INVESTIGATION OF POLYURIA/POLYDIPSIA SYNDROME WITH THE ARGININE-STIMULATED COPEPTIN TEST

TARGET AUDIENCE	Specialists in Endocrinology including specialist nurses, registrars and consultants
PATIENT GROUP	Adult patients aged 16 years and over referred to the Endocrinology service for investigation and management of polyuria/polydipsia syndrome

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Clinical Guideline Summary

- Differentiating between primary polydipsia and arginine vasopressin deficiency (AVP-D: previously termed diabetes insipidus (DI)) can be difficult considering the limitations and practical challenges of water deprivation testing.
- The gold standard test – the hypertonic saline infusion test – can only be performed in large centres with medical staffing and facilities for immediate electrolyte analysis by means of blood gas testing.
- The arginine-stimulated copeptin test (ACT) provides an alternative diagnostic test with high accuracy that can be performed in the District General Hospital setting without the need for a medically staffed day patient area.
- Pre-test screening with blood samples in the outpatient clinic is recommended prior to referral for an ACT.
- The blood samples taken during the ACT itself are sent to a reference laboratory with a turnaround time of approximately 3 weeks.

Background

Polyuria/polydipsia syndrome (PPS) is an uncommon but important condition referred to the endocrinology service. The differential diagnosis is typically between primary polydipsia (PP) and arginine vasopressin deficiency (AVP-D) or resistance (AVP-R), previously termed cranial/central diabetes insipidus and nephrogenic diabetes insipidus, respectively. Differentiating between PP and AVP-D is often challenging due to limitations in both the availability and reliability of the previously gold standard investigation, the water deprivation test (WDT). The arginine-stimulated copeptin test (ACT) is an alternative test that is less time consuming, more straightforward, and has higher diagnostic accuracy than the WDT.

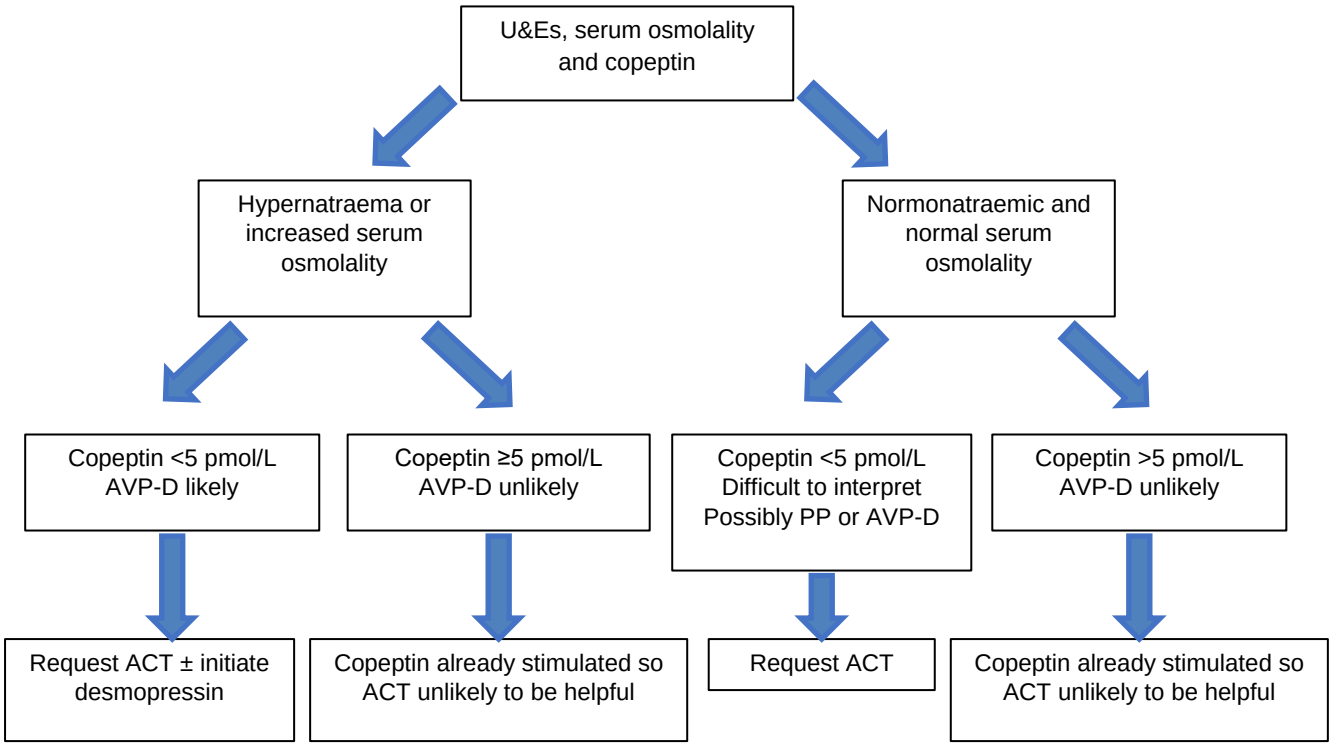
Copeptin is a peptide cleavage product of AVP synthesis and release. Copeptin has no endocrine activity of its own but is more stable and easier to measure in the blood than AVP. The relationship between copeptin and AVP is essentially analogous to the one between c-peptide and insulin.

