NORADRENALINE (NOREPINEPHRINE)

SCOPE (Area): FOR USE IN: Intensive Care Unit, Coronary Care Unit, ED, CVS and Theatre
EXCLUSIONS: Paediatrics (seek Paediatrician advice) and General Wards

SCOPE (Staff): Medical, Nursing and Pharmacy

Note: Noradrenaline (norepinephrine) is the Therapeutic Goods Administration’s official drug name. For simplicity in this guideline it will be referred to as noradrenaline.

BRAND NAMES
Levophed® and generic brands.

PHARMACOLOGY AND PHARMACOKINETICS
Noradrenaline is a naturally occurring sympathomimetic which is an agonist on alpha\textsubscript{1}, alpha\textsubscript{2} and beta\textsubscript{1} receptors and has little or no effect on beta\textsubscript{2} or dopamine receptors. Noradrenaline raises systolic and diastolic blood pressure via alpha effects causing peripheral vasoconstriction, which may reduce blood flow in the kidneys, liver and skeletal muscle. The positive inotrope and chronotrope effect of noradrenaline is less than of other sympathomimetics. Noradrenaline is predominantly metabolised by catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO). Noradrenaline has a rapid onset of action (1-2 minutes), and a fast elimination when the infusion is ceased due to the short half life of 3 minutes. Sodium metabisulfite is present in the injection as a preservative.

INDICATIONS
- Acute hypotension requiring a vasoconstrictor e.g. septic shock (treatment of choice) or central axial anaesthesia (spinal, epidural).

CONTRAINDICATIONS
- Hypotension from hypovolaemia - correct before using noradrenaline. If uncorrected, severe peripheral and visceral vasoconstriction may occur leading to tissue hypoxia.
- Hypertension.

PRECAUTIONS
- Extravasation – can cause tissue necrosis and sloughing. Peripheral extravasation is treated by infiltration with the alpha blocker phentolamine (5-10 mg diluted in 10 to 15 mL of sodium chloride 0.9% – on imprest in Theatre).
- Profound hypoxia or hypercapnia - may sensitise the myocardium to the effect of noradrenaline, increasing the risk of ventricular tachycardia or fibrillation. Correct before use where possible.
● Mesenteric or peripheral vascular thrombus – noradrenaline may extend the infarction, and should only be used in life saving situations.

● Hyperthyroidism or ischaemic heart disease - increased risk of cardiovascular adverse effects.

● Elderly – may require lower doses of noradrenaline.

● Allergy - noradrenaline vials contain sodium metabisulfite, which can cause severe allergy in susceptible patients (asthmatics are of greatest risk).

PREGNANCY AND BREASTFEEDING
Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS

● Tricyclic antidepressants - dysrhythmias and hypertension may result when used with noradrenaline. Avoid combination if possible, monitor for dysrhythmias and hypertension. Reduce noradrenaline dose if necessary.

● Ergot derivatives – co-administration with noradrenaline may increase vasoconstriction and increase risk of severe hypertension. Avoid if possible.

● Monoamine oxidase inhibitors (phenelzine, tranylcypromine, moclobemide), selegiline and linezolid – may inhibit the metabolism of noradrenaline resulting in hypertension. Use with caution, noradrenaline dose may need decreasing.

● Drugs with hypertensive or vasoconstrictive effects, and to a lesser degree arrhythmogenic effects – noradrenaline increases the risk of these effects when co-administered with these drugs. Use combinations cautiously, monitoring blood pressure, ECG, and haemodynamic parameters.

● Entacapone – may inhibit the metabolism of noradrenaline resulting in hypertension. Monitor carefully and reduce noradrenaline dose if necessary.

● Beta blockers - may allow the alpha receptor-mediated effects of noradrenaline (vasoconstriction) to predominate, as such marked hypertension followed by bradycardia may result. The effect is likely to be greater with a nonselective beta-blocker (oxprenolol, pindolol, propranolol). Monitor blood pressure and heart rate closely when used with any beta blocker.

● Alpha-blockers (eg prazosin, phenoxybenzamine, phentolamine) – may lead to hypotension rather than an increase in blood pressure due to unopposed beta effect.

● SNRIs, atomoxetine – may increase tachycardia and pressor effects of noradrenaline. Avoid if possible.

● Clozapine – noradrenaline may not have same pressor effects, vasopressin may be preferred.

● Cocaine - topical use may potentiate noradrenaline’s actions.

● Spironolactone – may decrease the vasoconstricting effect of noradrenaline. Monitor.

DOSAGE AND ADMINISTRATION

Requires continuous ECG monitoring.
For administration only
  - in Intensive Care Unit, Cardiology Care Unit, ED, CVS and Theatre
  - by MET or Code Blue

Administer via CVC or midline only – see Precautions re extravasation. A large peripheral vein (antecubital or proximal to this) may be used only in an emergency and where central access is planned. If administering peripherally use a dedicated line and monitor the site for extravasation (a second peripheral line is required for other infusions/access). Do not administer on lines where other infusions may be bolused or flushed.

Noradrenaline must be diluted prior to use.
Noradrenaline doses in this guideline refer to noradrenaline base, with each vial containing 4 mg/4 mL. The packaging for noradrenaline also refers to noradrenaline acid tartrate – this is not used for dosage purposes.

