Noradrenaline

1 Name and description of analyte

1.1 Name of analyte
Noradrenaline

1.2 Alternative names
Norepinephrine
4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol

1.3 NLMC code
To follow

1.4 Description of analyte
Noradrenaline is a catecholamine produced predominantly by chromaffin bodies of adrenergic nerves and, to a lesser extent, by chromaffin cells of the adrenal medulla. Noradrenaline is synthesised from tyrosine. Its plasma half-life is in the order of several minutes; it is metabolised by methylation and deamination.

1.5 Function of analyte
Noradrenaline functions predominantly as both a neurotransmitter, exerting its effects locally, and a hormone, exerting its effects throughout the entire body. It is the most important sympathetic neurotransmitter. Noradrenaline binds both α and β adrenergic receptors but higher concentrations are required to activate β receptors. Its major action is to cause arteriolar vasoconstriction in the kidneys, intestine and skin and generalised venoconstriction. Noradrenaline also plays a role in the following, although to a lesser extent than adrenaline owing to a weaker affinity for β adrenergic receptors:

- arteriolar vasodilatation of skeletal muscle and heart
- relaxation of smooth muscle surrounding bronchioles, thus facilitating breathing
- raising blood glucose concentrations by promoting glycogenolysis
- promotion of lipolysis.

Cumulatively, these effects increase the availability of energy substrates and oxygen in the circulation and preferentially deliver these to the brain, heart and skeletal muscle.

2 Sample requirements and precautions

2.1 Medium in which measured
Noradrenaline is typically measured in plasma (lithium heparin) and urine. Serum is not suitable because catecholamines are stored in platelets and may be released during clotting and owing to its short half-life.

2.2 Precautions re sampling, handling etc.
1. A strict collection protocol is necessary for plasma noradrenaline. It is recommended that patients are supine, and have an indwelling catheter inserted at least 30 min prior to sample collection for basal samples. Blood should be collected into a chilled lithium-heparin tube.

2. Noradrenaline is labile in plasma. Samples should be centrifuged at 4 °C immediately following collection (never >20min after collection). The resulting plasma should be frozen immediately, using either dry-ice or a -40 °C freezer.
3. Urine samples must be collected into containers with acid (pH <3.5). A 24 h collection is preferred for adults and a random collection for children. In difficult cases, analysis of three separate collections may increase the clinical sensitivity of the test.

3 Summary of clinical uses and limitations of measurements

3.1 Uses
Noradrenaline measurements are used exclusively in the diagnosis and management of catecholamine-secreting tumours (see 6.1).

3.2 Limitations
Measurement of plasma noradrenaline concentrations are, in general, only useful when an individual with a suspected catecholamine-secreting tumour is experiencing an acute attack.

4 Analytical considerations

4.1 Analytical methods
Noradrenaline is measured by high performance liquid chromatography (HPLC) with electrochemical detection or HPLC coupled to liquid-chromatography tandem mass spectrometry (LC-MS/MS). Both methods require extraction of catecholamines prior to analysis.

4.2 Reference method
None

4.3 Reference materials
None

4.4 Interfering substances
Grossly haemolysed samples are unsuitable for analysis.

4.5 Sources of error
Amitryptiline can interfere with HPLC analysis of plasma noradrenaline, causing falsely elevated results.
Several drugs used to treat psychiatric patients prevent catecholamine reuptake and may increase urinary excretion.
The following can interfere in urine noradrenaline measurement:

- β-blockers
- paracetamol
- tricyclic antidepressants.

5 Reference intervals and variance

5.1.1 Reference interval (adults)
Plasma: <4.14 nmol/L
Urine: <560 nmol/24 h (derived in a hypertensive population)

5.1.2 Reference intervals (children)

Plasma: noradrenaline is not routinely measured in infants owing to artefacual increases caused by the stress of collection; however, reference ranges are as follows: 2–10 d <7.0 nmol/L; 10 d–3 m <12.3 nmol/L; 3 m–12 m <6.6 nmol/L; 1–2 y <10.7 nmol/L; 2–3 y <8.7 nmol/L; 3–15 y <7.4 nmol/L.

Urine: 0–24 m <280 nmol/mmol creatinine; 2–4 y <80 nmol/mmol creatinine; 5–9 y <59 nmol/mmol creatinine, 10–19 <55 nmol/mmol creatinine. A comprehensive schedule of reference values is provided in Davidson DF *et al*, Ann Clin Biochem 2011;48:358-366.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: (plasma) no data; 66.7% (urine)

5.1.3.2 Intraindividual CV: 19.5% (plasma) 39.9% (urine)

5.1.3.3 Index of individuality: no data; 0.60 (urine)

5.1.3.4 CV of method: approximately 10%

5.1.3.5 Critical difference 114% (urine)

5.1.4 Sources of variation

Stress, exercise, smoking and pain are all known to elevate plasma [noradrenaline] and hence urinary excretion. Hypertensive individuals are also known to have increased concentrations compared to normotensive individuals.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation

Measurements of noradrenaline are used:

- in the diagnosis of catecholamine-secreting tumours e.g. phaeochromocytomas and paragangliomas
- for localisation of phaeochromocytomas when venous catheterisation is performed
- to assess completeness of surgical removal of catecholamine-secreting tumours
- to assess recurrence of a catecholamine-secreting tumour following surgical removal
- to assist in confirmation of catheterization of an adrenal vein.
- (in urine) in the investigation of multiple endocrine neoplasia (MEN2)

6. Causes of abnormal results

7.1 High values

7.1.1 Causes

- phaeochromocytomas
- paragangliomas.

7.1.2 Investigation

When high concentrations or urinary excretion of noradrenaline are demonstrated, further investigation is by imaging and/or venous sampling for localisation of the source.

7.2 Low values

7.2.1 Causes

Pathologically low values do not occur.

7.2.2 Investigation

Not applicable

7.3 Notes
None

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions
Diagnosis of phaeochromocytomas: the values given are approximate. Exact values will depend on the precise cut-offs used.
Plasma: sensitivity 90%; specificity 90%
Urine: sensitivity 95%; specificity 95%.

9 **Systematic reviews and** guidelines

9.1 Systematic reviews
Peaston RT. Weinkove C. Measurement of catecholamines and their metabolites. Ann Clin Biochem 2004;41:17-38.

9.2 Guidelines
None identified

9.3 Recommendations
Pacak KG Eisenhofer G Ahlman H *et al*. International Symposium on Pheochromocytoma: recommendations for clinical practice from the First International Symposium, October 2005. Nat Clin Prac Endocrinol Metab 2007;3:92-102.

10. Links

10.1 Related analytes

Normetadrenaline is a metabolite of noradrenaline. This can be measured in both plasma and urine and is considered more sensitive than noradrenaline in the investigation of phaeochromocytomas.

10.2 Related tests
Noradrenaline is usually measured as part of a catecholamine assay set in combination with adrenaline and dopamine.

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