Saline stress test for investigation of Diabetes Insipidus

1. Introduction

1.1 Scope and Purpose

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 <600mOsm/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.

1.2 **Responsibility**

The protocol will be jointly implemented by endocrinology and chemical pathology teams with the assistance of medical day case unit staff.

1.3 **Definitions**

Nil relevant

1.4 **Indications**

Those where diabetes insipidus is highly suspected and requires differentiation between sub-types. This test is **not** suitable for differentiating psychogenic polydipsia from Diabetes insipidus – consider other more simple tests or water deprivation.

1.5 **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.

1.6 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
- 10ml syringes to draw blood from the cannula each time for sampling
- Yellow top (serum) tubes x7 for measurement of copeptin and osmolality (there is no requirement to take samples on ice for copeptin) and VBG syringes.

2. 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 48437 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.

3. **Procedure:**

3.1 **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.

3.2 For differentiation of Central DI/Polydipsia

- Follow worksheet in Appendix B
- Measure BP and weight hourly, the patient should be supine throughout.
- Insert cannulae into ante-cubital veins in both arms. Choose one arm to take blood samples with aid of a cuff. Consistently use the other arm for infusion.
- **Take baseline sample for U&E, Osmolality, glucose and copeptin**
- **Initial infusion:** administer 250-ml bolus of 3% saline infusion over 20 minutes into non-blood sampling arm
- **Further infusion:** infuse 3% saline at 0.15 ml/kg/min into the non-blood sampling arm,. NB If severe DI suspected reduce infusion rate to 0.07 ml/kg/min.
- Take samples for blood gas and lab serum samples at 30-minute intervals from start of infusion. Record these clearly with time of sampling in the patient notes. **Refer to sample collection table (Appendix B) for tests to be taken at each 30-min time interval.**
    - Serum samples should be sent urgently to the laboratory by hand
    - **Use the VBG sodium result at each 30minute interval and stop the infusion when the VBG sodium result >/=150mmol/L is reached. Wait for the lab sodium result – the saline infusion is confirmed to be stopped if the lab sodium confirms a result of >/=148mmol/L.**
    - If the lab sodium result is <148mmol/L, then the saline infusion should be considered for a further 30mins to the next sampling point. Note: the serum sodium level may continue to rise for a short period of time after stopping the infusion so recommencing may not always be necessary if limited oral fluid has yet been taken.

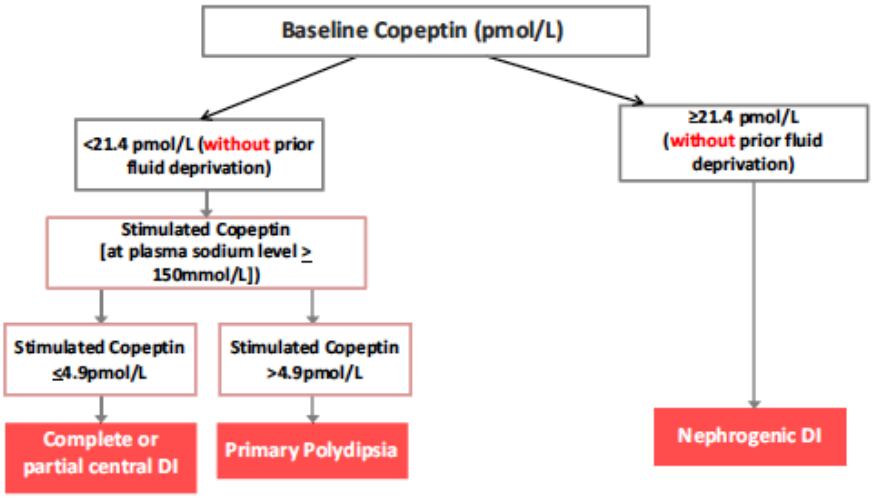
- At the point the procedure is stopped, go to Step G in the Appendix A protocol table and follow the sample collection at the specified time interval. Give the patient water orally (30 ml of water per kilogram).
- At 90minutes post the stopping of the procedure, if the sodium remains >/=148mmol/L, give 500ml 5% glucose as per point J in protocol table.

