PRODUCT INFORMATION

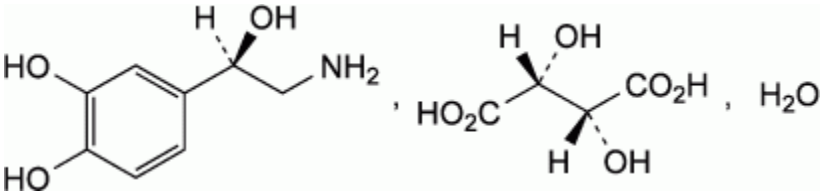
Noradrenaline BNM 1:1000
Noradrenaline (norepinephrine) (as acid tartrate monohydrate)

Concentrate for IV Injection

NAME OF THE MEDICINE

Noradrenaline (norepinephrine) (as acid tartrate monohydrate) 1:1000 concentrate for intravenous injection

The chemical structure for noradrenaline (norepinephrine) acid tartrate monohydrate is shown below:



Chemically, noradrenaline (norepinephrine) acid tartrate monohydrate, (1*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate monohydrate, is a white or almost white crystalline powder. It is freely soluble in water, and slightly soluble in ethanol (96%).

Molecular formula: $C_8H_{11}NO_3,C_4H_6O_6,H_2O$

Molecular weight: 337.3

CAS registry no.: 69815-49-2

DESCRIPTION

Noradrenaline BNM is a sterile noradrenaline (norepinephrine) concentrated solution for injection available in ampoules.

Each 1 mL ampoule contains noradrenaline (norepinephrine) 1 mg in 1 mL (1:1000), present as 2 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 1 mL.

Each 4 mL ampoule contains noradrenaline (norepinephrine) 4 mg in 4 mL (1:1000), present as 8 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 4 mL.

Each ampoule also contains the excipients sodium chloride 8.4 mg/mL for tonicity, and water for injections.

The solution has a pH of 3.0 to 4.5.

PHARMACOLOGY

Actions

Noradrenaline (norepinephrine), 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, noradrenaline (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, noradrenaline (norepinephrine) helps raise the blood pressure to an optimal level and establish a more adequate circulation.

INDICATIONS

For the restoration of blood pressure in certain acute hypotensive states (e.g. phaeochromocytomectomy, sympathectomy, poliomyelitis, spinal anaesthesia, myocardial infarction, septicaemia, 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 BNM should not be given to patients who are hypotensive from hypovolaemia except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed.

If Noradrenaline BNM 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 BNM should not be given to patients with mesenteric or peripheral vascular thrombosis (because of the risk of increasing ischaemia and extending the area of infarction) unless, in the opinion of the attending physician, the administration of Noradrenaline BNM is necessary as a lifesaving procedure.

The use of Noradrenaline BNM during cyclopropane and halothane anaesthesia 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 BNM in patients with profound hypoxia or hypercarbia.

PRECAUTIONS

Warnings
Noradrenaline BNM 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.

Avoid hypertension
Because of the potency and varying responses to noradrenaline (norepinephrine), the possibility exists that hypertension may be produced with overdoses of this pressor agent. Hence it is desirable to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, and then every five minutes if administration is to be continued. The rate of flow must be watched constantly, and the patient should not be left unattended whilst receiving Noradrenaline BNM. Headache may be a symptom of hypertension due to overdose.

Hypersensitivity
Certain patients may be hypersensitive to the effects of noradrenaline (norepinephrine), e.g. patients with hyperthyroidism (see **ADVERSE EFFECTS**).

Site of infusion
Noradrenaline BNM 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. 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 noradrenaline (norepinephrine). As occlusive vascular diseases are more likely to occur in the lower rather than in the upper extremity, the leg veins in elderly patients or in those suffering from such disorders should be avoided. Gangrene has been reported in a lower extremity when infusions of noradrenaline (norepinephrine) 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 BNM 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 may also 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 changing the infusion site at intervals to allow the effects of local vasoconstriction to subside. The antidote for extravasation ischaemia is phentolamine. To prevent sloughing and necrosis in areas in which extravasation has occurred, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing 5 mg to 10 mg of phentolamine. Using a syringe with a fine hypodermic needle, the solution is infiltrated liberally throughout the area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperaemic changes

if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after extravasation is noted.

Pharmaceutical incompatibilities
Infusion solutions containing noradrenaline (norepinephrine) acid tartrate monohydrate have been reported to be incompatible with iron salts, alkalis and oxidising agents, barbiturates, chlorphenamine maleate (chlorpheniramine maleate), chlorothiazide, nitrofurantoin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole.

Effects on fertility
Studies have not been performed.

Use in pregnancy (Category B3)
Noradrenaline BNM should be given to a pregnant woman only if clearly needed.

