421300373-00

Noradrenaline Sintetica 1 mg/ml
Noradrenaline tartrate
Solution for infusion

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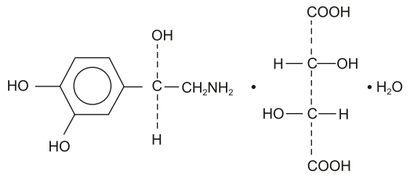
Rx only

DESCRIPTION

Noradrenaline (sometimes referred to as *l-arterenol/ Levarterenol* or *l- norepinephrine)* is a sympathomimetic amine which differs from adrenaline by the absence of a methyl group on the nitrogen atom.
Noradrenaline tartrate is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate and has the following structural formula:



Noradrenaline Sintetica is supplied in sterile aqueous solution (water for injections) in the form of the tartrate salt to be administered by intravenous infusion following dilution. Noradrenaline is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each mL contains the equivalent of 1 mg base of noradrenaline and sodium chloride for isotonicity. It has a pH of 3 to 4.5. The air in the ampoules has been displaced by nitrogen gas.

CLINICAL PHARMACOLOGY

Noradrenaline, a sympathomimetic amine, acts predominantly on α receptors and on β receptors in the heart. It therefore causes peripheral vasoconstriction (α-adrenergic action), and a positive inotropic effect on the heart and dilation of coronary arteries (β-adrenergic action). These actions result in an increase in systemic blood pressure and coronary artery blood flow. 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 ischaemia 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.

INDICATIONS AND USAGE

For the restoration of blood pressure in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions).
As an adjunct in the treatment of cardiac arrest.
To restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means.

CONTRAINDICATIONS

Noradrenaline Sintetica should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If Noradrenaline Sintetica 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.
Noradrenaline Sintetica 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 Noradrenaline Sintetica 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 adrenaline or noradrenaline. Hence, the use of Noradrenaline Sintetica 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 Noradrenaline Sintetica in patients with profound hypoxia or hypercarbia.

WARNINGS

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

PRECAUTIONS

General

Avoid Hypertension: Because of the potency of Noradrenaline Sintetica and because of 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 two minutes from the time administration is started until the desired blood pressure is obtained, then every five 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 Noradrenaline Sintetica. Headache may be a symptom of hypertension due to overdosage.
Site of Infusion: Whenever possible, infusions of Noradrenaline Sintetica 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 in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions of Noradrenaline Sintetica were given in an ankle vein.

Extravasation: The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of Noradrenaline Sintetica 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 mL to 15 mL of saline solution containing from 5 mg to 10 mg of **phentolamine**, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade 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.

Hypersensitivity: *Certain patients may be hypersensitive to the effects of Noradrenaline Sintetica, e.g. hyperthyroidism patients (see Adverse Reactions).*
Drug Interactions: Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered adrenaline or noradrenaline. Hence, the use of Noradrenaline Sintetica during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. Noradrenaline Sintetica infusion solutions should not be mixed with other medicines. Infusion solutions containing noradrenaline acid tartrate have been reported to be incompatible with alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole. The same type of cardiac arrhythmias may result from the use of Noradrenaline Sintetica in patients with profound hypoxia or hypercarbia. Noradrenaline Sintetica should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies have not been performed.

Pregnancy: Animal reproduction studies have not been conducted with Noradrenaline Sintetica. It is also not known whether Noradrenaline Sintetica can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Noradrenaline Sintetica should be given to a pregnant woman only if clearly needed.

Nursing Mothers: 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 Noradrenaline Sintetica is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients has not been established.

Geriatric Use: Clinical studies of Noradrenaline Sintetica did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Noradrenaline Sintetica infusions should not be administered into the veins in the leg in elderly patients (see PRECAUTIONS, General).

ADVERSE REACTIONS

The following reactions can occur:
Body as a Whole: Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.
Cardiovascular System: Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias.
Nervous System: Anxiety, transient headache.
Respiratory System: 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 Noradrenaline Sintetica 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.

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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.

OVERDOSAGE

Overdosage with Noradrenaline Sintetica 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 Noradrenaline Sintetica until the condition of the patient stabilizes.

DOSAGE AND ADMINISTRATION

Noradrenaline Sintetica is a concentrated, potent drug which must be diluted in glucose containing solutions prior to infusion. An infusion of Noradrenaline Sintetica should be given into a large vein (see PRECAUTIONS).

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, Noradrenaline Sintetica can be administered before and concurrently with blood volume replacement.

Diluent: Noradrenaline Sintetica should be diluted in 5 percent glucose solution or 0.9 percent sodium chloride with 5 percent glucose. These glucose containing fluids are protection against significant loss of potency due to oxidation. Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example, by use of a Y-tube and individual containers if given simultaneously). Noradrenaline Sintetica contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue.

Chemical and physical in-use stability (following dilution) has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Average Dosage: Add 2 mL of the Noradrenaline Sintetica to 500 mL, or 4 mL of Noradrenaline Sintetica to 1000 mL of a 5 percent glucose solution or 0.9 percent sodium chloride with 5 percent glucose. Each mL of this dilution contains 4 mcg of the base of Noradrenaline Sintetica. Give this solution by intravenous infusion. 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. An IV drip chamber or other suitable metering device is essential to permit an accurate estimation of the rate of flow in drops per minute. After observing the response to an initial dose of 2 mL to 3 mL (from 8 mcg to 12 mcg of base) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 mm Hg to 100 mm Hg systolic) sufficient to maintain the circulation to vital organs. In previously hypertensive patients, it is recommended that the blood pressure should be raised no higher than 40 mm Hg below the preexisting systolic pressure. The average maintenance dose ranges from 0.5 mL to 1 mL per minute (from 2 mcg to 4 mcg of base).

High Dosage: Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of Noradrenaline Sintetica should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg base) 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. Dilution can be varied depending on the clinical fluid volume requirement

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

Duration of Therapy: The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. The infusion rate of Noradrenaline Sintetica should be reduced gradually, avoiding 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

Infusions of Noradrenaline Sintetica are 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.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use, whenever solution and container permit.

Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

Avoid contact with iron salts, alkalis, or oxidizing agents.

HOW SUPPLIED

Noradrenaline Sintetica (noradrenaline tartrate) contains the equivalent of 1 mg base of noradrenaline per 1 mL (4 mg/4mL). Supplied as:

Unit of Sale	**Concentration**
10 in a Carton	4 mg/4mL (1 mg/mL) 1 mg/mL

Store below 30°C and protect from light. Do not refrigerate or freeze

Manufactured by Sintetica SA Via Penate 5 CH-6850 Mendrisio Switzerland

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