Naloxone for the Reversal of Opioid Adverse Effects
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Since its introduction in 1971, naloxone has served a variety of functions in pediatrics, from reversal of severe respiratory depression in infants born to mothers who received opioids during labor to reduction of adverse effects in children treated with parenteral opioids for pain management.1 This review will provide guidelines for the administration of naloxone for opioid reversal in children and adults, as well as information on its use in other settings.

Mechanism of Action
Naloxone is a pure opioid antagonist. It prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension, by direct competition at mu, kappa, and sigma opioid receptor binding sites. Naloxone reverses both exogenous and endogenous opioids (endorphins, enkephalins, and dynorphins). It has no agonist properties; and, in the absence of opioids, naloxone exhibits little significant pharmacologic activity.1-3

Pharmacokinetics
Naloxone is administered parenterally. Although it is relatively well absorbed after oral administration, it undergoes extensive first-pass metabolism, making this route of delivery ineffective. After intravenous (IV) administration, naloxone is rapidly distributed throughout the body. It is highly lipophilic and readily crosses into the brain. Onset of action after IV dosing is within 2 minutes, and is only slightly longer with intramuscular (IM), subcutaneous, or endotracheal administration. Duration of action is dependent on route and dose. IV dosing typically provides a duration of action of 20 to 60 minutes. IM use produces a longer effect than IV administration, but absorption from this route is erratic. Naloxone is hepatically metabolized, primarily through conjugation to naloxone-3-glucuronide. The elimination half-life in adults is approximately 60 minutes.2,3 Elimination is prolonged in neonates, with a half-life ranging from 1.2 to 3.1 hours.4,5

Clinical Uses
Full Reversal of Opioid Intoxication
All patients considered to have opioid intoxication should have a stable airway and adequate ventilation established before the administration of naloxone. For an acute opioid overdose in infants (including premature infants) and children under the age of 5 years or less than 20 kg, the American Academy of Pediatrics (AAP) and American Heart Association recommend an IV or IM naloxone dose of 0.1 mg/kg. In children greater than 5 years or 20 kg, a naloxone dose of 2 mg is recommended for rapid, total reversal when respiratory compromise is present.2,3,6-13

For neonatal resuscitation, naloxone (0.1 mg/kg) is specifically indicated in infants with severe respiratory depression whose mothers received opioids within 4 hours of delivery.6-11

In adults, an initial naloxone dose of 0.4 mg to 2 mg is recommended, with the selection of dose determined by the patient’s respiratory status and likelihood of precipitating opioid withdrawal. This dose may be repeated every 2 to 3 minutes until full reversal is achieved or to a maximum of 10 mg.2,3,6-13

The duration of action for naloxone is shorter than that of most opioids, so patients must be closely monitored for recurrence of opioid toxicity when the antagonist effects of naloxone wane. Additional doses, given at intervals of 20 minutes to 2 hours, may be necessary to maintain reversal. It has been recommended that patients who receive naloxone be continuously observed for a minimum of 2 hours after the last dose.9

In the case of overdoses involving long-acting opioids or prolonged treatment, a naloxone infusion may be necessary. In 1984, Tenenbein reported the successful use of high-dose continuous naloxone infusions in two infants.14 The first case involved an accidental ingestion of...
100 mg normethadone by a 1 year old. The patient was initially treated with multiple bolus doses of naloxone, but when respiratory depression recurred, an infusion of 0.04 mg/kg/hr was started. The infusion was continued for 2.5 days. The second infant, a 3 day old, received an inadvertent morphine overdose of 5 mg due to a dosing error while hospitalized. This patient was given 4 naloxone boluses, followed by an infusion of 0.16 mg/kg/hr. The infusion was continued for 5 days, during which repeated attempts to wean the infusion resulted in further worsening of respiratory function. In both cases, the patients were discharged without sequelae. The author stated that the infusion rates in these cases were based on the hourly naloxone requirements during bolus dosing. Other investigators have suggested using two-thirds the total bolus dose as the hourly infusion rate.\textsuperscript{1,15}

**Partial Reversal for Respiratory Depression**

In patients for whom full reversal is not desired, such as those with respiratory depression during pain management or after anesthesia, lower initial doses should be used. A naloxone dose of 0.01 to 0.03 mg/kg for children < 5 years and 0.1 to 0.2 mg for older children and adults is recommended for partial reversal, with the dose repeated every 2 to 3 minutes until the desired response is achieved.\textsuperscript{6-11}

**Ultrarapid Detoxification**

A new use for naloxone, ultrarapid detoxification, involves administration of the drug to opioid-dependent patients under general anesthesia to provoke acute withdrawal. This process allows for controlled management of withdrawal symptoms, reduces patient discomfort, and avoids the need for a prolonged opioid wean. Ultrarapid detoxification has been used for several years in adults, but has only recently been attempted in pediatric patients.