Animal studies indicate noradrenaline (norepinephrine) may impair placental perfusion and induce foetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to foetal asphyxia in late pregnancy. However, the clinical significance of these changes to a human foetus is unknown. These possible risks to the foetus should therefore be weighed against the potential benefit to the mother.

Use in lactation
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 BNM is administered to a nursing woman.

Paediatric use
Safety and effectiveness in paediatric patients has not been established.

Use in the elderly
Clinical studies of noradrenaline (norepinephrine) injection 1:1000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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 BNM infusion solutions should not be administered into the veins in the leg in elderly patients.

Genotoxicity
Studies have not been performed.

Carcinogenicity
Studies have not been performed.

INTERACTIONS WITH OTHER MEDICINES

Noradrenaline BNM infusion solutions should not be mixed with other medicines. Extreme caution should be exercised in patients receiving monoamine oxidase (MAO) inhibitors and antidepressants of the triptyline or imipramine types (see **PRECAUTIONS: Warnings**).

ADVERSE EFFECTS

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 BNM 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 ischaemic injury. Gangrene of extremities has been rarely reported. Bradycardia sometimes occurs, probably as a reflex result of a rise in blood pressure. 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.

The following reactions can occur:

Body as a whole
Ischaemic injury due to potent vasoconstrictor action and tissue hypoxia.

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

Nervous system
Anxiety, transient headache.

Respiratory system
Respiratory difficulty.

Skin and appendages
Extravasation necrosis at injection site.

DOSAGE AND ADMINISTRATION

Noradrenaline BNM is a concentrated solution for injection which must be diluted in glucose containing solutions prior to infusion. An infusion of Noradrenaline BNM should be given into a large vein (see **PRECAUTIONS**).

Noradrenaline BNM must be administered in 5% glucose solution in distilled water or 5% glucose in saline solution, and must not be administered in saline solution alone. Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

This product contains no antimicrobial preservative; to reduce microbiological hazard use as soon as practicable after preparation. If storage is necessary, hold at 2 to 8°C for not more than 24 hours. In-use storage times and conditions prior to use are the responsibility of the user.

Noradrenaline BNM is for single use in one patient only. Discard any residue. Discoloured solutions or those containing a precipitate should not be used. Avoid contact with iron salts, alkalis or oxidising agents.

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

Average dosage
Add 1 mL of Noradrenaline BNM (1:1000) to 250 mL, or 4 mL of Noradrenaline BNM (1:1000) to 1 litre, of 5% glucose solution. Each 1 mL of this dilution contains 4 micrograms of noradrenaline (norepinephrine) (= 8 micrograms of noradrenaline (norepinephrine) acid tartrate monohydrate). Give this dilution intravenously via a catheter well advanced centrally into the vein and securely fixed, if possible, avoiding a catheter tie-in technique as it 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 (8 to 12 micrograms of base) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 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 pre-existing systolic pressure.

The average maintenance dose ranges from 0.5 to 1 mL per minute (2 to 4 micrograms of base). Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of Noradrenaline BNM should be titrated according to the response of the patient. Occasionally much larger daily doses (as high as 68 mg base or 68 x 1 mL ampoules or 17 x 4 mL ampoules) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Dilution can be varied depending on the clinical fluid volume requirement.

Duration of therapy
The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. The infusion rate should then 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 BNM 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. Noradrenaline's (norepinephrine's) 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, Noradrenaline BNM is used in the same manner as described under **Restoration of blood pressure in acute hypotensive states**.

Paediatric use
Safety and effectiveness in paediatric patients has not been established.

Use in the elderly
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 BNM infusion solutions should not be administered into the veins in the leg in elderly patients.

OVERDOSAGE

Overdosage with Noradrenaline BNM may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. Headache may indicate severe hypertension.

For information on the management of overdose, contact the Poison Information Centre in Australia on 13 11 26; in New Zealand on 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Noradrenaline BNM is a concentrated solution for injection available as 1 mL and 4 mL single use glass ampoules (1 mg noradrenaline (norepinephrine) base/1 mL ampoule or 4 mg noradrenaline (norepinephrine) base/4 mL ampoule). Both presentations are supplied in packs of 10 ampoules per carton.

Not all presentations may be distributed in Australia and New Zealand.

Store below 25ºC. Do not refrigerate or freeze. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Australian sponsor
Boucher & Muir Pty Ltd
Level 9, 76 Berry Street
North Sydney NSW 2060

New Zealand sponsor
Boucher & Muir (NZ) Ltd
39 Anzac Road
Browns Bay
Auckland 0753

Ph: 0800 565 633

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

20 July 2016

DATE OF MOST RECENT AMENDMENT

23 March 2017