

Norepinephrine (Levophed®)

Scope **C3IFT**

CCT

Generic Name: Norepinephrine

Trade Name: Levophed®

Chemical Class: Vasopressor

Therapeutic Class: Vasopressor

Actions: Mechanism of Action: Norepinephrine acts predominantly on alpha-adrenergic receptors to produce constriction of resistance and capacitance vessels, thereby increasing systemic blood pressure and coronary artery blood flow. Norepinephrine also acts on beta1-receptors, although quantitatively less than either epinephrine or isoproterenol. In relatively lower doses, the cardiac-stimulant effect of norepinephrine is predominant; with larger doses, the vasoconstrictor effect predominates. Similar to epinephrine, norepinephrine has direct agonist effects on effector cells that contain alpha- and beta-receptors. As with other catecholamines, the intracellular action of norepinephrine is mediated via cyclic adenosine monophosphate (cAMP), the production of which is augmented by beta stimulation and attenuated by alpha stimulation. The primary pharmacodynamic effects of norepinephrine are cardiac stimulation, particularly at lower doses, and vasoconstriction, which tends to predominate with moderate to higher doses of the drug. Metabolic effects observed with epinephrine, such as glycogenolysis, inhibition of insulin release, and lipolysis, also occur with norepinephrine but are much less pronounced. The hemodynamic consequences of norepinephrine's cardiovascular stimulation include increases in systolic, diastolic, and pulse pressures. Cardiac output is generally unaffected, although it can be decreased, and total peripheral resistance is also elevated. The elevation in resistance and pressure result in reflex vagal activity, which slows the heart rate and increases stroke volume. The elevation in vascular tone or resistance reduces blood flow to the major abdominal organs as well as to skeletal muscle. As with epinephrine, however, coronary blood flow is substantially increased secondary to the indirect effects of alpha stimulation. Therefore, unlike epinephrine, norepinephrine does not significantly increase myocardial oxygen consumption, except in patients with variant angina who are hyperresponsive to alpha stimulation.

Pharmacokinetics: **Absorption:** IV administration results in complete bioavailability.

Distribution: Concentrates in sympathetic nervous tissue. Does not cross the blood-brain barrier but readily crosses the placenta.

Metabolism and Excretion: Taken up and metabolized rapidly by sympathetic nerve endings.

Half-life: Unknown.

TIME/ACTION PROFILE (effects on BP)

ROUTE	ONSET	PEAK	DURATION
IV	immediate	rapid	1–2 min

Indications: Produces vasoconstriction and myocardial stimulation, which may be required after adequate fluid replacement in the treatment of severe hypotension and shock.

Contraindications/ **Contraindicated in:**

Considerations:

- Vascular, mesenteric, or peripheral thrombosis;

-
- OB: ↓ uterine blood flow;
 - Hypoxia;
 - Hypercarbia;
 - Hypotension secondary to hypovolemia (without appropriate volume replacement);
 - Hypersensitivity to bisulfites.

Use Cautiously in:

- Hypertension;
- Concurrent use of MAO inhibitors, tricyclic antidepressants, or cyclopropane or halothane anesthetics;
- Hyperthyroidism;
- Cardiovascular disease;
- Lactation: Safety not established

Precautions:

Hepatic Impairment

Specific guidelines for dosage adjustments are not available; however, the rate of metabolism of norepinephrine may be decreased in individual patients with hepatic impairment. Titrate the norepinephrine infusion rate to attain clinical goals.

Renal Impairment

Specific guidelines for dosage adjustments are not available; it appears that no dosage adjustments are needed. Titrate the norepinephrine dosage to attain clinical goals.

Intermittent hemodialysis:

It is unknown whether norepinephrine is dialyzable. Titrate the norepinephrine infusion rate to attain clinical goals.

Pregnancy Cat: Norepinephrine is classified as FDA pregnancy risk category C

Side Effects: **Severe**

- arrhythmia exacerbation
 - pulmonary edema
 - bradycardia
 - lactic acidosis
 - tissue necrosis
 - anaphylactic shock
-

Moderate

- photophobia
- hypertension
- sinus tachycardia
- premature ventricular contractions (PVCs)
- angina
- dyspnea
- palpitations
- ST-T wave changes
- hypovolemia
- hypoxia

Administration:

NOTE: Volume depletion should always be corrected before initiation of vasopressor therapy. However, in an emergency, when intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, norepinephrine can be administered prior to and concurrently with volume replacement therapy.

NOTE: Norepinephrine is available commercially only as the bitartrate salt, although the dosage is expressed in terms of norepinephrine base (2 mg norepinephrine bitartrate equals 1 mg norepinephrine base).

Injectable Administration

Visually inspect parenteral products for particulate matter and discoloration prior to administration.

Intravenous Administration

Administer by intravenous infusion.

Monitor blood pressure every 2—3 minutes until stabilized and then every 5 minutes. ECG should be continuously monitored.

Do not administer into the veins of the legs in elderly patients.

Avoid extravasation (see Precautions). If extravasation occurs, infiltrate the site as soon as possible with 10—15 ml of NS containing 5—10 mg of phentolamine for adults (see Phentolamine Dosage). Use a syringe with a fine hypodermic needle and liberally infiltrate throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and noticeable local hyperemic changes if the area is infiltrated within 12 hours of extravasation. For prevention of extravasation, phentolamine (10 mg) may be added to each 1000 ml of solution containing norepinephrine.

