

PRESCRIBING INFORMATION

NOREPINEPHRINE BITARTRATE INJECTION

1 mg / mL norepinephrine
(as norepinephrine bitartrate monohydrate)

Sterile Solution for Intravenous Infusion

Manufacturer's Standard

Sympathomimetic Amine for Use in Hypotensive Emergencies

Preservative Free

Acala Pharmaceuticals Inc.
(a division of Fernbank Management Corporation)
224 King Street W, Suite 1702
Toronto, ON M5H 0A6
Canada
Submission Control No: 241796

Date of Revision: October 13, 2021

DESCRIPTION

Norepinephrine (sometimes referred to as *l-arterenol/Levarterenol* or *l-norepinephrine*) is a sympathomimetic amine which differs from epinephrine by the absence of a methyl group on the nitrogen atom.

ACTION AND CLINICAL PHARMACOLOGY

Norepinephrine functions as a powerful peripheral vasoconstrictor (alpha-adrenergic action) and as a potent inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action). Both of these actions result in an increase in systemic blood pressure and coronary artery blood flow. Cardiac output will vary reflexly in response to systemic hypertension but is usually increased in the hypotensive person when the blood pressure is raised to an optimal level. In myocardial infarction accompanied by hypotension, norepinephrine usually increases aortic blood pressure, coronary artery blood flow, and myocardial oxygenation, thereby helping to limit the area of myocardial ischemia and infarction. Venous return is increased and the heart tends to resume a more normal rate and rhythm than in the hypotensive state.

In hypotension that persists after correction of blood volume deficits, norepinephrine helps raise the blood pressure to an optimal level and establish a more adequate circulation.

In myocardial infarction norepinephrine has been shown to increase greatly the patient survival rate. Norepinephrine not only corrects systemic shock (through cardiostimulant and peripheral vasoconstrictor action), but also markedly dilates the coronary arteries, thereby increasing coronary blood flow, reducing the area of ischemia and promoting myocardial oxygenation. There is increased venous return and the heart tends to resume a more normal rate and rhythm.

On the coronary arteries norepinephrine causes about two and one half times the degree of vasodilatation that epinephrine produces and therefore has a greater effect in increasing coronary flow. It has only a slight effect on sugar metabolism, its hyperglycemic action being far less pronounced than epinephrine, and is not contraindicated in diabetic patients.

Note: With norepinephrine administration, bradycardia sometimes occurs, probably as a direct result of the rise in blood pressure to normal levels.

INDICATIONS AND CLINICAL USE

Norepinephrine Bitartrate Injection is recommended for the restoration and maintenance of blood pressure in acute hypotensive or shock states, such as surgery, trauma, hemorrhage, myocardial infarction, pheochromocytectomy, sympathectomy, spinal anesthesia, septicemia, drug reactions, poliomyelitis, and blood transfusion reactions. Because of the selective peripheral vasoconstrictive action of norepinephrine, pooled or stagnant blood in the dilated capillaries is driven into the central

circulation, thus maintaining vital functions (e.g. brain, heart, kidneys, etc.).

It may also be a useful adjunct in treating cardiac arrest and profound hypotension.

CONTRAINDICATIONS

Use in patients who are hypotensive from blood volume deficits is contraindicated except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If norepinephrine is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, poor systemic blood flow despite "normal" blood pressure, tissue hypoxia, and lactate acidosis.

Norepinephrine should also not be given to patients with mesenteric or peripheral vascular thrombosis (because of the risk of increasing ischemia and extending the area of infarction) unless, in the opinion of the attending physician, the administration of norepinephrine is necessary as a life-saving procedure.

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or levarterenol. Hence, the use of norepinephrine during cyclopropane and halothane anesthesia is generally considered contraindicative because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of norepinephrine in patients with profound hypoxia or hypercarbia.

WARNINGS

Norepinephrine Bitartrate Injection should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Norepinephrine Bitartrate Injection should be used with caution in the context of aneurysmal subarachnoid hemorrhage (SAH) due to the risk of overdose and associated adverse events. Whenever clinical symptoms rather worsen after the augmentation of blood pressure, reverse hypertensive therapy is advised.

PRECAUTIONS

Avoid Hypertension: Because of the potency of norepinephrine and because of the varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every 2 minutes from the time administration is started until the desired blood pressure is obtained, then every 5 minutes if administration is to be continued. The rate of flow must be watched constantly,

and the patient should never be left unattended while receiving norepinephrine. Headache may be a symptom of hypertension due to overdosage.

Site of Infusion: Whenever possible, norepinephrine should be given into a large vein, particularly an antecubital vein because, when administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is apparently very slight. Some authors have indicated that the femoral vein is also an acceptable route of administration. A catheter tie-in technique should be avoided, if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity. Therefore, one should avoid the veins of the leg or dorsum of the hand in elderly patients, or in those suffering from such disorders. Gangrene has been reported in a lower extremity when norepinephrine was given in an ankle vein.

Extravasation: The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of norepinephrine into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. **Blanching along the course of the infused vein**, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This also may progress on rare occasions to superficial slough, particularly during infusion into leg veins, in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

Pregnancy and Lactation: Norepinephrine administration was reported to induce fetal bradycardia most likely as a result of uterine/peripheral vasoconstriction by norepinephrine, however transplacental passage cannot be excluded. It was shown to exert a contractile effect on the pregnant uterus and may lead to fetal hypoxia in late pregnancy. These possible risks to the fetus should therefore be weighed against the potential benefit to the mother.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norepinephrine Bitartrate Injection is administered to a nursing woman.

