NALOXONE HCL

(nal-*ox*-one) Narcan®

ANTIDOTE; OPIATE ANTAGONIST

Prescriber Highlights

- Injectable opiate antagonist
- Contraindications: Hypersensitivity to it. Caution: Preexisting cardiac abnormalities or opioid dependent
- Reversal effect may last for a shorter time than opioid effect; monitor & re-dose as needed

Uses/Indications

Naloxone is used in veterinary medicine almost exclusively for its opiate reversal effects, but the drug is being investigated for treating other conditions (*e.g.*, septic, hypovolemic or cardiogenic shock). Naloxone may also be employed as a test drug to see if endogenous opiate blockade will result in diminished tail chasing or other self-mutilating behaviors. It, potentially, could be useful for treating overdoses of clonidine or the CNS effects of benzodiazepines (ivermectin?), but more research is necessary before recommending its use.

Pharmacology/Actions

Naloxone is considered a pure opiate antagonist and it has no analgesic activity. The exact mechanism for its activity is not understood, but it is believed that the drug acts as a competitive antagonist by binding to the *mu*, *kappa*, and *sigma* opioid receptor sites. The drug apparently has its highest affinity for the *mu* receptor.

Naloxone reverses the majority of effects associated with high-dose opiate administration (respiratory and CNS depression). In dogs, naloxone apparently does not reverse the emetic actions of apomorphine.

Naloxone may be useful in treating adverse effects associated with overdoses of propoxyphene, pentazocine, buprenorphine and loperamide, but larger naloxone doses may be required.

Naloxone has other pharmacologic activity at high doses, including effects on dopaminergic mechanisms (increases dopamine levels) and GABA antagonism.

Pharmacokinetics

Naloxone is only minimally absorbed when given orally as it is rapidly destroyed in the GI tract. Much higher doses are required if using this route of administration for any pharmacologic effect. When given IV, naloxone has a very rapid onset of action (usually 1–2 minutes). If given IM, the drug generally has an onset of action within 5 minutes of administration. The duration of action usually persists from 45–90 minutes, but may act for up to 3 hours.

Naloxone is distributed rapidly throughout the body with high levels found in the brain, kidneys, spleen, skeletal muscle, lung, and heart. The drug also readily crosses the placenta.

Naloxone is metabolized in the liver, principally via glucuronidative conjugation, with metabolites excreted into the urine. In humans, the serum half-life is approximately 60–100 minutes.

Contraindications/Precautions/Warnings

Naloxone is contraindicated in patients hypersensitive to it. It should be used cautiously in animals that have preexisting cardiac abnormalities or that may be opioid dependent. The veterinary manufacturer of the product once marketed for veterinary use states to use the drug ". . . cautiously in animals who have received exceedingly large doses of narcotics…it may produce an acute withdrawal syndrome and smaller doses should be employed." (Package Insert; *P/M® Naloxone HCl Injection*—Mallinckrodt)

Adverse Effects

At usual doses, naloxone is relatively free of adverse effects in non-opioid dependent patients.

Because the duration of action of naloxone may be shorter than that of the narcotic being reversed, animals that are being treated for opioid intoxication or with clinical signs of respiratory depression should be closely monitored as additional doses of naloxone and/or ventilatory support may be required.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***A*** (*Probably safe. Although specific studies may not have proved he safety of all drugs in dogs and cats, there are no reports of adverse effects in laboratory animals or women.*)

It is not known whether the drug is excreted in maternal milk. Use caution when administering to nursing patients.

Overdosage/Acute Toxicity

Naloxone is considered a very safe agent with a very wide margin of safety, but very high doses have initiated seizures (secondary to GABA antagonism?) in a few patients.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving naloxone and may be of significance in veterinary patients:

- **OPIOID PARTIAL-AGONISTS** (*e.g.*, **butorphanol**, **pentazocine**, or **nalbuphine**): Naloxone may also antagonize the effects these agents (respiratory depression, analgesia). It should not be relied upon to treat respiratory depression caused by **buprenorphine**.
- **CLONIDINE:** Naloxone may reduce the hypotensive and bradycardic effects of clonidine; potentially useful for clonidine overdoses
- **YOHIMBINE:** Naloxone may increase the CNS effects of yohimbine (anxiety, tremors, nausea, palpitations) and increase plasma cortisol levels

Doses

- **DOGS & CATS:**

  For opioid reversal:

  a) 0.002–0.02 mg/kg IV or IM; duration of effect 0.5–1 hour (Bednarski 1989)

  b) Dogs: 0.04 mg/kg IV, IM or SC (Package Insert; *P/M® Naloxone HCl Injection*—Mallinckrodt), (Kirk 1989)

  c) Cats: 0.05–0.1 mg/kg IV (Muir and Swanson 1989)

  d) 0.02–0.04 mg/kg IV (Morgan 1988)

