Naloxone prescribing: room for finesse

In terms of pain relief, few drugs are as effective and potent as opioids. Morphine and its many derivatives are commonly used in acute and chronic disease, surgery and palliative care, and are also widely used as recreational drugs. Clinicians from all fields therefore need to be comfortable with managing the adverse effects of opioid toxicity.

The most commonly used antidote is naloxone. Its mechanism of action is not completely understood, but it likely acts as a non-selective and competitive opioid receptor antagonist (Jordan and Morrisonponce, 2018).

Naloxone is a highly lipophilic structure, meaning it is rapidly distributed and taken up by cells within the CNS (Nestler et al, 2009). This explains its rapid onset of action, quoted as 1–2 minutes when given intravenously according to the American Hospital Formulary Service (McEvoy and American Society of Health-System Pharmacists, 2004). Unfortunately naloxone has a reported half-life of 1 hour (Berkowitz, 1976) in contrast to the longer half-lives of many common opiate and opiate-derived drugs (*Table 1*). This explains the potential of renarcosis and the need for repeat doses.

Table 1. Common opioids and their respective half-lives

Opioid	Plasma half-life (hours)
Morphine (immediate release)	2–3.5
Codeine	3
Buprenorphine	3–5
Fentanyl	3–4
Methadone	24
Naloxone	1

From Trescot et al (2008)

Dr James Gilham, Foundation Year 1 Doctor, Department of Medicine, Royal Devon and Exeter Hospital, Exeter EX2 5DW

Dr Gavin Lloyd, Consultant Emergency Physician, Emergency Department, Royal Devon and Exeter Hospital, Exeter

Correspondence to: Dr G Lloyd (gavin.lloyd@nhs.net)

A common mistake with naloxone prescribing is using a one size fits all approach, with many clinicians using the standard 400 µg dose and applying that universally. As the following cases demonstrate, a degree of finesse can and should be used.

Case examples

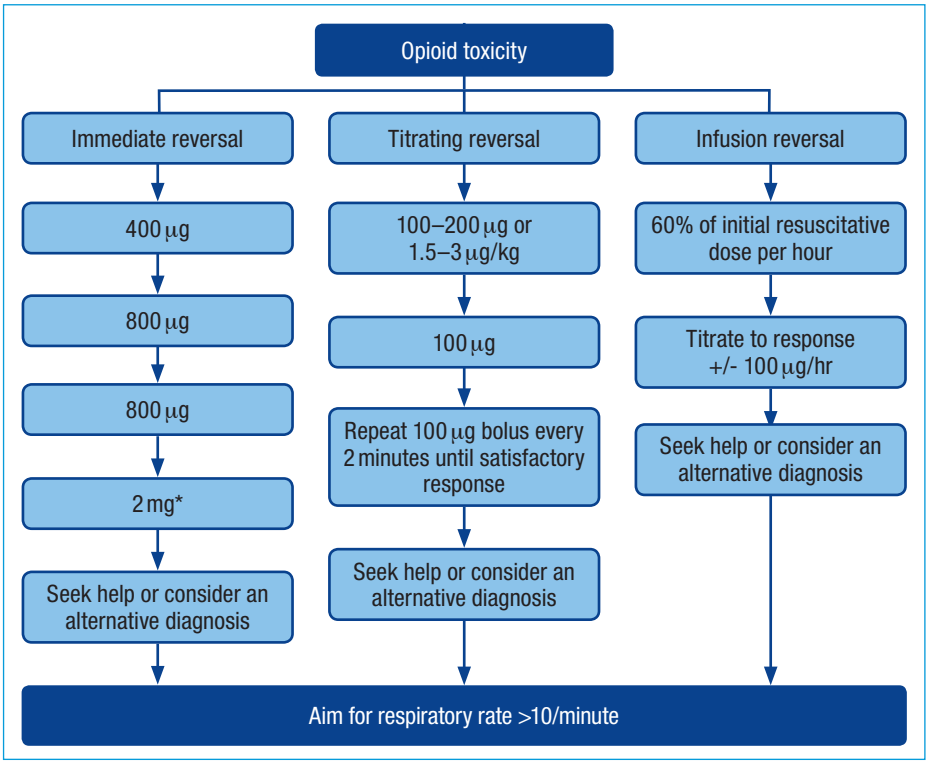
Immediate reversal

A 34-year-old man of no fixed abode was brought to the emergency department having been found unresponsive in a local park. The paramedic crew noted that his Glasgow coma score was 8/15 and his respiratory rate was 6 per minute. He had pinpoint pupils and evidence of recent intravenous drug use with needle marks in his left antecubital fossa. The crew treated him with naloxone 400 µg on the scene which produced minimal response. On arrival in the emergency department he was maintaining his own airway, but his breathing was noisy suggesting a degree of airway obstruction. His cold peripheries prevented any reliable oxygen saturation traces. His previous emergency department notes reveal a history of intravenous drug use and repeat attendances for heroin overdoses.