In 2000, Greenberg reported two cases of ultrarapid detoxification in infants, ages 9 and 18 months, who had developed physiologic dependence after receiving prolonged, high-dose opioid therapy following surgery for congenital heart disease.\textsuperscript{16} After administering propofol and clonidine, both patients were given naloxone by IV bolus (10 mg/kg) followed by an infusion of 10 mcg/kg/hr in an intensive care unit. Naloxone was continued until the patients were extubated and free of withdrawal symptoms. The author suggests that ultrarapid detoxification may be a useful alternative to opioid tapers in children, but more research is needed to evaluate the safety and long-term effects of this treatment method before it can routinely be recommended.

**Prevention or Treatment of Pruritus**

Pruritus occurs in 10-50\% of patients receiving opioids, with the highest incidence associated with epidural opioid administration. Naloxone has been used since the mid-1970’s to prevent or treat opioid-induced pruritus. Several studies have demonstrated the efficacy of naloxone in postoperative patients with morphine-induced pruritus, using low-dose infusions of 0.17 to 2 mcg/kg/hr. This wide range reflects considerable interpatient variability in response.\textsuperscript{17-19}

In 2000, Vrchoticky published a retrospective review of naloxone infusions to treat pruritus in 30 children receiving opioids.\textsuperscript{17} The children ranged from 4 to 19 years of age (average 12.6 years). The majority (17/30) were being treated for vaso-occlusive crisis associated with sickle cell disease. Twenty-five of the patients were receiving morphine in the form of patient-controlled analgesia. The average duration of opioid treatment was 4.3 days, and time to develop pruritus was 8.7 hours. Naloxone was initiated on average 1.1 days after starting opioid therapy. The average effective naloxone dose was 2.3±0.68 mcg/kg/hr. All of the children had a reduction in pruritus, with 63\% experiencing complete resolution. Dose titration above 3 mcg/kg/hr resulted in loss of analgesic effect for 3 of the 6 patients in whom it was attempted. Infusions were continued for an average of 2.7 days. The author concluded that naloxone was an effective option in children for opioid-induced pruritus refractory to antihistamines.

Opioid antagonists have also proven useful in the management of patients with uremia or cholestasis whose pruritus is not relieved by antihistamines. The mechanism for their efficacy is not well understood, but may involve antagonism of excessive endogenous opioids and/or inhibition of afferent nerve impulses transmitted by unmyelinated C fibers.\textsuperscript{18}

**Prevention or Reversal of Constipation**

Opioids produce constipation by stimulation of receptors in the CNS and the gastrointestinal (GI) tract. They delay gastric emptying, slow GI transit time, and increase anal sphincter tone. Constipation occurs in approximately 30 to 40\% of patients receiving long-term opioid therapy. Standard treatment consists of laxatives and cathartics, but these agents may not be effective in all patients and may be contraindicated in patients with electrolyte instability.\textsuperscript{18}

Several case reports and small-scale studies have shown naloxone to be effective in reversing opioid-induced delays in GI transit times and producing relief of constipation.\textsuperscript{20,21} As in the
management of pruritus, careful dose titration is necessary to avoid negating the analgesic effects of the opioid or producing acute withdrawal.

Earlier this year, Liu and Wittbrodt published the results of a double-blind, randomized study of naloxone in 9 adults receiving opioids for chronic pain. All six of the patients given naloxone (2 to 4 mg three times daily) experienced an increase in stool frequency, compared to only one of the patients given placebo. Unfortunately, three of the six naloxone patients also required an increase in opioid dose to remain pain-free, with one patient having complete reversal of her analgesia. One of the controls also required a dose increase, and another dropped out of the study because of inadequate pain control.

Naloxone has also been used in patients with intestinal pseudoobstruction or chronic idiopathic constipation who have not received exogenous opioids. It is believed that these patients may release abnormally high levels of endogenous opioids in the GI tract, producing the equivalent of a morphine-induced ileus.

