Avoiding the Pitfalls of Opioid Reversal with Naloxone

With its wide margin of safety, low cost, and multiple routes of administration, naloxone is an ideal antidote for opioid toxicity but it should only be used to reverse respiratory depression while closely monitoring the patient.
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Clinical situations may arise when opioid reversal is required. Using a case-based approach, Dr. Scharman provides the clinician with practical guidelines for the appropriate use of naloxone along with specific patient monitoring parameters.
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Case Description

A 76 year-old male with a history of cervical and lumbar spinal stenosis undergoes elective surgery to repair a broken hip he sustained in a fall. For the previous 2 years, the patient has been taking morphine SR 60mg orally every 12 hours for pain. Other chronic medications include pregabalin, enalapril, hydrochlorothiazide, clopidogrel, aspirin, and bisacodyl. Vital signs in the recovery room, just prior to moving the patient to the floor are: HR 76 bpm, BP 115/78 mmHg, RR 12; oxygen saturation 96%. The surgeon orders 10mg of morphine to be given intravenously every 3 hours as needed for post-operative pain in addition to re-institution of the patient's oral morphine SR 60mg every 12 hours to begin that evening. Upon arrival to the floor, his vital signs are: HR 78 bpm, BP 114/76 mmHg, RR 12, oxygen saturation 96%.

The patient is doing well until his first post-operative dose of morphine is given by the floor nurse. Within minutes of receiving the prescribed injection, he develops a marked decrease in level of consciousness. Vital signs are rapidly assessed: HR 58 bpm, BP 62/40 mmHg, RR 4, oxygen saturation 55%. Because this patient has clinically significant respiratory depression, naloxone should be administered.

Discussion

Opiate toxicity is classically defined as a triad of respiratory depression, central nervous system depression, and miosis.[1] In severe cases, hypotension is also present.[1,2] Clinically, miosis may be underreported as clinicians may not assess for this sign given the more pressing medical concerns these patients present with; e.g., respiratory arrest. The timing of this patient's change in level of consciousness in relationship to his last dose of morphine, along with the physical findings of respiratory depression and hypotension, make opiate toxicity the likely cause of this patient's worsening condition.

Naloxone is the antidote for opiate toxicity.[3,4] It works by competitively binding to the opiate receptor. This competitive inhibition is most pronounced at the mu receptor although opiate binding at the kappa and delta receptors is competitively blocked as well.[3,4] In addition to being effective, naloxone has many features that make it an ideal antidote in the emergency setting: it is inexpensive (less than $ 1.00 for the average starting dose), it can be given via multiple routes, it has a very wide margin of safety, and it causes no side effects when given in large doses to people without exposure to opiates.[3-6] For these reasons, it is often given diagnostically when the possibility of opiate toxicity is in question; e.g., a person found unconscious following an overdose of an unknown drug.7 Unfortunately, these are also the reasons that naloxone is often over-utilized.

There is no need to administer naloxone in the absence of respiratory depression.[6] The clinically

important endpoint of therapy when naloxone is given is the reversal of respiratory depression, not the return of the patient to wakefulness. In those cases where the patient's respiratory depression has been managed by intubation, or cases in which the patient has been intubated to protect his/her airway following a multi-drug exposure, naloxone administration is not required and should not be administered.

Clinical Considerations

Although naloxone has a wide margin on safety when given to those who are not opioid-dependent, care must be used when administering naloxone to an opioid-dependent patient in order to prevent the abrupt onset of opiate withdrawal.[3,6] Despite the fact that opiate withdrawal is not life-threatening, withdrawal reactions can be very distressing to the patient and can complicate the medical care of patients with comorbid medical conditions. Signs and symptoms of a withdrawal reaction include vomiting, diarrhea, myalgias, chills, diaphoresis, lacrimation, rhinorrhea, and yawning.[6] Increases in blood pressure and heart rate are also possible although these increases are usually mild.[4] Opioid-dependent patients who are pregnant require even more caution when naloxone is administered as withdrawal may be precipitated in the fetus.

Another group of patients who require special care when naloxone is administered are those, like this patient, who currently require opioids for the treatment of moderate-to-severe pain.[3] The administration of naloxone, while reversing the respiratory depression, may result in the abrupt onset of significant pain.

> "After naloxone is successfully administered, patients will require continued monitoring for recurrence of respiratory depression for at least two hours.[6] The duration of action of naloxone is approximately 90 minutes."