Arginine (also termed l-arginine) is an amino acid which, when administered by intravenous infusion, stimulates the release of AVP from the posterior pituitary. As an increased serum osmolality is a more potent stimulus for AVP (and, therefore, copeptin) release than arginine infusion, the hypertonic saline infusion test (HSIT) has a higher degree of diagnostic accuracy but carries risks associated with inducing hypernatraemia and must be closely supervised by medical staff. The ACT, however, does not result in electrolyte derangement and can be safely carried out without medical supervision.

L-arginine monohydrochloride, 210.7 mg per 1 ml solution for infusion, is the medicinal product used during the test. This is imported from a non-UK manufacturer and is an unlicensed medicine. The appropriate unlicensed medicine authorisation was sought and approved when this clinical guideline was accepted.

Pre-test biochemical screening

When evaluating a patient with PPS in clinic, it is recommended to check U&Es, serum osmolality and random copeptin prior to requesting the ACT:



N.B. Extremely high copeptin (>21.4 pmol/L) suggests AVP-R: an ACT is not indicated to make the diagnosis.

How to request the ACT

One the decision is made to request an ACT, the referring clinician dictates a referral letter to the Planned Investigation Unit (or equivalent day unit area) so that an appointment can be arranged and the patient can be sent a pre-test information leaflet. Secretarial staff will send a PIU pack including test request sheet and day unit prescription chart to allow the clinician to prescribe the arginine infusion.

The dose of arginine infused during the test is weight dependent (0.5g/kg to a maximum of 40g). Use the patient's clinic weight rounded to the nearest 5kg:

Weight (kg)	Dose of l-arginine (g)	Number of l-arginine 20 ml ampoules	Volume of l-arginine solution (ml)	Volume of 0.9% sodium chloride (ml)
50	25	6	120	380
55	27.5	6.5	130	370
60	30	7	140	360
65	32.5	7.5	150	350
70	35	8	160	340
75	37.5	9	180	320
≥80	40	9.5	190	310

For example, in a 75kg patient, the prescription is written as follows:

"L-arginine hydrochloride (21%) 180 ml in 0.9% sodium chloride 320 ml
IV over 30 minutes (1000 ml/hour)"

Patient preparation

The referring clinician should discuss the test with the patient when making the referral. The patient must sign a consent form to acknowledge that they will receive a medicine sourced from a foreign manufacturer. A written information leaflet will be provided when they are given an appointment for the test and will include the following instructions:

- Fast from midnight prior to the test (which will be a morning appointment).
- Fluids are permitted until 2 hours prior to the test.
- If prescribed desmopressin, this **must** be discontinued for 24 hours prior to the test.
- All other medications, including non-desmopressin pituitary hormone replacement, can be taken as normal.
- Unrestricted fluid intake, diet and desmopressin (if prescribed) can resume at the end of the test.

Test protocol

Requirements

- L-arginine hydrochloride (21%) solution for infusion 20 ml ampoules (6 to 10)
- 0.9% sodium chloride 500 ml
- 4 gold top blood tubes
- IV cannula (pink 20G)

Patient preparation

- The patient should be warned that arginine can cause nausea and irritation at the infusion site – if only mild symptoms are experienced, the test can continue.
- Potential rarer side effects include headache, vomiting, vertigo and facial paraesthesia – if any of these occur and are severe, the test should be abandoned.
- Arginine can cause vasospasm, so it is recommended to use a minimum cannula size of 20G (pink) inserted into a vein in the antecubital fossa.
- Ensure the patient is lying on a bed or fully reclined chair during the test as hypotension can result (BP may fall by approximately 20-30 mmHg during the infusion).

Procedure

- Inform the laboratory that samples for copeptin will be arriving – they should be received by the laboratory within 2 hours of sampling.
- Record pulse and BP at the start of the test then every 15 minutes until the test is completed.
- Insert IV cannula (pink 20G) into an antecubital vein and take blood for the baseline samples (see table below).
- Infuse l-arginine diluted in 0.9% sodium chloride over 30 minutes as per prescription chart.
- Take blood for the 60-minute samples (see table below).
- The patient can now eat and drink normally and resume their desmopressin (if prescribed).