In this instance the patient is likely to be profoundly toxic and warrants immediate reversal to improve both his Glasgow coma score and his respiratory effort to prevent further decline and a possible respiratory arrest.

For immediate reversal in patients with opiate overdose, the British National Formulary recommends an increasing dose regimen starting at 400 µg intravenous (naloxone can be given intramuscularly if there is no intravenous access) and continuing up to a single 2 mg bolus if no adequate response is seen (*Figure 1*). In this

Figure 1. Adult naloxone prescribing pathway. *Doses greater than 2 mg may be necessary with highly potent opioids such as fentanyl or carfentanyl.



case, a repeat bolus of 800 µg produced a good clinical response (target V on the Alert Voice Pain Unresponsive (AVPU) scale) and the patient was observed in the department until fit for discharge. Reversal to A (alert) on the AVPU scale will likely lead to a non-compliant patient at risk of renarcosis should he leave early, with the naloxone wearing off before the recreational opiate does.

It is worth noting that the differential diagnosis for an unconscious adult with pinpoint pupils includes pontine lesions (e.g. haemorrhage) and organophosphate or nerve agent poisoning. If no adequate response is seen after a 2 mg bolus of naloxone it is wise to question whether opiate toxicity is the correct diagnosis.

Titrating reversal

A 71-year-old woman recovering from a left-sided hemicolectomy for bowel cancer on the surgical ward triggered a review for a high early warning score. The patient's observations were stable other than her respiratory rate was 10 per minute, saturations were 91% and she was P on the AVPU scale. The patient was being treated with a patient-controlled analgesia device.

In this instance management should start with airway manoeuvres or adjuncts if needed, supplementary oxygen aiming for saturations above 94% and temporarily stopping the patient-controlled analgesia. The next step is to give naloxone, but not the same dose as indicated in the previous case. The British National Formulary has a separate treatment pathway for postoperative respiratory depression and suggests giving 100–200 µg or 1.5–3 µg/kg of patient weight as a single bolus (Joint Formulary Committee, 2018). Repeated doses of 100 µg can be given at 2-minute intervals until a satisfactory response is seen.

In this case a single dose of 200 µg was given, which effectively treated her CNS depression and respiratory effort while maintaining adequate pain relief. Following this, her patient-controlled analgesia was inspected and recommenced after altering the bolus amount to prevent renarcosis.

This gentler titrating approach for postoperative patients minimizes the risk of over-treating the patient and reversing the crucial analgesic effects of the morphine which could cause unnecessary pain. Again, if repeated boluses of naloxone are not providing a response, the diagnosis should be questioned.

Infusion reversal

An 84-year-old woman from a nursing home was admitted to the medical assessment unit with a 3-day history of fever, cough and dyspnoea. She was seen in the emergency department first, given a provisional diagnosis of community-acquired pneumonia and started on broad spectrum antibiotics. On arrival to the unit she was drowsy and her saturations remained in the low 90s despite supplementary oxygen with a respiratory rate of 8 per minute. Examination of her medication and past medical history from GP records gave details of extensive heart disease and Zomorph 140 mg (modified-release morphine sulphate) daily for chronic pain. This in combination with blood results showing an acute kidney injury suggested possible opiate toxicity from her long-acting Zomorph.

An initial trial of naloxone 400 µg delivered a good response, but 15 minutes later her drowsiness and poor saturations returned. Another 400 µg was given, with a similar pattern of brief improvement followed by returning narcosis.

Naloxone infusion is indicated as this patient is not only taking long-acting opioids which have a half life longer than naloxone (as indicated by Zomorph's 12-hourly dosing instruction via the British National Formulary), but also the patient's renal impairment was allowing active opiate metabolites to accumulate (Conway et al, 2006).

For naloxone infusions the British National Formulary recommends starting at 60% of the initial resuscitative dose per hour, which in this case works out as 240 µg/hour. This 60% dose has been theorised to keep plasma naloxone levels within the therapeutic window (Goldfrank et al, 1986). The rate can then be titrated (up and down by 100 µg/hour) guided by clinical response. In this case the infusion had good clinical effect and was eventually reduced to 140 µg/hour before being discontinued after 4 hours.

Particularly in cases like this it is important to try and limit further opioid exposure, something that is often overlooked. Patients who have become opioid toxic as a result of oral ingestion should be considered for activated charcoal (50 g in adults, 1 g/kg in children) if they present within 1 hour and possibility later with modified release preparations. Clinicians should also be vigilant for opioid-based patches (fentanyl and buprenorphine) and remove them to prevent further toxicity.