Other Uses
Naloxone has been shown to be useful in the reversal of CNS depression induced by overdoses of several non-opioid drugs, including ibuprofen, clonidine, tetrahydrozoline, and valproic acid. It has been suggested that the mechanism for naloxone in treating valproic acid overdose may be antagonism of gamma-aminobutyric acid (GABA), as well as reversal of endogenous opioid effects. Naloxone has also been studied in adults for the reversal of alcoholic coma and to improve circulation of patients in shock.

Adverse Effects
As described earlier, naloxone produces little clinically significant pharmacologic effect in the absence of endogenous or exogenous opioids, so there are few adverse effects associated with its use. The abrupt reversal of an opioid by naloxone may produce symptoms of acute withdrawal such as agitation, nausea and vomiting, diarrhea, diaphoresis, tachycardia, hypertension, shivering, yawning, tremors, or seizures in patients with physiologic dependence, including neonates whose mothers were chronic opioid users. In postoperative patients, particularly those with underlying cardiac disease, the administration of naloxone has been associated with changes in blood pressure, ventricular tachycardia or fibrillation, asystole, and pulmonary edema. The mechanism for these reactions may be an increase in sympathetic tone induced directly by naloxone or mediated indirectly through hypercapnia.

While most patients tolerate naloxone without incident, the potential for long-term adverse effects on neurologic development in infancy is not known. There is concern that administration at the time of delivery may adversely affect the release of endorphins and response to opioids in neonates. In a study of young rats, administration of naloxone over a 15 day period produced hyperalgesia and a blunted response to morphine lasting up to three months.

Product Availability and Preparation
Naloxone is available as Narcan® (Endo Pharmaceuticals) and as a generic product. The 0.4 mg/ml strength is produced in 1 ml amps and 1 ml syringes, as well as 1, 2, and 10 ml vials. The 1 mg/ml concentration is available in 2 ml amps and 10 ml vials. The 0.02 mg/ml strength, referred to as the neonatal injection, is available in 2 ml amps or vials. The use of this lower concentration is no longer recommended, as it can result in delivery of excessive fluid volumes. Naloxone may be diluted with normal saline or 5% dextrose solutions. It should not be mixed with preparations containing bisulfites or drugs with an alkaline pH.

Summary
Naloxone remains an important antidote for the reversal of opioid-induced respiratory and CNS depression. It is also useful in the management of constipation and pruritus, where careful dose titration can produce relief without reversing analgesic efficacy. As our understanding of the role of naloxone in modulating endogenous opioids and opioid dependency grows, it is likely that its use will expand to an even wider variety of clinical settings in the future.

References

Pharmacology Literature Review

Pyrazinamide kinetics

The pharmacokinetic profile of oral pyrazinamide was evaluated in this multicenter study of 67 adults and 23 children with active tuberculosis. Several differences were found between the pediatric and adult subjects. Incomplete or delayed absorption of pyrazinamide occurred more frequently in the younger subjects. Volume of distribution was significantly larger in the children (0.75 versus 0.57 L/kg in adults). Clearance was also more rapid, resulting in a half-life of 6 hours in the children versus 3.5 hours in the adults. Zhu M, Starke JR, Burman WF, et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. Pharmacotherapy 2002;22:686-95.

Isradipine toxicity

This case report describes the outcome of a 5 year old child who developed toxicity after receiving an overdose of isradipine. On initial presentation, the patient had abdominal distention and bradycardia, which progressed to asystole. The dose administered by the family was not known, but an initial serum concentration was 260.7 ng/ml (typical concentrations after maintenance therapy range between 2-8 ng/ml). Cardiopulmonary resuscitation, followed by a period of cardiac pacing, allowed full recovery without sequelae. In addition to the case description, the authors provide a thorough review of the symptoms associated with calcium channel blocker poisoning and its management. Romano MJ, Gaylor A, Sang CJ. Life-threatening isradipine poisoning in a child. Pharmacotherapy 2002;22:766-70.

Reye’s syndrome

The authors of this review present the evidence in favor of and against aspirin as a cause of Reye’s syndrome. While the authors acknowledge the temporal association between a decrease in aspirin use and the dramatic reduction of Reye’s cases seen in the 1980’s, they suggest that a causal link is unlikely. Orlowski JP, Hanhan UA, Fiallos MR. Is aspirin a cause of Reye’s syndrome? A case against. Drug Safety 2002;25:225-31.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in July.

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