DESCRIPTION

Naloxone hydrochloride is 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride; C_{19}H_{21}NO_4.HCl. It is an off-white powder which is soluble in water. It is an opioid antagonist and is a synthetic congener of oxymorphone. CAS 51481-60-8. Its chemical structure is:

[Chemical Structure Image]

Naloxone Hydrochloride Injection USP is a clear, sterile, aqueous, colourless solution containing 0.4 mg naloxone hydrochloride (as dihydrate) per mL. The solution also contains sodium chloride.

PHARMACOLOGY

Naloxone is a competitive antagonist at opiate receptor sites. It can prevent or reverse the effects of opioids including respiratory depression, sedation and hypotension. It can also reverse the respiratory depression caused by pentazocine.

When naloxone is administered intravenously, the effects are usually apparent within 2 minutes; the onset of action is only slightly less rapid when it is administered intramuscularly or subcutaneously. The duration of action is dependent upon the dose and the route of administration but is usually in the region of 1 to 4 hours. Intramuscular injection produces a more prolonged effect than intravenous administration.

Following parenteral administration, naloxone is rapidly distributed in the body. It is metabolised in the liver primarily by glucuronide conjugation and the metabolites are excreted in the urine. It is 50% protein bound. The elimination half life in adults is 60-90 minutes and 180 minutes in neonates.

INDICATIONS

Naloxone is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic opioids such as codeine, diamorphine, methadone, morphine and propoxyphene. It is also indicated for the diagnosis of suspected acute opioid overdosage.

CONTRAINdications

Patients with known hypersensitivity to naloxone hydrochloride, or to any of the other ingredients in naloxone hydrochloride injection.
PRECAUTIONS
Administer with caution to patients who have received large doses of opioids, or to those physically dependent on opioids, as a too rapid reversal may precipitate an acute withdrawal syndrome. When naloxone hydrochloride is used in the management of an acute opioid overdose, other standard resuscitative measures should be readily available (cardiopulmonary resuscitation and vasopressor agents). A withdrawal syndrome may also be precipitated in new-born infants of opioid dependent mothers.

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, diarrhoea, 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.

Following the use of opioids during surgery, excessive doses of naloxone hydrochloride should be avoided as they may cause excitement, increase blood pressure and reverse analgesia. A too rapid reversal of opioid effects may cause nausea, vomiting, sweating or tachycardia, seizures, ventricular tachycardia and fibrillation, pulmonary oedema, and cardiac arrest which may result in death.

Use with caution in patients (including the elderly) with pre-existing cardiovascular disease and in those receiving medications with potential adverse cardiovascular effects, such as hypotension, ventricular tachycardia or fibrillation, and pulmonary oedema. Serious adverse cardiovascular effects, such as ventricular tachycardia, fibrillation, acute pulmonary oedema, hypotension, hypertension and cardiac arrest have been reported. Death, coma and encephalopathy have been reported as sequelae of these events. It has been suggested that the pathogenesis of pulmonary oedema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary oedema, 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.

Patients who have responded to naloxone should be carefully monitored, as the duration of action of some opioids may be greater than that of naloxone.

Naloxone is not effective against respiratory depression caused by non-opioid drugs.

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. In one small study in patients with liver cirrhosis, plasma naloxone concentrations were approximately six times higher than in patients without liver disease. Caution should be exercised when naloxone hydrochloride is administered to patients with liver disease.
The naloxone is in a single use MIN-I-JET prefilled syringe. Once the unit is assembled and used, any remaining portion of the solution must be discarded with the entire unit.

_Carcinogenicity/Mutagenicity_
Carcinogenicity and mutagenicity studies have not been performed with naloxone.

_Use in Pregnancy (Category B1)_
Teratogenic Effects: Reproductive studies in rodents given naloxone hydrochloride in doses up to 1000 times the usual human dose have produced no evidence of impaired fertility or harm to the foetus. However there are no adequate and controlled studies using the drug in pregnant women. Naloxone should therefore be used in pregnant women only when 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 foetal dependence. Naloxone crosses the placenta and may precipitate withdrawal in the foetus as well as in the mother.

Use in Labour and Delivery: It is not known if naloxone hydrochloride affects the duration of labour and/or delivery.

_Use in Lactation_
Naloxone hydrochloride should be used with caution in nursing mothers as it is not known whether the drug is secreted in breast milk.

_Interactions with Other Drugs_
No drug or chemical agent should be added to naloxone unless its effect on the chemical and physical stability of the solution has first been established. Naloxone should not be mixed with preparations containing sulfite, metabisulfite, long chain or high molecular weight anions, or any solution having an alkaline pH.

_ADVERSE REACTIONS_
Postoperative: The following adverse events have been associated with the use of naloxone hydrochloride in postoperative patients: hypotension, ventricular tachycardia and fibrillation, dyspnoea, pulmonary oedema 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).