- **RABBITS, RODENTS, SMALL MAMMALS:**

  a) For opioid reversal in rodents: 0.01–0.1 mg/kg SC or IP as needed (Huerkamp 1995)

  b) Rabbits: 0.005–0.1 mg/kg IM or IV (Ivey and Morrisey 2000)

  c) Hamsters, Gerbils, Mice, Rats, Guinea pigs, Chinchillas: 0.01–0.1 mg/kg SC, IP (Adamcak and Otten 2000)

- **HORSES:** (**Note:** ARCI UCGFS Class 3 Drug)
  For opioid reversal:
  a) 0.01–0.022 mg/kg to reverse sedative and excitatory effects of narcotic agonists (Clark and Becht 1987)
  b) 0.01 mg/kg IV to limit increases in locomotor activity secondary to narcotic agonists (Muir 1987)
  c) 0.01–0.02 mg/kg IV (Robinson 1987)

Monitoring
- Respiratory rate/depth
- CNS function
- Pain associated with opiate reversal

Client Information
- Should be used with direct professional supervision only

Chemistry/Synonyms
An opiate antagonist, naloxone HCl is structurally related to oxymorphone. It occurs as a white to slightly off-white powder with a pK_a of 7.94. Naloxone is soluble in water and slightly soluble in alcohol. The pH ranges of commercially available injectable solutions are from 3–4.5.

Naloxone HCl may also be known as: N-allylnoroxymorphone hydrochloride; cloridrato de naloxona, EN-15304, naloxoni hydrochloridum and *Narcan*®.

Storage/Stability/Compatibility
Naloxone HCl for injection should be stored at room temperature (15–30°C) and protected from light.

Sterile water for injection is the recommended diluent for naloxone injection. When given as an IV infusion, either D_5W or normal saline should be used. Naloxone HCl injection **should not** be mixed with solutions containing sulfites, bisulfites, long-chain or high molecular weight anions or any solutions at alkaline pH.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Naloxone HCl Injection: 0.4 mg/mL in 1 mL amps, syringes and 1, 2, and 10 mL vials; *Narcan*® (DuPont Pharm.); generic; (Rx)

Naloxone HCl Neonatal Injection: 0.02 mg/mL in 2 mL vials; generic; (Rx)

NALTREXONE HCL

(nal-*trex*-ohne) Trexan®, ReVia®

OPIATE ANTAGONIST

Prescriber Highlights
- Oral opiate antagonist that might be useful in determining if adverse behaviors have a significant endorphin component & for the short-term treatment of same
- Contraindications: Patients physically dependent on opiate drugs, in hepatic failure, or with acute hepatitis. Caution: hepatic dysfunction or who have had a history of allergic reaction to naltrexone or naloxone.
- Adverse Effects: Relatively free of adverse effects. Potentially: Abdominal cramping, nausea & vomiting, nervousness, insomnia, joint or muscle pain, skin rashes, & pruritus. Dose-dependent hepatotoxicity is possible.
- May cause withdrawal clinical signs in physically dependent patients
- Expensive

Uses/Indications
Naltrexone might be useful in determining if adverse behaviors (*e.g.*, self-mutilating or tail-chasing) in dogs or cats have a significant endorphin component. Its relative expense and other more accepted treatments have largely supplanted the use of this drug in animals for treatment of behavioral disorders.

Pharmacology/Actions
Naltrexone is an orally available narcotic antagonist. It competitively binds to opiate receptors in the CNS, thereby preventing both endogenous opiates (*e.g.*, endorphins) and exogenously administered opiate agonists or agonist/antagonists from occupying the site. Naltrexone may be more effective in blocking the euphoric aspects of the opiates and less effective at blocking the respiratory depressive or miotic effects.

Naltrexone may also increase plasma concentrations of luteinizing hormone (LH), cortisol, and ACTH. In dogs with experimentally-induced hypovolemic shock, naltrexone (like naloxone) given IV in high dosages increased mean arterial pressure, cardiac output, stroke volume, and left ventricular contractility.

Pharmacokinetics
In humans, naltrexone is rapidly and nearly completely absorbed, but undergoes a significant first-pass effect as only 5–12% of a dose reaches the systemic circulation. Naltrexone circulates throughout the body and CSF levels are approximately 30% of those found in plasma. Only about 20–30% is bound to plasma proteins. It is unknown whether naltrexone crosses the placenta or enters milk. Naltrexone is metabolized in the liver primarily to 6-beta-naltrexol, which has some opiate blocking activity. Naltrexone's metabolites are eliminated primarily via the kidney. In humans, serum half-life of naltrexone is about 4 hours and about 13 hours for 6-beta-naltrexol.

Contraindications/Precautions/Warnings
Naltrexone is contraindicated in patients physically dependent on opiate drugs, in hepatic failure, or with acute hepatitis. The benefits of the drug versus its risks should be weighed in patients with hepatic dysfunction or with a history of allergic reaction to naltrexone or naloxone.