NALOXONE (Systemic)

Category

Opioid (narcotic) antagonist.

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Toxicity, opioid (narcotic) (diagnosis and treatment) 1, 4, 5, 24, 25 or

Respiratory depression, opioid (narcotic)-induced (treatment) 1, 4, 5, 24, 25¾Naloxone is considered the drug of choice to reverse respiratory depression caused by opioid drugs, including those with mixed agonist/antagonist activity such as buprenorphine (although the effects of buprenorphine are especially resistant to reversal by naloxone), butorphanol, nalbuphine, and pentazocine, and other effects due to known or suspected opioid overdose, including sedation, coma, excitation, or convulsions. Naloxone will not increase respiratory depression caused by nonopioid medications or disease processes and may therefore be used when the cause is unknown. A satisfactory response to naloxone confirms the diagnosis of opioid toxicity.
When naloxone is given to reverse postoperative opioid depression, the dose must be carefully titrated to avoid interfering with control of postoperative pain or causing other adverse effects.
Naloxone is also indicated in neonates to reverse respiratory depression caused by opioids given to the mothers during labor and delivery.

Shock, septic (treatment adjunct) *¾Naloxone is indicated as an adjunctive agent to treat hypotension in the management of septic shock 1, 6, 7.

[Opioid dependence (diagnosis)] *¾Naloxone is used to diagnose opioid dependence or suspected illicit opioid use because it precipitates withdrawal symptoms in patients who are physically dependent on opioids (except for buprenorphine). Use of laboratory methods to detect an opioid drug in the urine of the suspected addict may be preferable. However, a naloxone challenge test is recommended to detect possible opioid use or dependence prior to initiation of naltrexone therapy in opioid addicts who have completed a detoxification regimen 35.

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

The precise mechanism by which naloxone reverses most of the effects of opioid analgesics has not been fully determined. It has been proposed that there are multiple subtypes of opioid receptors within the central nervous system (CNS), each mediating different therapeutic and/or side effects of opioid

drugs. At least two of these types of receptors (mu and kappa) mediate analgesia as well as side effects. A third type of receptor (sigma) may not mediate analgesia; actions at this receptor may produce the subjective and psychotomimetic effects characteristic of opioids with mixed agonist/antagonist activity (i.e., butorphanol, nalbuphine, and pentazocine). Naloxone apparently displaces previously administered opioid analgesics from all of these types of receptors and competitively inhibits their actions 1.

Antagonism of opioid actions may precipitate withdrawal symptoms in patients who are physically dependent on opioid drugs (except for buprenorphine). Naloxone has no opioid agonist activity of its own.

Precautions to Consider

Pregnancy/Reproduction

Fertility¾Reproduction studies in mice and rats receiving up to 1000 times the human dose have not shown that naloxone impairs fertility.
Pregnancy¾Naloxone crosses the placenta. Adequate and well-controlled studies in humans have not been done 1.

Studies in rats and mice receiving up to 1000 times the human dose have not shown teratogenic or other harmful effects in the fetus 1.

Risk-benefit must be considered before naloxone is administered to a pregnant woman who is known or suspected to be opioid-dependent because maternal dependence leads to fetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the fetus as well as in the mother 1.

FDA Pregnancy Category B 1.

Labor and delivery¾It is generally not advisable to give naloxone to a pregnant woman just prior to delivery 13.

Endogenous endorphins may help the fetus withstand the stress of delivery. Blocking these endogenous endorphins usually is not desirable 13, 14.

Breast-feeding

It is not known if naloxone is distributed into breast milk 1.

Problems in humans have not been documented.

Pediatrics

Studies have not demonstrated pediatrics-specific problems that would limit the usefulness of naloxone in children.
Naloxone should be administered cautiously to neonates of mothers who are physically dependent on opioids.

Geriatrics

Appropriate studies with naloxone have not been performed in the geriatric population. However, geriatrics-specific problems that would limit the usefulness of this medication in the elderly are not expected.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Butorphanol or

Nalbuphine or

Pentazocine

(naloxone reverses the analgesic and side effects of these opioid agonist/antagonist analgesics and may precipitate withdrawal symptoms in physically dependent patients)

Opioid agonist analgesics, including alfentanil, fentanyl, remifentanil, and sufentanil

(naloxone reverses the analgesic and side effects of opioid agonist analgesics and may precipitate withdrawal symptoms in physically dependent patients, including patients being treated for opioid dependence with methadone)
(when naloxone is used to reverse the effects of opioid agonists used as anesthesia adjuncts, the dose of naloxone must be carefully titrated to achieve the desired effect without interfering with control of postoperative pain or causing other adverse effects)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Allergic reaction to naloxone, history of

