Suspected Opioid toxicity – Clinical Guideline



If respiratory rate greater than 8 but signs of opioid toxicity:

- Stop regular opioids until sustained improvement in respiratory rate and conscious level (prn opioids at half dose)
- Continue regular obs 15-30 mins for first 4 hours
- Urgent bloods (U+E, LFT, Ca)
- Try to determine cause; too rapid titration, ?renal failure/liver failure, introduction of more effective analgesia ie pregabalin/radiotherapy, poorly opioid responsive pain, pyrexia with fentanyl, drug interactions ie CYP3A4 inhibitors increase fentanyl and alfentanil concentrations
- Prescribe IV fluids to increase opioid clearance
- Consider completely stopping long acting opiates and switching to shorter acting opiate prn or alfentanil driver. Alfentanil driver can be stopped and drug cleared 30-60mins. Also use alfentanil if concerned renal function deteriorating (or if eGFR less than 30ml/min)
- If opioids to continue reduce opioid dose by 1/2 and ensure prn doses also halved.

Naloxone for opioid toxicity – how to administer

Purpose

To reverse opioid-induced respiratory depression

Items required (kept in "Drugs for Opioid Toxicity" box – in Clinic Room)

Naloxone 400 microgram per ml in 1ml ampoules 1 x 3,2 pink needles, 2 orange subcutaneous needles, 10ml syringe, 1ml syringe, 3 x 10ml sodium chloride 0.9% for dilution & flushing

Method of administration

Slow IV injection (can be given IM or SC but only if IV route unavailable; same dose as IV) Onset of action – 1-2min IV, 2-5 min SC/IM Duration of Action - 15-90 min IV

Contraindications

Proven allergy to naloxone. No other absolute contraindications when used to reverse opioidinduced respiratory depression.

Undesirable Effects Nausea and vomiting; occasionally severe hypertension, pulmonary oedema, tachycardia, arrhythmias and cardiac arrest. If physically opioid dependent full reversal will lead to severe pain, hyperalgesia and agitation, and acute withdrawal syndrome.

Gradual titration to avoid loss of analgesia

For respiratory depression that is not imminently life threatening RR 4 - 8

Smaller doses of naloxone must be used as full reversal will lead to severe pain, hyperalgesia and agitation and acute withdrawal syndrome.

- Try other conservative methods to stimulate respiratory rate ie oxygen, bag-valve-mask⁴
- Dilute an ampoule of naloxone 400microgram to 10ml with sodium chloride 0.9% for injection ⁷
- Administer 100mcg (2.5ml) IV stat.^{2,4} Flush cannula between doses.
- Dose can be given SC/IM if no IV access. Consider obtaining IV access.
- Administer 100mcg (2.5ml) every 2min if IV or every 5mins if SC until the patient's respiratory status is satisfactory and sustained >8.
- It is important to titrate against respiratory rate not level of consciousness as total antagonism will cause return of severe pain with hyperalgesia and physical withdrawal/agitation.
- Further boluses may be necessary if RR drops below 8 because naloxone is shorteracting than many opioids, consider continuous SC infusion(see below)
- If SaO2 less than 90% give supplemental oxygen, consider bag-valve-mask ventilation.
- Consider whether transfer to acute hospital appropriate

Emergency full reversal

For imminently life threatening respiratory depression (RR less than 4) If physically opioid dependent full reversal will lead to severe pain, hyperalgesia and agitation, and acute withdrawal syndrome

- Dilute an ampoule of naloxone 400microgram to 10ml with sodium chloride 0.9% for injection
- Administer 400mcg (10ml) IV stat ^{1,5}
- If no IV access give IM/SC. If using SC use undiluted. Obtain IV access as soon as possible.
- Consider transfer to acute hospital, call 999 as assisting ventilation via bag-valve- mask may be required
- If SaO2 less than 90% give supplemental oxygen and attempt bag-valve- mask ventilation.
- If IV Assess each dose after 1 minute and if no response move to the next dose
- 800mcg → 800mcg → 2mg to 4mg ^{1,4,5}
- If IM/SC administer next dose after 2-3 mins, repeat 400mcg dose every 2-3mins until effect seen or IV access obtained.^{4, 6}
- If no response to 2-4mg consider alternative diagnosis, eg other sedative, neurological event, sepsis.
- NB buprenorphine will require higher doses (see below)
- If necessary set up an IVI set to deliver hourly dose (see below).

Naloxone - How to Administer Continuous Infusions

Caution 1 – naloxone is cleared more quickly than many opioids, acting for 15 mins to 90mins; thus further doses or a continuous infusion may be needed.