The usual starting dose of intravenous naloxone is often cited as 0.4mg to 2mg.[1,2,4] For this reason, 2mg is a common bolus dose in many settings.[6] However, an initial dose of 0.4mg is sufficient to reverse respiratory depression in the majority of patients, including those who are opioid-dependent. The use of a 2mg naloxone dose in an opioid-dependent patient is likely to precipitate acute opioid withdrawal and should be avoided if possible. In patients who are being treated with opioids for moderate-to-severe pain, doses above 0.4mg are likely to result in the recurrence of pain and should also be avoided if possible.[3] In both opioid and non-opioid dependent patients, if reversal of respiratory depression is not seen within 1 to 2 minutes, additional 0.4mg doses can be administered until respiratory depression is reversed. Expect to use larger doses (up to 10mg) if an opioid with a strong affinity for the kappa or delta opioid receptor—such as pentazoxine or butorphanol—is involved or if propo-xyphene, which is poorly antagonized by naloxone, has been ingested.[2,4,8] Although prescribing information states that the dose of naloxone in patients less than 5 years of age is 0.01mg/kg, the American Academy of Pediatrics Committee on Drugs recommends that a 0.1mg/kg dose be utilized. The higher dose is recommended to ensure effectiveness and to simplify dosing.10 Since naloxone has a wide margin of safety in the non-opioid dependent patient and to simplify dosing further, some texts advocate using the same 0.4mg dose in both adults and pediatric patients.[4,11]

For patients with recurrent symptoms, bolus doses can be re-administered or a continuous infusion of naloxone can be given. Administer the intravenous solution so that 2/3 of the bolus dose of naloxone found to be effective is administered every hour while making sure to monitor the amount of fluid given hourly to avoid fluid overload.[12,13] Bolus doses may be given in addition to the continuous infusion if required. One should attempt to taper the infusion once the patient's respiratory status has been normal for a couple of hours and watch for symptom recurrence. Continuous infusions are unlikely to be required unless a long-acting opioid, such as methadone, or a modified release opioid product is involved.

Because naloxone is such an effective antidote, patients with a documented history of opiate exposure and who do not respond to naloxone therapy should be evaluated for hypoxic brain injury if other causes for their clinical condition cannot be excluded (e.g., other ingested drugs/ toxins, trauma).[6]

Patient Monitoring After Naloxone Administration

After naloxone is successfully administered, patients will require continued monitoring for recurrence of respiratory depression for at least two hours.[6] The duration of action of naloxone is approximately 90 minutes. However, the duration of action may be longer or shorter depending on the amount and type of opioid the patient was exposed to and the amount of naloxone given.

When moderate-to-severe pain is precipitated following naloxone administration to patients requiring opioids for pain management, a couple of options exist. The first option is to attempt to control the pain with an injectable non-steroidal anti-inflammatory drug—for example, ketorolac—until the effects of the naloxone wear off. An alternative option is to treat the patient with low doses of a short acting opioid, such as fentanyl, and titrated to effect while closely monitoring the patient's respiratory status. One should avoid giving large quantities of longer acting opiates as the patient is more likely to develop respiratory depression as soon as the effects of the administered naloxone abate.

If opioid withdrawal results from naloxone administration, no treatment should be provided; withdrawal symptoms will abate when the effects of naloxone wear off. However, opioid withdrawal in the setting of a combined cocaine overdose may be more problematic.[14] In opioid-dependent patients with a combined cocaine and opiate overdose, rapid reversal of opiate toxicity can potentially result in unopposed sympathetic stimulation which can worsen cocaine toxicity. It is especially important to give the smallest effective dose possible in this population.

Opiates, especially heroin and meth-adone, can cause non-cardiogenic pulmonary edema (NCPE) as an additional complication following an overdose. Although naloxone has been implicated as a cause of NCPE, all cases of NCPE following naloxone administration have been in patients who have overdosed on opiates. It is, therefore, unlikely that naloxone is the cause of the pulmonary edema. It is more likely that the reversal of hypoxemia following naloxone administration is unmasking NCPE that was not recognized in the setting of respiratory depression.[4,6,11] If large quantities of fluids have been given to manage opioid-induced hypotension, NCPE may be more likely to occur.

Case Follow-up

The patient is given oxygen and bag ventilation is performed while 0.4mg of naloxone is administered. His respiratory status returns to normal. When the controlled substances drawer is reconciled at the end of the shift, it is discovered that the patient received an injection of hydromorphone 10mg instead of morphine 10mg. As 1.5mg of hydromorphone would have been equivalent to the 10mg of morphine the patient was to have received, a 10mg dose of hydromorphone signifies a significant overdose.[15] As with other medications, opioids with similar sounding names should not be stored in close proximity to each other. Naloxone should be kept in all patient care areas where opioids are administered.

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Last updated on: January 6, 2012

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