Cardiovascular disease or

Pulmonary disease

(sudden exacerbation of underlying cardiovascular or pulmonary disease may occur 15, 16, 17, 18, 19, 20, 21)

Opioid dependence or addiction, current

(naloxone may precipitate withdrawal 1)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Convulsions 26; fast or irregular heartbeat 1, 4, 28; increased or decreased blood pressure 1, 4, 15, 28, 32; pulmonary edema 1, 4, 17, 21, 26, 30, 31, 33, 34; ventricular arrhythmia 16; violent behavior 26, 27
Those indicating need for medical attention only if they continue or are bothersome

Increased sweating; nausea or vomiting; nervousness, restlessness, excitement, or irritability 1, 4; trembling 1, 4
Those indicating possible precipitation of withdrawal in a patient physically dependent on opioids

In all patients except neonates

Body aches 29; diarrhea 29; fever, runny nose, or sneezing 29; gooseflesh; increased sweating; increased yawning; nausea or vomiting 29; nervousness, restlessness, or irritability 29; shivering or trembling 29; stomach cramps 29; tachycardia; weakness

Note: A degree of physical dependence may occur during prolonged administration of an opioid analgesic as an adjunct to anesthesia. It has been proposed that adverse effects occurring after administration of naloxone for reversal of opioid effects following lengthy surgical procedures may be manifestations of an induced withdrawal syndrome in acutely dependent individuals 2.

Alternatively, adverse effects occurring after administration of naloxone may be due to the abrupt reversal of analgesia in patients with significant acute postoperative pain 39.

In neonates

Convulsions; diarrhea; excessive crying; fever; hyperactive reflexes; sneezing; tremors; unusual irritability; vomiting; yawning

General Dosing Information

When naloxone is used to antagonize the effects of buprenorphine, butorphanol, nalbuphine, or pentazocine, larger doses may be needed than are required to antagonize the effects of most opioids having only agonist activity 36.

Propoxyphene overdose may also require larger doses of naloxone 37.

Use of naloxone should be supplemented by other resuscitative procedures, such as administration of oxygen and/or vasopressors, artificial respiration, mechanical ventilation, and/or cardiac massage 1.

When naloxone is used to treat opioid toxicity, continued monitoring of the patient is necessary after naloxone is administered. If the duration of action of the opioid exceeds that of naloxone, re-emergence of opioid toxicity following initial reversal is likely 38.

Lack of significant improvement of CNS depression and/or respiratory depression following administration of an adequate dose (10 mg) of naloxone usually indicates that the condition is either due to a nonopioid CNS depressant not affected by the antagonist or to disease processes 1.

However, the effects of buprenorphine (a partial mu-receptor opioid agonist with high affinity for the mu receptor) are especially resistant to reversal by naloxone; doses of naloxone as high as 16 mg have been ineffective.

When naloxone is administered to a patient known or suspected to be physically dependent on an opioid analgesic, the dose should be carefully titrated. Withdrawal symptoms may occur within a few minutes and may last up to 2 hours. The duration and severity of the withdrawal syndrome depend upon the dose of the antagonist, the specific opioid involved, and the degree to which dependence has developed. However, naloxone does not precipitate withdrawal symptoms in buprenorphine-dependent individuals.

The naloxone challenge test (recommended prior to initiation of naltrexone therapy in detoxified opioid addicts 35) should not be administered if withdrawal symptoms are present or the patient's urine contains opioids. Naloxone may be administered intravenously or subcutaneously. If the intravenous route is used, one fourth of the total dose should be administered and the patient observed for 30 seconds for withdrawal symptoms; if none occurs, the remainder of the dose should be administered and the patient observed for 20 minutes. If the subcutaneous route is used, the full dose should be administered and the patient observed for 45 minutes for withdrawal symptoms. If withdrawal symptoms occur, the naloxone challenge should be repeated at 24-hour intervals until absence of opioid dependence is confirmed.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

NALOXONE HYDROCHLORIDE INJECTION USP

Usual adult and adolescent dose

Toxicity, opioid (narcotic)¾
[Endotracheal] * 22 , intravenous (preferred in emergencies), intramuscular, or subcutaneous, 400 mcg (0.4 mg) to 2 mg as a single dose 1, 4.

The intravenous dose may be repeated at two- to three-minute intervals as needed 1, 4.

Note: If the patient is suspected of being physically dependent on an opioid medication and is not in immediate danger, the dose may be reduced to 100 to 200 mcg (0.1 to 0.2 mg). This dose may be repeated at two- to three-minute intervals as needed.