Dilution:

The concentrate for injection must be diluted prior to administration. Fluids

containing dextrose offer protection against loss of potency due to oxidation; therefore, 5% dextrose in water (D5W) or 5% percent dextrose and sodium chloride (D5NS) are generally the preferred diluents. Although the manufacturer states that norepinephrine should not be diluted in normal saline (NS) alone, available data support the stability of norepinephrine in NS at concentrations up to 16 mcg/ml.

The manufacturer recommends diluting 4 mg norepinephrine in 1000 ml of D5W for a concentration of 4 mcg/ml. However, a more commonly used dilution in clinical practice is 4 mg norepinephrine in 250 ml of D5W injection for a concentration of 16 mcg/ml. In fluid-restricted patients, concentrations up to 32 mcg/ml have been used.

Intravenous infusion:

Infuse IV preferably into the antecubital vein of the arm using an infusion pump or other device to control the flow rate. The femoral vein may also be used. Do not use a catheter tie-in technique because the obstruction to flow around the tubing may lead to stasis and increased local concentration of norepinephrine. Rate should be titrated according to patient response.

Observe IV infusion site frequently during administration. If blanching along the vein occurs, change infusion site. Care should be taken to avoid extravasation because norepinephrine can cause local necrosis.

For the treatment of acute hypotension, cardiogenic shock, sepsis, or septic shock.

Intravenous dosage

Adults

Initially, up to 8 to 12 mcg/minute, as an IV infusion, titrated to desired hemodynamic response (usually to maintain systolic BP of 80 to 100 mm Hg). Infusions are typically initiated and titrated in increments of 0.02 mcg/kg/minute (or more in emergency cases). Usual maintenance dose is 2 to 4 mcg/minute. Individual response is highly variable. Patients with refractory shock may require dosages of 8 to 30 mcg/minute. There are rare situations in which much larger doses (as high as 68 mg/day or 47 mcg/minute) may be necessary if the patient remains hypotensive; however, rule out hidden blood volume depletion. One trial limited infusions to a maximum of 0.19 mcg/kg/minute, then added additional agents for the treatment of shock. Septic shock clinical practice guidelines recommend norepinephrine as the first-line vasopressor. Target a mean arterial pressure (MAP) of 65 mmHg initially. Titrate to an endpoint reflecting perfusion; reduce rate or discontinue the vasopressor if worsening hypotension or arrhythmias occur. Compared to other vasopressors, norepinephrine increases MAP with little change in heart rate and less increase in stroke volume. Discontinuation of therapy should occur when adequate blood pressure and tissue perfusion are maintained following gradual tapering of the infusion rate. NOTE: In general, norepinephrine should not be used for treating hypotension during anesthesia; the benefits and risks of using norepinephrine should be evaluated.

Infants†, Children†, and Adolescents†

0.1 mcg/kg/minute IV initially, then titrate upward to attain hemodynamic goals (Usual Max: 2 mcg/kg/minute IV). When discontinuing norepinephrine, reduce the infusion rate gradually; avoid abrupt withdrawal.

Neonates†

0.2 to 0.5 mcg/kg/minute IV initially titrated upward every 30 minutes to attain clinical goals was used in an observational study of 22 neonates (gestational age older than 35 weeks) with hypotension due to septic shock refractory to fluid resuscitation and dopamine or dobutamine infusion. The norepinephrine infusion rate required to correct hypotension ranged from 0.2 to 2 mcg/kg/minute (mean 0.5 mcg/kg/minute), and the individual maximum infusion rate to sustain normal systolic blood pressure ranged from 0.2 to 7.1 mcg/kg/minute. A dose range of 0.1 to 2 mcg/kg/minute is recommended by the Pediatric Advanced Life Support guidelines. When discontinuing norepinephrine, reduce the infusion rate gradually; avoid abrupt withdrawal.

†Indicates off-label use

Supply: Levophed/Norepinephrine/Norepinephrine Bitartrate Intravenous Inj Sol: 1mg, 1mL

- Notes:**
- ***BOXED WARNING:*** Extravasation, geriatric, peripheral vascular disease, tissue necrosis. Caution should be observed to avoid extravasation of norepinephrine during intravenous administration. Check the infusion site frequently for free-flow. Peripheral vasoconstriction or ischemia, tissue necrosis, and/or gangrene in the surrounding area can occur following extravasation. 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 geriatric patients or in those suffering from obliterative peripheral 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. If extravasation occurs, the affected area should be infiltrated as soon as possible, to prevent necrosis, using a normal saline solution containing phentolamine, injecting liberally throughout the ischemic area using a fine hypodermic needle. The ischemic area may be identified by a cool, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and noticeable local hyperemic changes if the area is infiltrated within 12 hours of extravasation. The phentolamine antidote should be given as soon as possible after the extravasation is observed.
 - Use with **cyclopropane** or **halothane anesthesia**, **cardiac glycosides**, **doxapram**, or local use of **cocaine** may result in ↑ myocardial irritability.
 - Use with **MAO inhibitors**, **methyl dopa**, **doxapram**, or **tricyclic antidepressants** may result in severe hypertension.

-
- **Alpha-adrenergic blockers** can prevent pressor response.
 - **Beta blockers** may exaggerate hypertension or block cardiac stimulation.
 - Concurrent use with **ergot alkaloids** (**ergotamine** , **methylergonovine** , or **oxytocin**) may result in enhanced vasoconstriction and hypertension.