Glucose containing solutions provide protection against loss of potency from oxidation, check the Australian Injectable Drugs Handbook (‘Yellow book’) for further information.

**IV infusion (via CVC):**

Use noradrenaline 4 mg/4 mL vials to prepare infusion.
Withdraw 6 mL from a 100 mL glucose 5% minibag.
Noradrenaline 6 mg (6 mL from TWO vials) added to remaining 94 mL glucose 5% in the minibag.
**Total Volume:** 100 mL.
**Final concentration:** 60 microgram/mL.
**Starting rate:** 1-3 microgram/min (1-3 mL/hr).
**Rate increase:** Can increase rate every 3-5 minutes. Use blood pressure to titrate dose.
**Coronary Care Unit dose range:** 1-10 microgram/min (1-10 mL/hr).
**Coronary Care Unit maximum rate:** 10 microgram/min (10 mL/hr).
**ICU, ED, Theatre and CVS usual rate range:** 1-20 microgram/min (1-20 mL/hr). Higher rates may be required. Consider adding vasopressin if noradrenaline reaches 20 microg/min (20 mL/hr) – see DRG0041 Vasopressin (Argipressin) Intravenous infusion.
**ICU, ED, Theatre and CVS maximum rate:** 120 microgram/min (120 mL/hr) in extreme cases.

**Ceasing infusion:** Wean gradually to avoid hypotension.

**Note: for high dose patients (greater than 20 microg/min) consider the following:**

Use noradrenaline 4 mg/4 mL vials to prepare infusion.
Noradrenaline 16 mg (16 mL from FOUR vials) added to 250 mL glucose 5% IV bag.
**Total Volume:** 266 mL.
**Final concentration:** 60 microgram/mL.

**Infusion details as above**

**Syringe Unit/Pump IV infusion (via CVC):**

Use noradrenaline 4 mg/4mL vials to prepare infusion.
Noradrenaline 3 mg (3 mL from vial) diluted to 50 mL with glucose 5% in a luer lock syringe.
**Total Volume:** 50 mL.
**Final concentration:** 60 microgram/mL.
**Rate:** as for IV infusion above.

**Process for changing syringes to minimise disruption to infusions given the short drug half-life:**

- Prepare the replacement syringe and prime a new syringe line
- Attach a second syringe pump module to the controller (AKA ‘the brain’) and program as per the currently running infusion
- Commence new infusion on the pump and then changeover the connected line with the replacement line
- Stop completed infusion pump
**General Administration Information**

- **Infusion preparation:**
  Mix infusion thoroughly after adding noradrenaline to avoid inadvertently giving a more concentrated dose.
  Discoloured solutions (brown) or solutions containing precipitates should not be used.
  Glucose 5% can be substituted for different compatible IV fluid as requested by the Medical Officer.
  Infusion stable for 24 hours.

- **Infusion pump:** Alaris® LVP or syringe unit with Guardrails® or syringe pump in ED.

- **Routes of administration:**
  - IV injection: No
  - IV intermittent infusion (15-60 minutes): No
  - IV continuous infusion: Yes
  - IM injection: No
  - Subcut injection: No

- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook (‘Yellow book’) in your ward area. Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.

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**MONITORING (INCLUDING BLOOD TESTS)**

- Excessive dosing may lead to hypertension.
- Assess for organ ischaemia due to vasoconstriction including kidneys, gastrointestinal tract and peripheral extremities – see adverse effects.

- Dose range and clinical goals should be documented by the Medical Officer.
- A diminished therapeutic effect may occur with prolonged noradrenaline infusions due to down-regulation of receptors.

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**NURSING PRACTICE POINTS**

- Continuous ECG monitoring.
  - When patient is unstable or infusion rate requires adjustment, monitor blood pressure every 2-5 minutes, or continuously via arterial line. Doses above 5 microg/min ideally require continuous monitoring via arterial line.
  - When blood pressure stable, monitor blood pressure every 15-30 minutes, or continuously via arterial line. Doses above 5 microg/min ideally require continuous monitoring via arterial line.
  - Baseline 12 lead ECG, and then daily.
  - If noradrenaline is being administered peripherally, monitor IV site for blanching and extravasation – see Precautions. Monitor limb distal to IV site for signs of ischaemia.
  - Monitor fluid balance.
  - All injections and infusions are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.

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**ADVERSE EFFECTS:**

- **Common** – anxiety, palpitations and headache.
- **Infrequent** – hypertension, ischaemia (myocardial, mesenteric, renal or peripheral (digital) ischaemia – can manifest as acute myocardial infarction, gastrointestinal infarction, decreased urine output/creatinine clearance or gangrene), bradycardia (reflex consequence of increased blood pressure), arrhythmias, angina, urinary retention, restlessness, tremor, vomiting, extravasation (may cause sloughing, necrosis and gangrene).
- **Rare** - allergic reaction (sodium metabisulfite in products).
DRUG PRESENTATIONS AND STORAGE
Noradrenaline 4 mg/4 mL vials (equivalent to noradrenaline acid tartrate 8 mg/4 mL).
Store below 25°C. Protect ampoules from light. Do not freeze.