

NALOXONE HYDROCHLORIDE- naloxone hydrochloride injection
International Medication Systems, Limited

NALOXONE HYDROCHLORIDE
INJECTION, USP
Opioid Antagonist

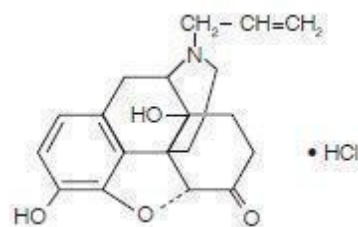
Rx Only

DESCRIPTION

Naloxone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

NALOXONE HYDROCHLORIDE

(-)-17-Allyl-4,5 α -epoxy-3,14-dihydroxymorphinan-6-one hydrochloride



Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone Hydrochloride Injection is available as a sterile solution for intravenous, intramuscular and subcutaneous administration in 1 mg/mL concentration. pH is adjusted to 3.5 ± 0.5 with hydrochloric acid. Each mL also contains 8.35 mg of sodium chloride. Naloxone Hydrochloride Injection is preservative-free.

CLINICAL PHARMACOLOGY

Complete or Partial Reversal of Opioid Depression

Naloxone hydrochloride prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. Also, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonist such as pentazocine.

Naloxone hydrochloride is an essentially pure opioid antagonist, i.e., it does not possess the “agonistic” or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.

Naloxone hydrochloride has not been shown to produce tolerance or cause physical or psychological dependence. In the presence of physical dependence on opioids, naloxone hydrochloride will produce withdrawal symptoms. However, in the presence of opioid dependence, opiate withdrawal symptoms may appear within minutes of naloxone hydrochloride administration and subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone hydrochloride and to the degree and type of opioid dependence.

While the mechanism of action of naloxone hydrochloride is not fully understood, *in vitro* evidence suggests that naloxone hydrochloride antagonizes opioid effects by competing for the μ , κ and σ opiate

When naloxone hydrochloride is administered intravenously (I.V.), the onset of action is generally apparent within two minutes. The onset of action is slightly less rapid when it is administered subcutaneously (S.C.) or intramuscularly (I.M.). The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride. Intramuscular administration produces a more prolonged effect than intravenous administration. Since the duration of action of naloxone hydrochloride may be shorter than that of some opiates, the effect of the opiate may return as the effects of naloxone hydrochloride dissipates. The requirement for repeat doses of naloxone hydrochloride will also be dependent upon the amount, type and route of administration of the opioid being antagonized.

Adjunctive Use in Septic Shock

Naloxone hydrochloride has been shown in some cases of septic shock to produce a rise in blood pressure that may last up to several hours; however, this pressor response has not been demonstrated to improve patient survival. In some studies, treatment with naloxone hydrochloride in the setting of septic shock has been associated with adverse effects, including agitation, nausea and vomiting, pulmonary edema, hypotension, cardiac arrhythmias, and seizures. The decision to use naloxone hydrochloride in septic shock should be exercised with caution, particularly in patients who may have underlying pain or have previously received opioid therapy and may have developed opioid tolerance.

Because of the limited number of patients who have been treated, optimal dosage and treatment regimens have not been established.

PHARMACOKINETICS

Distribution

Following parenteral administration, naloxone hydrochloride is rapidly distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

Metabolism and Elimination

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours. After an oral or intravenous dose, about 25-40% of the drug is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours.

INDICATIONS AND USAGE

Naloxone hydrochloride injection is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids including, propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine and butorphanol and cyclazocine. Naloxone hydrochloride is also indicated for the diagnosis of suspected or known acute opioid overdose.

Naloxone hydrochloride injection may be useful as an adjunctive agent to increase blood pressure in the management of septic shock. (see CLINICAL PHARMACOLOGY; **Adjunctive Use in Septic Shock**).

CONTRAINDICATIONS

Naloxone hydrochloride injection is contraindicated in patients known to be hypersensitive to it or to any of the other ingredients in naloxone hydrochloride.

WARNINGS

Drug Dependence

Naloxone hydrochloride should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include, but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In the neonate, opioid withdrawal may also include: convulsions, excessive crying, and hyperactive reflexes.

Repeat Administration

The patient who has satisfactorily responded to naloxone hydrochloride should be kept under continued surveillance and repeated doses of naloxone hydrochloride should be administered, as necessary, since the duration of action of some opioids may exceed that of naloxone hydrochloride.

Respiratory Depression due to Other Drugs

Naloxone hydrochloride is not effective against respiratory depression due to non-opioid drugs and in the management of acute toxicity caused by levopropoxyphene. Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone. If an incomplete response occurs, respirations should be mechanically assisted as clinically indicated.