Additional single doses of naloxone may be administered intravenously as needed. However, longer-lasting effects may be obtained if supplemental doses are administered via the intramuscular route.

Also, initial treatment may be followed by continuous intravenous infusion of naloxone, with adjustment of the infusion rate according to the response of the patient.
Respiratory depression, opioid (narcotic)-induced¾
Intravenous, 100 to 200 mcg (0.1 to 0.2 mg) every two to three minutes until adequate ventilation and alertness without significant pain are obtained 1, 4.

If necessary, the dose may be repeated at one- or two-hour intervals 1, 4.

Note: The dose should be titrated to avoid interference with control of postoperative pain; initial doses as low as 0.5 mcg (0.0005 mg) per kg of body weight have been recommended.
Shock, septic *¾
Intravenous, 30 mcg (0.03 mg) to 200 mcg (0.2 mg) per kg of body weight initially, followed by an intravenous infusion of 0.03 to 0.3 mg per kg of body weight per hour for one to twenty-four hours 1, 3, 6, 7, 9.

Note: The optimal dose of naloxone in the treatment of hypotension due to septic shock has not been established 1.

Some patients unresponsive to fluids and pressor agents experience an immediate, transient increase in blood pressure after receiving naloxone 7.

The effectiveness of naloxone appears to be greater if it is administered early in the course of septic shock 8.

The use of naloxone as an adjunctive treatment for hypotension in septic shock has not been shown to reduce mortality 1.

[Opioid dependence diagnosis] *¾
Intravenous, 200 mcg (0.2 mg) initially, followed by 600 mcg (0.6 mg) thirty seconds later if withdrawal symptoms are not apparent 35 ; or
Subcutaneous, 800 mcg (0.8 mg) 35.

If necessary to confirm that the patient is not opioid-dependent, a rechallenge with 1.6 mg of naloxone administered intravenously may be performed.

Usual pediatric dose

Toxicity, opioid (narcotic)¾
[Endotracheal] * 22 , intravenous (preferred in emergencies), intramuscular, or subcutaneous, 10 mcg (0.01 mg) per kg of body weight. If this dose does not result in improvement in the condition of the patient, an additional 100 mcg (0.1 mg) per kg of body weight may be given 1.

Note: Doses higher than those listed above have been used to treat opioid toxicity 23.

The American Academy of Pediatrics (AAP) recommends an initial dose of 0.1 mg per kg of body weight for infants and children up to 5 years of age and weighing less than twenty kg. For children 5 years of age and older or weighing more than twenty kg, an initial dose of 2 mg is recommended by AAP 23.

Respiratory depression, opioid (narcotic)-induced¾
Intravenous, 5 to 10 mcg (0.005 to 0.01 mg) every two to three minutes until adequate ventilation and alertness without significant pain are obtained. If necessary, the dose may be repeated at one- or two-hour intervals [1], [4].

Respiratory depression, opioid (narcotic)-induced, neonatal¾
Intravenous via the umbilical vein (preferred), intramuscular, or subcutaneous, 10 mcg (0.01 mg) per kg of body weight. The intravenous dose may be repeated at two- to three-minute intervals until the desired response is obtained.

Strength(s) usually available

U.S.¾With preservatives (methylparaben and propylparaben)

400 mcg (0.4 mg) per mL (Rx)[Narcan] [Generic]

1 mg per mL (Rx)[Narcan] [Generic]

Without preservatives

20 mcg (0.02 mg) per mL (Rx)[Narcan] [Generic]

400 mcg (0.4 mg) per mL (Rx)[Narcan] [Generic]

1 mg per mL (Rx)[Narcan] [Generic]

Canada¾With preservatives (methylparaben and propylparaben)

20 mcg (0.02 mg) per mL (Rx)[Narcan]

400 mcg (0.4 mg) per mL (Rx)[Narcan]

1 mg per mL (Rx)[Narcan]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from light. Protect from freezing.

Preparation of dosage form:

When given by intravenous injection, naloxone may be diluted with sterile water for injection if a larger volume is needed [1].

For continuous intravenous infusion¾Add 2 mg (5 mL of solution containing 400 mcg [0.4 mg] per mL or 2 mL of solution containing 1 mg per mL) of naloxone hydrochloride to 500 mL of 0.9% sodium chloride injection or 5% dextrose injection to prepare a solution containing 4 mcg (0.004 mg) per mL [1].

Stability:

After dilution for intravenous infusion, the solution should be used within 24 hours. Any unused solution should be discarded after 24 hours 1.

Naloxone should not be mixed with any preparation containing bisulfite, metabisulfite, or long-chain or high molecular weight anions, or with any solution having an alkaline pH 5.