Opioid Depression: Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary oedema, and cardiac arrest which may result in death (see PRECAUTIONS).
Opioid Dependence: (see PRECAUTIONS)
Agitation and paresthesias have been infrequently reported with the use of naloxone hydrochloride injection.

**DOSAGE AND ADMINISTRATION**
Naloxone hydrochloride may be administered intravenously, intramuscularly or subcutaneously. The most rapid onset of action is achieved with the intravenous route and is recommended in emergency situations. Naloxone may be diluted for intravenous infusion by adding 2 mg naloxone hydrochloride to 500 mL of either normal saline or 5% dextrose. The resulting solution will contain 4 microgram/mL of naloxone. Infusion should be commenced as soon as practicable after preparation of the mixture in order to reduce microbial hazards. Preparations not used within 24 hours should be discarded. The rate of infusion should be titrated against the response of the patient. Do not use the solution if it contains particulate matter and/or is discoloured.

Since the duration of action of some narcotics may exceed that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary.

**Adult dosage**
For the treatment of known opioid overdose, or as an aid in the diagnosis of suspected opioid overdose:

Initial dose is 0.4 - 2.0 mg intravenously given at 2 to 3 minute intervals if necessary. If there is no response after a total dose of 10 mg has been given, the depressed condition may be due to a drug or disease process not responsive to naloxone. When the intravenous route cannot be used, the drug may be given by intramuscular or subcutaneous injection.

For use postoperatively to reverse central depression caused by opioids used during surgery:

The usual dose is 0.1 to 0.2 mg intravenously given at 2 to 3 minute intervals. The aim is to achieve an optimum respiratory response whilst maintaining adequate analgesia. Additional doses may be necessary at 1 to 2 hour intervals depending on the response of the patient and the dose and duration of action of the opioid administered. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

**Paediatric dosage**
The usual initial dose for children is 10 microgram/kg body weight (0.01 mg/kg) given intravenously. If the dose does not result in adequate clinical improvement, a subsequent dose of 100 microgram/kg (0.1 mg/kg) may be given. If the intravenous route is not available, naloxone may be given intramuscularly or subcutaneously in divided doses. If necessary, naloxone can be diluted with Water for Injections.

**Neonatal dosage**
For reversing opioid-induced depression in a neonate resulting from opioid dependence or analgesia given to the mother during labour:

An injection of 10 microgram/kg (0.01 mg/kg) may be given to the infant by the intramuscular, intravenous or subcutaneous route and repeated at intervals of 2 to 3 minutes if necessary.

Alternatively, for a more prolonged action, a single intramuscular dose of 60 microgram/kg (0.06 mg/kg)
may be given at birth.

**OVERDOSAGE**

There is limited clinical experience with naloxone hydrochloride overdosage in humans.

In a study, 36 adult patients with acute stroke received a loading dose of 4 mg/kg (10 mg/m\(^2\)/min) of naloxone hydrochloride followed immediately by 2 mg/kg/hr for 24 hours. There were a few reports of serious adverse events: seizures (2 patients), severe hypertension (1), and hypotension and/or bradycardia (3).

At doses of 2 mg/kg and 4 mg/kg in normal subjects, cognitive impairment and behavioural symptoms, including irritability, anxiety, tension, suspiciousness, sadness, difficulty concentrating, and lack of appetite have been reported. In addition, somatic symptoms, including dizziness, heaviness, sweating, nausea, and stomach aches were also reported. Although complete information is not available, behavioural symptoms were reported to often persist for 2-3 days.

Patient Management: Patients who experience a naloxone overdose should be treated symptomatically in a closely-supervised environment. Physicians should contact the Poisons Information Centre on 131 126 for the most up-to-date patient management information.

Some chemical impurities in naloxone, i.e. noroxymorphone and bisnaloxone, have been shown to produce emesis in dogs when administered alone at i.v. doses equivalent to impurity levels present in naloxone at 60 times the usual human dose (10 mg/day).

**PRESENTATION**

Naloxone hydrochloride injections are supplied in a concentration of 0.4 mg/mL in single use prefilled MIN-I-JET syringes. The injections are available in two pack sizes containing 0.8 mg naloxone hydrochloride in 2 mL or 2.0 mg naloxone hydrochloride in 5 mL.

**STORAGE**

Store below 25ºC. Protect from light. Do not freeze.

Manufactured by: International Medication Systems, Limited 1886 Santa Anita Avenue, South El Monte, CA 91733 USA

Ashton Pharmaceuticals Limited Vale of Bardsley, Ashton-under-Lyne, Lancashire, OL7 9RR, United Kingdom

Distributed by: CSL Limited ABN 99 051 588 348, 45 Poplar Road, Parkville 3052, Victoria Australia

Date of TGA Approval: 14 February 1996
Date of notification of safety-related changes: 19 June 2006
Date of notification of minor editorial changes: 19 June 2006