TOP TIPS

- If intravenous access is not available, naloxone can be given via the intramuscular or subcutaneous route, but has a slower onset of action.
- Do not forget to limit further exposure – activated charcoal can be used in patients presenting within 1 hour of opioid ingestion and remove opioid-based patches.
- Identify the opioid; for example derivatives such as carfentanyl are 100 times more potent than fentanyl and may require boluses beyond 2 mg.
- For children (under 12 years of age) doses of 100 µg/kg are recommended, up to a maximum of 2 mg.
- Infusion dose is calculated by dividing the initial resuscitative dose by 100 and then multiplying by 60 to get a 60% dose per hour.
- Infusion doses can be made up by adding 2 mg of naloxone to 500 ml of normal saline to give a concentration of 4 µg/ml. Use 4 mg/500 ml for patients likely to need higher rates or longer infusions (8 µg/ml).

Alternative methods of delivery

As previously mentioned, naloxone can be delivered through various means if intravenous access is unavailable for whatever reason. The intramuscular route is becoming increasingly common in the community setting in the form of 'take home kits'; pre-filled syringes provided by local authorities directly to opioid abusers or their family and friends, in combination with training on how to administer. Doses are identical to the intravenous form and onset of action is estimated to be only marginally slower than intravenous according to Kelly et al (2005) (median onset of 4 minutes).

An intranasal form of naloxone also exists, which is currently more popular in the United States, with efficacy similar to that of intravenous or intramuscular administration (Robinson and Wermeling, 2014).

Nebulised naloxone is another alternative to be considered in spontaneously breathing patients in whom intravenous or intramuscular access may be difficult to obtain (Weber et al, 2012).

KEY POINTS

- The dose of naloxone in response to opioid toxicity depends on the clinical scenario – acute, postoperative or acute on chronic.
- Opioid overdoses with an immediate threat to life should be treated with larger doses of naloxone.
- Lower doses should be used in postoperative patients and those using opioids for chronic pain.
- Infusions should be considered in patients taking long-acting opioids or evidence of liver and/or renal impairment.
- If after multiple doses of naloxone there is no response, consider an alternative cause for the presentation.
- Patients should be monitored for up to 24 hours post treatment, depending on the opiate implicated.

Assessing response

In all instances of prescribing naloxone the British National Formulary refers to a 'satisfactory response', but what exactly is this? And how long should patients be observed for potential renarcosis?

According to Christenson et al (2000) there are three parameters which are indicative of improvement in a patient receiving naloxone – respiratory rate, oxygen saturations and Glasgow coma score – all of which should increase within approximately 2 minutes if the dose is adequate. In addition to this they also suggest that patients can be discharged from the emergency department 1 hour following naloxone administration if they meet the following criteria:

1. The patient can mobilize as usual
2. The patient has oxygen saturations on room air of >92%
3. The patient has a respiratory rate of >10 and <20 breaths per minute
4. The patient has a temperature >35.0°C and <37.5°C
5. The patient has a heart rate >50 and <100 beats per minute
6. The patient has a Glasgow coma score of 15.

However, Toxbase recommends observing patients (specifically Glasgow coma score and respiratory rate) for a minimum of 6, 12 and 24 hours for standard release, slow release and methadone opioids respectively.

The emphasis is not to achieve a Glasgow coma score of 15 as soon as possible – Toxbase recommends that the main focus should be reversing respiratory depression and reducing airway obstruction or aspiration risk in those with impaired consciousness. A gradual and more controlled return to normal cognition promotes better concordance and reduces the risk of precipitating side effects.

Side effects

With naloxone prescribing clinicians are often walking a tightrope (Clarke et al, 2005) between renarcosis and inducing side effects, the most common of which are acute withdrawal symptoms such as agitation, nausea, vomiting and diarrhoea. For patients at risk of acute withdrawal symptoms (recreational users or patients with chronic pain and longstanding opioid use) it may be worth using the lower dose (100–200 μg) pathway to prevent the development of acute withdrawal symptoms.

Clinicians should be wary when reversing opioids used for pain control (both acute and chronic) as they run the risk of inducing intense pain which can cause hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest (NHS England, 2014). Because of these rare but potentially fatal complications, naloxone should ideally be used in settings where cardiac monitoring and defibrillation are readily available. Note that transfer to these areas should not delay administration of naloxone.

Conclusions

Naloxone is a highly effective opioid antagonist that can be used in one of three ways: high doses for immediate reversal, low doses for postoperative respiratory depression and as an infusion in patients taking long-acting opioids or presenting with organ failure.

When faced with opioid overdoses clinicians should attempt to identify the route and timing of administration, the total amount taken and the opioid implicated to guide treatment.

Patients requiring naloxone are opioid toxic and thus unstable and should be closely monitored with attention to respiratory rate, Glasgow coma score and oxygen saturations. These should respond within minutes of an effective dose.

Potential side effects include cardiac arrhythmias and pulmonary oedema but more common is the precipitation of acute withdrawal symptoms, especially in those taking opioids long term and recreational users. **BJHM**

Conflict of interest: none.

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