4. Results reporting

- Samples for sodium and osmolality will be processed through the urgent sample pathway in the automated laboratory– it is important that samples are clearly marked, sent separate to other samples so as not to be lost, and transported urgently to the lab, ideally within 10minutes of sampling to ensure no delay in analysis prior to the next sampling point.
- The baseline copeptin and the 1st copeptin where the lab sodium rises to >/=148mmol/L will be sent to the referral lab by the biochemistry department. All other Copeptins, both subsequent samples where the sodium is high, will be stored for 2 weeks
- It should take 2 weeks for the copeptin results to be returned with appropriate comments on interpretation (See Appendix A)

5. 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



6. References:

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Appendix A – Interpretative comments on Copeptin results

Action limit	Other factors to consider/tests to add
Stimulated Copeptin >4.9pmol/L	COP1 Copeptin response to hyperosmolar stimulation is .... normal and not consistent with a diagnosis of .... central diabetes insipidus (most patients with .... central DI do not achieve a copeptin concentration .... above 5pomol/L upon saline infusion).
Day 1 post-surgery copeptin <5.0pmol/L	COP2 Central diabetes insipidus cannot be excluded. .... However, some healthy individuals have a low .... serum copeptin in the absence of significant .... osmotic stimulus. Samples taken where there is not .... sufficient osmotic stimulus may be of limited .... diagnostic use.
Stimulated Copeptin <5.0pmol/L	COP3 This copeptin concentration under hyperosmolar .... stimulation suggests central diabetes insipidus .... (most patients without central DI achieve a .... copeptin of at least 5pmol/L with osmotic .... stimulation).
Day 1 post-surgery copeptin >4.9pmol/L	COP4 Samples taken where there is not sufficient .... osmotic stimulus may be of limited diagnostic .... use. However, central diabetes insipidus is .... unlikely in view of copeptin concentration (most .... patients with central DI do not achieve a copeptin .... concentration above 5pmol/L upon water deprivation .... or saline infusion).
Unstimulated >21.4pmol/L	COP5 This result if taken without osmotic stimulus (i.e .... a random sample) suggests nephrogenic diabetes .... insipidus.

Appendix B: HYPERTONIC SALINE STRESS TEST WORKSHEET

Hospital no:
NHS no:
Surname:
Forename:

Step	Clock Time	Time	Procedure(s)	Samples (ensure labelled with time)	Biochemistry	Additional comments
A		-30	Consent □ Weight □ Patient to lay supine □ Blood pressure □ Insert cannulae into ante-cubital veins in both arms □ Take blood samples after 30 minutes of rest □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.** **Wait for results prior to starting infusion!** **If lab sodium ≥148 mmol/L – STOP TEST AND PROCEED TO STEP G.**	Lab Sodium …… VBG Sodium …….. Urea …….. Osmolality …….. Glucose ……..	
B		0	Administer 250 mL bolus infusion of hypertonic saline infusion over 20 minutes □			

C		20	Infuse hypertonic saline at 0.15 mL/kg/min □ (Until a serum sodium concentration of ≥148 mmol/L or a total infusion time exceeded 120 minutes into non-blood sampling arm)			**Prescribe as 0.15 x weight in kg x 100 mL over 100 minutes**
D		30	Take blood samples □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.** **If VBG sodium ≥150 mmol/L – STOP TEST AND WAIT FOR CONFIRMATION BY LAB SODIUM. PROCEED TO STEP G IF LAB SODIUM >/= 148MMOL/L.**	Lab Sodium …… VBG Sodium …….. Urea …….. Osmolality ……..	
E		60	Take blood samples □ Blood pressure □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.** **If VBG sodium ≥150 mmol/L – STOP TEST AND WAIT FOR CONFIRMATION BY LAB SODIUM. PROCEED TO STEP G IF LAB SODIUM >/= 148MMOL/L.**	Lab Sodium …… VBG Sodium …….. Urea …….. Osmolality ……..	

F		90	Take blood samples □ Blood pressure □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.** **If VBG sodium ≥150 mmol/L – STOP TEST AND WAIT FOR CONFIRMATION BY LAB SODIUM. PROCEED TO STEP G IF LAB SODIUM >/= 148MMOL/L.**	Lab Sodium …… VBG Sodium …….. Urea …….. Osmolality ……..	
G		120	**Stop saline infusion** □ Take blood samples □ Blood pressure □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.**	Lab Sodium …… VBG Sodium ……. Urea …….. Osmolality ……..	

H		135	Take blood samples □ Give patient water orally (30 mL of water per kilogram) □	1x yellow top (U&Es, osmolality, glucose, copeptin). **Also run VBG for sodium and document.**	Lab Sodium …… VBG Sodium Urea …….. Osmolality …….. Glucose ……..	
I		180	Take blood samples □ Blood pressure □ Weight □	1x yellow top (U&Es, osmolality) **Also run VBG for sodium and document.**	Lab Sodium …… VBG Sodium Urea …….. Osmolality ……..	
J		210	**If required (sodium remains ≥148 mmol/L)** - give patient 500 mL infusion of 5% glucose □ Blood pressure □	1x yellow top (U&Es, osmolality). **Also run VBG for sodium and document.**	Lab Sodium …… VBG Sodium …….. Urea …….. Osmolality ……..	