PRECAUTIONS

General

In addition to naloxone hydrochloride, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.

Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death. Excessive doses of naloxone hydrochloride in postoperative patients may result in significant reversal of analgesia and may cause agitation (see PRECAUTIONS and DOSAGE AND ADMINISTRATION; **Usage in Adults- Postoperative Opioid Depression**).

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had preexisting cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone hydrochloride should be used with caution in patients with preexisting cardiac disease or patients who have received medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Drug Interactions

Large doses of naloxone are required to antagonize buprenorphine since the latter has a long duration

Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression. The barbiturate methohexital appears to block the acute onset of withdrawal symptoms induced by naloxone in opiate addicts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals to assess the carcinogenic potential of naloxone hydrochloride have not been conducted. Naloxone hydrochloride was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.

Reproduction studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride.

Use in Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratology studies conducted in mice and rats at doses 4-times and 8-times, respectively, the dose of a 50 kg human given 10 mg/day (when based on surface area or mg/m^2), demonstrated no embryotoxic or teratogenic effects due to naloxone hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone hydrochloride should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Risk-benefit must be considered before naloxone hydrochloride is administered to a pregnant woman who is known or suspected to be opioid-dependent since maternal dependence may often be accompanied by fetal dependence. Naloxone crosses the placenta, and may precipitate withdrawal in the fetus as well as in the mother. Patients with mild to moderate hypertension who receive naloxone during labor should be carefully monitored as severe hypertension may occur.

Use in Labor and Delivery

It is not known if naloxone hydrochloride affects the duration of labor and/or delivery. However, published reports indicated that administration of naloxone during labor did not adversely affect maternal or neonatal status.

Nursing Mothers: It is not known whether naloxone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone is administered to a nursing woman.

Pediatric Use

Naloxone hydrochloride injection, USP may be administered intravenously, intramuscularly or subcutaneously in children and neonates to reverse the effects of opiates. The American Academy of Pediatrics, however, does not endorse subcutaneous or intramuscular administration in opiate intoxication since absorption may be erratic or delayed. Although the opiate-intoxicated child responds dramatically to naloxone hydrochloride, he/she must be carefully monitored for at least 24 hours as a relapse may occur as naloxone is metabolized.

When naloxone hydrochloride is given to the mother shortly before delivery, the duration of its effect lasts only for the first two hours of neonatal life. It is preferable to administer naloxone hydrochloride directly to the neonate if needed after delivery. Naloxone hydrochloride has no apparent benefit as an additional method of resuscitation in the newly born infant with intrauterine asphyxia which is not related to opioid use.

Usage in Pediatric Patients and Neonates for Septic Shock: The safety and effectiveness of naloxone hydrochloride in the treatment of hypotension in pediatric patients and neonates with septic shock have not been established. One study of two neonates in septic shock reported a positive pressor response; however, one patient subsequently died after intractable seizures.

Geriatric Use

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Insufficiency/Failure

The safety and effectiveness of naloxone hydrochloride in patients with renal insufficiency/failure have not been established in well-controlled clinical trials. Caution should be exercised when naloxone hydrochloride is administered to this patient population.

Liver Disease

The safety and effectiveness of naloxone hydrochloride in patients with liver disease have not been established in well-controlled clinical trials. Caution should be exercised when naloxone hydrochloride is administered to patients with liver disease.

ADVERSE REACTIONS

Postoperative

The following adverse events have been associated with the use of naloxone hydrochloride in postoperative patients: hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in postoperative patients may result in significant reversal of analgesia and may cause agitation (see PRECAUTIONS and DOSAGE AND ADMINISTRATION; **Usage in Adults-Postoperative Opioid Depression**).

Opioid Depression

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death (see PRECAUTIONS).

Opioid Dependence

Abrupt reversal of opioid effects in persons who are physically dependent on opioids may precipitate an acute withdrawal syndrome which may include, but is not limited to, the following signs and symptoms: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal may also include: convulsions; excessive crying; hyperactive reflexes (see WARNINGS).

Adverse events associated with the postoperative use of naloxone hydrochloride are listed by organ system and in decreasing order of frequency as follows:

Cardiac Disorders: pulmonary edema, cardiac arrest or failure, tachycardia, ventricular fibrillation, and ventricular tachycardia. Death, coma, and encephalopathy have been reported as sequelae of these events.

Gastrointestinal Disorders: vomiting, nausea

Nervous System Disorders: convulsions, paraesthesia, grand mal convulsion

Psychiatric Disorders: agitation, hallucination, tremulousness

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, respiratory depression, hypoxia

Skin and Subcutaneous Tissue Disorders: nonspecific injection site reactions, sweating

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