PRESCRIBING INFORMATION

NOREPINEPHRINE BITARTRATE INJECTION USP

(Norepinephrine base)
1 mg base/mL

THERAPEUTIC CLASSIFICATION

Sympathomimetic

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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 reflexibly 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 cardiotonic 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

The restoration and maintenance of blood pressure in acute hypotensive or shock states, such as surgery, trauma, myocardial infarction, pheochromocytomectomy, sympathectomy, spinal anesthesia, septicemia, drug reactions, poliomyelitis, blood transfusion reactions, and hemorrhage.

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.). Also 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 IV 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 trachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of norepinephrine in patients with profound hypoxia or hypercarbia.

WARNINGS

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

Norepinephrine contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

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.

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.

Sympathetic nerve block has also been suggested.

Pregnancy and Lactation: It is not known whether norepinephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. It should be given to a pregnant woman only if clearly needed. 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 is administered to a nursing woman.

ADVERSE EFFECTS

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

Cardiovascular: Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias.

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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your

health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

Overdosage with norepinephrine may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, discontinue the drug until the condition of the patient stabilizes.

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

DOSAGE AND ADMINISTRATION

Restoration of Blood Pressure in Acute Hypotensive States: Add 4 mL of the solution to 1000 mL of dextrose solution 5% or dextrose in saline (1 mL of dilution contains 4 mcg of norepinephrine base): Fluids containing dextrose are protection against significant loss of potency due to oxidation. Administration in saline solution alone is not recommended. Inject IV (preferably through polyethylene tubing) through a drip bulb. After observing the response to an initial dose of 2 to 3 mL (from 8 to 12 mcg of base) per minute, adjust the flow to establish and maintain the desired blood pressure, which usually is from 80 to 100 mmHg systolic 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 base) per minute. 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 base or 17 ampoules) 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. If large volumes of fluid are needed, administer a more dilute solution than 4 mcg/mL. Conversely, when the fluid volume should be restricted (e.g. in congestive heart failure), higher concentrations than 4 mcg/mL may be used. Continue therapy until the patient can maintain normotension (from hours up to 6 days). Gradually reduce infusion rate: avoid abrupt withdrawal. Whole blood or plasma, if indicated, should be administered separately (e.g. by Y tube from separate bottles).

Adjunctive Treatment in Cardiac Arrest: Norepinephrine is usually administered IV during cardiac resuscitation to restore and maintain an adequate blood pressure after an effective hearbeat 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 30°C.

The chlorobutyl rubber stopper is not made with natural rubber latex.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of solution contains: norepinephrine base 1 mg (norepinephrine bitartrate 1.88 mg), sodium metabisulfite 2 mg, sodium chloride for isotonicity and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH.

Norepinephrine Bitartrate Injection USP 1 mg base/mL is available in 4 mL single use vials. Boxes of 10.