Time (minutes)	Samples collected
0: baseline	2 gold top blood tubes: (1) U&Es and serum osmolality (2) Copeptin
60: end of test	2 gold top blood tubes: (1) U&Es and serum osmolality (2) Copeptin

Interpretation of results

If the 60-minute sample shows a copeptin <3.8 pmol/L, this is suggestive of AVP-D (93% sensitivity, 92% specificity and 93% diagnostic accuracy).

If the 60-minute sample shows a copeptin >3.8 pmol/L, this is more suggestive of PP.

References

Refardt, J. *et al.* (2023) 'Arginine or Hypertonic Saline–Stimulated Copeptin to Diagnose AVP Deficiency', *The New England journal of medicine*, 389(20), pp. 1877–1887. Available at: https://doi.org/10.1056/NEJMoa2306263.

Winzeler, B. *et al.* (2019) 'Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study', *The Lancet (British edition)*, 394(10198), pp. 587–595. Available at: https://doi.org/10.1016/S0140-6736(19)31255-3.

Appendices

1. Governance information for Guidance document

Lead Author(s):	Dr Craig Thurtell
Endorsing Body:	ADTC
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Responsible Person (if different from lead author)	

CONSULTATION AND DISTRIBUTION RECORD	
Contributing Author / Authors	Dr Craig Thurtell (UHM Consultant, Endocrinology & Diabetes)
Consultation Process / Stakeholders:	NHSL consultants in endocrinology & diabetes (across all 3 acute hospital sites) and the endocrinology specialist nurses (cross site).
Distribution	Circulate to Endocrinology departments and day patient areas in all 3 acute hospital sites

CHANGE RECORD			
Date	**Lead Author**	**Change**	**Version No.**
		e.g. Review, revise and update of policy in line with contemporary professional structures and practice	

2. Patient information to be sent to patient when test is requested

Patient information – Arginine-stimulated Copeptin Test (ACT)

Why am I being referred for this test?

The ACT is a test to help your doctor find out why you have been passing an excessive volume of urine (polyuria) and/or been experiencing excessive thirst (polydipsia).

The test relies on the measurement of a substance in the blood called copeptin which is released by your pituitary gland (hormone releasing gland on the underside of the brain) whenever it releases vasopressin – the main hormone involved in the regulation of water balance. Vasopressin itself is difficult to measure in a blood test which is why copeptin is used instead.

If a person does not produce enough vasopressin due to a problem with the pituitary gland, they tend to pass large volumes of urine each day and feel excessively thirsty as a result. This condition is referred to as *arginine-vasopressin deficiency (AVP-D)* which was previously termed *diabetes insipidus*. In this condition, the ACT would show low levels of copeptin.

Some people pass a large volume of urine each day because they drink a large volume of fluid. Their pituitary gland works normally. This is referred to as *primary polydipsia*. In this condition, the ACT would show normal levels of copeptin.

How is the test carried out?

You will be given a morning appointment in the Planned Investigation Unit (PIU) for the test. You will be asked to lie down on a reclined chair or bed for the duration of the test. Your pulse and blood pressure are checked periodically throughout.

An intravenous cannula (a plastic tube introduced into a vein using a needle) will be inserted into a vein in your arm near the elbow. Some blood samples are taken as the cannula is inserted. Once the cannula is secured in place with a dressing, a solution of a medication called arginine is given through it over 30 minutes. A final set of blood tests are taken 30 minutes after the arginine infusion has finished. After the second blood test has been taken you will be able to leave PIU. From start to finish, the whole procedure should take less than 2 hours.

What are the potential side effects?

The ACT is a safe test but there are some side effects you should be made aware of.

The arginine solution can result in irritation of the vein as the solution is given and it may also result in feeling nauseated. Your blood pressure may also decrease which is normal. You will be lying down throughout the test in case your blood pressure does decrease.

Rarer side effects of the arginine solution include headache, vomiting, vertigo (a feeling of things rotating or spinning around you) and numbness or pins and needles of the face. If these symptoms occur and are very mild, the test can continue. If, however, they are more severe, the test will be stopped early.

How should I prepare for the test?

Please follow these instructions to prepare for the test:

- Fast from midnight prior to the test (which will be a morning appointment);
- Fluids are permitted until 2 hours prior to the test;
- If prescribed desmopressin, this must be discontinued for 24 hours prior to the test;
- All other hormone replacement and medications can be taken as normal;
- Unrestricted fluid intake, diet and desmopressin (if prescribed) can resume at the end of the test.

When can I expect the result?

The blood samples for copeptin testing must be sent to a laboratory in Newcastle

with an estimated turnaround time of 3 weeks for the report. The doctor who requested the ACT will then need to interpret your results before communicating them to you and your GP. You can therefore expect to wait approximately 5-6 weeks to learn the result.