Caution 2 – buprenorphine will require higher doses of naloxone – 2mg stat over 90 secs, set up IVI naloxone 4mg/hr. Naloxone has been reported to be only partially effective in tramadol overdose(in a case series of tramadol toxicity 7 out of 11 had good response to naloxone, one patient had no response).

Caution 3 - analgesic benefit from the opioid will be partially reversed. Consider non-opioid alternative analgesics (e.g. paracetamol, NSAIDs, nefopam, ketamine).

Setting up a Continuous SC infusion of Naloxone

To maintain partial reversal until the opioid is cleared

- A consultant, a senior nurse, and the patient's own wishes should be included when discussing whether to transfer to an acute hospital or remain at the palliative care unit(SPCU).
- Naloxone is licensed to be given SC, but administration of the drug via a CSCI is off-label use.
- The initial dose required above will approximately guide the infusion dose required.
- Dilute 5 ampoules of 400micrograms (2mg) in 10ml sodium chloride 0.9% to give a concentration of 200 micrograms per ml.
- A typical hourly dose is 60% (range of 50-100%) of the total stat doses required to maintain satisfactory ventilation RR>8 for >15 mins with subsequent titration according to response/level of respiratory depression as detailed below ^{4,6}
- Usual infusion rate 0.25ml-0.5ml/hr(50mcg-100mcg/hr)via syringe driver given subcutaneously over 24 hours.
- The infusion of naloxone must not be mixed with any other drug.
- Prepared infusion must be used within 24 hours of preparation or discarded
- Adjust the naloxone infusion rate to keep the respiratory rate above 8 (do not titrate to level of consciousness).
- Patient's respiratory rate and pain level must be monitored closely during infusion
- Additional boluses may be required SC/IV
- If remaining at the SPCU, ensure PRN IV/ SC doses (as above, with doses suitable for likely
 degrees of respiratory depression) are prescribed in case respiratory depression recurs or
 the IV cannula dislodges, respectively.
- If respiratory depression recurs, the doctor should review need for increasing the rate.
- If pain recurs, the doctor should review need for reducing the rate.
- Consider writing up an alfentanil infusion (at least 50% dose reduction of opioid)if respiratory rate stable and pain returns as this can be stopped and drug cleared in 30-60 mins, should respiratory function be compromised again.

Setting up a Continous Intravenous infusion (IV) of Naloxone

To maintain reversal until the opioid is cleared

- A consultant, a senior nurse, and the patient's own wishes should be included when discussing whether to transfer to an acute hospital or remain at the SPCU.
- This will usually be the mode of administration of continuous naloxone in hospital.
- The initial dose required above will approximately guide the infusion dose required.
- Preferably administer via a central line to avoid potential venous irritation as preparation has a low pH. If given peripherally monitor closely for phlebitis.⁶
- Add 1mg of naloxone (2.5ml of 400micrograms/ml naloxone injection) to 100ml sodium chloride 0.9% to give a concentration of 10 micrograms/ml.⁷
- The typical hourly dose is 60% (range of 50%-100%) of the total stat doses required to maintain satisfactory ventilation RR>8 for >15 mins ^{2,4-6} with subsequent titration according to response/level of respiratory depression as detailed below.
- Usual infusion rate 5ml-10ml/hr(50mcg-100mcg/hr).
- Prepared Infusion must be used within 24 hours of preparation or discarded.
- Adjust the naloxone infusion rate to keep the respiratory rate above 8 (do not titrate to level of consciousness).
- Patient's respiratory rate and pain level must be monitored closely during infusion
- Additional IV boluses may be required.
- Ensure PRN IV/SCdoses (as above, with doses suitable for likely degrees of respiratory depression) are prescribed in case respiratory depression recurs or the IV cannula dislodges, respectively
- If respiratory depression recurs, the doctor should review need for increasing the rate.
- If pain recurs, the doctor should review need for reducing the rate.
- Consider writing up an alfentanil infusion (at least 50% dose reduction of opioid)if respiratory rate stable and pain returns as this can be stopped and drug cleared in 30-60 mins, should respiratory function be compromised again.

If unexplained SOB occurs or persistent hypoxaemia examine for pulmonary oedema which can be caused by opioid toxicity itself but also naloxone. This is extremely rare and usually occurs within the first hour but can occur up to 48 hours post naloxone.

Please fill in an incident form in all patients where naloxone has been administered so that naloxone use can be audited/or changes in practice initiated.

References

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