respiratory rate and depth
    - Heart rate and blood pressure
    - End-tidal CO2 or Blood gas pCO2
    - Sedation scores.

ADVERSE REACTIONS

- Acute opioid abstinence syndrome (also known as acute opioid *withdrawal* syndrome):
  - Nausea, vomiting, diarrhea, sweating, piloerection, yawning, anxiety, tremulousness, tachycardia and increased PAIN from reversal of opioid analgesic effects (in chronic pain patients).
- Pulmonary oedema – particularly in patients who have had a sustained period of hypoxemia and respiratory acidosis from their acute opioid toxicity.
- Hypertension / Hypotension
- Arrhythmias (rarely)
- Withdrawal encephalopathy, seizure (rarely)

REFERENCES

- Micromedex – Drugdex (accessed 21/03/22)
- Burridge N (2020) Australian Injectable Drugs Handbook. 8th Edition
- Epworth Healthcare () ‘Naloxone’ Drug Guideline
- Alfred Health (2020) ‘Naloxone Infusion’ Drug Guideline
- Austin Health (2020) ‘Naloxone’

KEYWORDS

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