IMPORTANT: Antidote for Extravasation Ischemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 to 15 mL of saline solution containing from 5 to 10 mg of phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle is used, and the solution is infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockage with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, **phentolamine should be given as soon as possible after the extravasation is noted.**

Some investigators add phentolamine (5 to 10 mg) directly to the infusion flask because it is believed that the drug used in this manner is an effective antidote against sloughing should extravasation occur, whereas the systemic vasopressor activity of the norepinephrine is not impaired.

Two investigators stated that, in the treatment of patients with severe hypotension following *myocardial infarction*, thrombosis in the infused vein and perivenous reactions and necrosis may usually be prevented if 10 mg of heparin are added to each 500 mL of infusion fluid (5 % dextrose) containing norepinephrine.

Sympathetic nerve block has also been suggested.

ADVERSE EFFECTS

Body as a Whole: Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.

Cardiovascular: Cardiogenic shock, arrhythmia, bradycardia, probably as a reflex result of a rise in blood pressure, stress cardiomyopathy.

Nervous System: Anxiety, transient headache.

Respiratory: Respiratory difficulty.

Skin and Appendages: Extravasation necrosis at injection site.

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when norepinephrine is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g. decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury. Gangrene of extremities has been rarely reported.

Overdoses or conventional doses in hypersensitive persons (e.g. hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating, and vomiting.

DRUG INTERACTIONS

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or

levarterenol. Hence, the use of norepinephrine during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of norepinephrine in patients with profound hypoxia or hypercarbia.

Norepinephrine Bitartrate Injection should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

OVERDOSAGE

Overdosage with norepinephrine may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. These may be accompanied by violent headache, pulmonary edema, photophobia, retrosternal pain, pallor, intense sweating and vomiting. Stress cardiomyopathy was also reported in the context of norepinephrine overdose. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, treatment with Norepinephrine Bitartrate Injection should be withdrawn and appropriate corrective measures initiated until the condition of the patient stabilizes.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

All parenteral preparations should be inspected visually to the extent possible for the presence of observable foreign and particulate matter, clarity, precipitate, discoloration and leakage prior to administration. The injection is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Restoration of Blood Pressure in Acute Hypotensive States:

Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, Norepinephrine Bitartrate Injection can be administered before and concurrently with blood volume replacement.

Diluent: Norepinephrine Bitartrate Injection (1 mg/mL) should be administered in 5% dextrose solution in distilled water or 5 % dextrose in saline solution. These fluids containing dextrose are protection against significant loss of potency due to oxidation. Administration in saline solution alone is not recommended. Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example by use of a Y-tube and individual flasks if given simultaneously).

Average Dosage: Add 4 mL of Norepinephrine Bitartrate Injection (1 mg/mL) to 1000 mL of 5% dextrose solution in distilled water or 5% dextrose in saline solution (each 1 mL of this dilution contains 4 mcg of norepinephrine). Give this dilution intravenously. Insert a plastic intravenous catheter through a suitable bore needle well advanced centrally into the vein and securely fixed with adhesive tape, avoiding if possible, a catheter tie-in technique as this promotes stasis. A drip bulb is necessary to permit an accurate estimation of the rate of flow in drops per minute. After observing the response to an initial dose of 2 to 3 mL (from 8 to 12 mcg of norepinephrine) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 to 100 mmHg systolic) sufficient to maintain the circulation to vital organs in previously normotensive patients (and even lower in patients in hemorrhagic or hypovolemic shock, pending replacement of circulating blood volume). In previously hypertensive patients, it is recommended that the blood pressure should be raised no higher than 40 mmHg below the pre-existing systolic pressure. The average maintenance dose ranges from 0.5 to 1 mL (2 to 4 mcg norepinephrine) per minute.

High Dosage: Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of norepinephrine should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg norepinephrine) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Central venous pressure monitoring is usually helpful in detecting and treating this situation.

Fluid Intake: The degree of dilution depends on clinical fluid volume requirements. If large volumes of fluid (dextrose) are needed at a flow rate that would involve an excessive dose of the pressor agent per unit of time, a more dilute solution than 4 mcg/mL should be used. On the other hand, when large volumes of fluid are clinically undesirable, a concentration greater than 4 mcg/mL may be used.

Duration of Therapy: The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. Gradually reduce infusion rate: avoid abrupt withdrawal. In some of the reported cases of vascular collapse due to acute myocardial infarction, treatment was required for up to six days.

Adjunctive Treatment in Cardiac Arrest: Norepinephrine is usually administered intravenously during cardiac resuscitation to restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means. (Norepinephrine's powerful beta-adrenergic stimulating action is also thought to increase the strength and effectiveness of systolic contractions once they occur.)

Average Dosage: To maintain systemic blood pressure during the management of cardiac arrest, norepinephrine is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

STORAGE AND STABILITY

Store between 15 and 25°C. All solutions should be protected from light. If the solution is brown, it should be discarded.

Do not refrigerate or freeze, and store in original package in order to protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Norepinephrine Bitartrate Injection is a clear, colourless solution with pH of 3.0-4.5. The solutions are supplied as single-dose containers, which are designed for use with a single patient as a single infusion.

Each mL of solution contains: norepinephrine 1 mg (as norepinephrine bitartrate monohydrate), sodium chloride for isotonicity and water for injection.

Norepinephrine Bitartrate Injection (1 mg/mL) is available in 1 mL and 4 mL single use USP Type I clear colourless glass ampoules. Boxes of ten (10).

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.