Information for Clinicians

Clinical Biochemistry Department

Investigation of Diabetes Insipidus using Copeptin

Principle:

Copeptin is the C-terminal peptide of the prohormone for AVP (arginine vasopressin) and is produced by the posterior pituitary on an equimolar basis with AVP (arginine vasopressin). It can be used to diagnose Diabetes Insipidus (DI).

In the absence of osmotic diuresis, polyuria (>3L/24hours) with early morning, fasted urine osmolality <750mOsm/Kg raises the possibility of:

- Central DI: insufficient production of the antidiuretic hormone arginine vasopressin (low AVP)
- Nephrogenic DI: reduced renal sensitivity to the antidiuretic activity of arginine vasopressin (high AVP)
- Primary polydipsia: primary excessive fluid intake (low/normal AVP).

Whilst AVP is difficult to measure due to pre-analytical variance, copeptin is stable and can be measured as a surrogate of AVP. Compared to the water deprivation test, copeptin has greater diagnostic accuracy than the water-deprivation test when measured during a hypertonic saline test.

Contra-indications:

Do not use in children or those with a significant history of cardiac failure, seizures, a history of significant cerebrovascular disease or severe uncontrolled hypertension.

Equipment

- Sphygmomanometer or BP recording machine
- Infusion pump with appropriate IV sets and cannulae
- 3 % saline (usually require 500-1000 ml)
- 5% glucose 500 ml
- Scales to weigh patient
- Yellow top (serum) tubes x7 for measurement of copeptin and osmolality (there is no requirement to take samples on ice for copeptin).

Preparation:

- Discontinue diuretic or antidiuretic medications for at least 24 hours before test.

- Fast patient from midnight before day of test. No tea, coffee, alcohol or smoking from midnight.
- Informed consent should be taken and the risks of the procedure documented.
- If taking pituitary hormone replacement therapy, this should continue at normal doses.
- Check serum sodium or plasma osmolality on morning of the test (urgent request) – must have result before starting infusion. Do not proceed if Na >147mmol/L.
- Telephone duty biochemist on extension 4050 on the morning of the test so they can oversee the sample handling in the lab
- Inform patient that they may experience symptoms of thirst, vertigo, mild headache, nausea and malaise.

Procedure:

1. For diagnosis of nephrogenic DI:

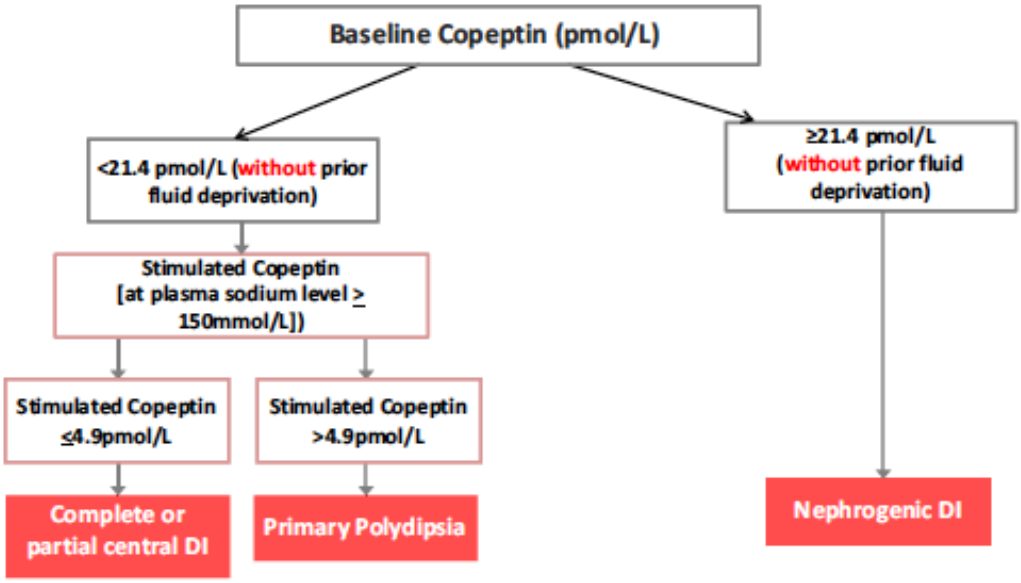
A single copeptin measurement **without water deprivation** is only validated when there is a strong clinical suspicion of nephrogenic diabetes insipidus (NDI). Send 1 yellow top (SST tube) to laboratory.

2. For differentiation of Central DI/Polydipsia

- Measure BP and weight hourly, the patient should be supine throughout.
- Insert cannulae into ante-cubital veins in both arms. Take blood sample from arm with cuff.
- Administer 250-ml bolus of 3% saline infusion over 20 minutes.
- Infuse 3% saline at 0.15 ml/kg/min into the non-blood sampling arm, until a serum sodium concentration of >150mmol/L is reached. **NB** If severe DI suspected reduce infusion rate to 0.07 ml/kg/min
- Take urgent blood gas samples for sodium at 30-minute intervals from start of infusion. Record these clearly with time of sampling in the patient notes.
- The total infusion time must not exceed 120 minutes.
- Whenever a patient achieves a sodium >150mmol/L – THE TEST IS STOPPED.
- Take Copeptin sample once Na >150mmol/L (yellow tube) and request a concurrent laboratory sodium.
- Give the patient water orally (30 ml of water per kilogram). Measure serum sodium again 1 hour after infusion stopped.

- If sodium remains high >150mmol/L give patient 500-ml infusion of 5% glucose. Measure serum sodium again 1 hour after the start of the glucose infusion to ensure that the levels are within the normal range before the patient is discharged

Interpretation:



- Nephrogenic DI, serum/plasma copeptin is inappropriately high (>21.4pmol/L) for the prevailing osmolality, consistent with vasopressin resistance; 100% sensitivity.

- Central DI have either undetectable copeptin levels during the progressive hyperosmolar stress, or values below 4.9pmol/L.

- In primary polydipsia, the relationship of serum/plasma copeptin to plasma osmolality is normal (copeptin >4.9pmol/L).

A stimulated copeptin level of at least 4.9pmol/L has 94% sensitivity and 96% specificity to differentiate primary polydipsia from CDI (partial and complete). (2)

References:

1. Fenske W, Quinkler M, Lorenz D, Zopf K, Haagen U, Papassotiriou J, Pfeiffer AF, Fassnacht M, Stork S & Allolio B. Copeptin in the differential diagnosis of the polydipsia-polyuria syndrome – revisiting the direct and indirect water deprivation tests. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1506–1515. (https:// doi.org/10.1210/jc.2010-2345)

2. Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Müller B, Katan M, and Christ-Crain M. Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study**.** J Clin Endocrinol Metab 2015 **100,** 2268–2274. (https://doi.org/10.1210/jc.2014-4507)

3. Christ-Crain M. New diagnostic approaches for patients with polyuria polydipsia syndrome. *European Journal of Endocrinology* 2019 **180**, R11–R21 (https://doi.org/10.1530/EJE-19-0163)

Amendment History

Issue	Status	Date	Reason for Change	Authorised