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ANTERIOR PITUITARY FUNCTION

BASAL INVESTIGATIONS

INDICATIONS

Initial investigation of pituitary function

CONTRAINDICATIONS

None

PRECAUTIONS

Be aware of relevant medication history including oestrogen containing preparations (elevate CBG and therefore false elevation of cortisol), exogenous steroid (may suppress endogenous cortisol secretion, or in the case of hydrocortisone or cortisol acetate, interfere with the assay), preparations which elevate prolactin etc

PREPARATION

None specific

PROCEDURE

Take blood sample for the following:

1. Gonadal axis:

Men – LH, FSH, testosterone (9am), SHBG

Women – LH, FSH, oestradiol, progesterone (day 21 if menstruating), SHBG

2. Growth hormone: GH, IGF-1

3. Prolactin: on 2 occasions and with relaxation if elevation suspected

4. Thyroid axis: TSH, fT4, (fT3 in specific cases)

5. Adrenocortical axis: serum cortisol (9am), plasma ACTH in specific cases

6. Posterior pituitary: paired plasma and urine osmolality

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INTERPRETATION

LH/FSH:

In the male, if serum testosterone is adequate then gonadotrophin secretion must be adequate. Inadequate gonadotrophin secretion may be diagnosed on the basis of a low testosterone without an appropriate rise in LH and FSH.

In the female, day 21 progesterone >30nmol/l implies ovulation and therefore a normal axis. LH, FSH and oestradiol must be interpreted in the context of the day of the cycle. (Hyperprolactinaemia can suppress LH and FSH in the absence of absolute deficiency.)

GH:

Secretion of GH is pulsatile and therefore of limited value although usually <1ng/mll in normal individuals.

Prolactin:

Estimation of prolactin on 3 occasions and after relaxation provides sufficient diagnostic information. You may need to request a dilution (to exclude a false low reading due to the 'hook effect' in the assay) or for PEG precipitation – the percentage recovered after this represents monomeric prolactin without macroprolactin.

TSH:

Low T4 without elevation of TSH indicates a hypothalamic or pituitary cause of hypothyroidism, except in the sick euthyroid syndrome, or where there are significant changes in binding proteins..

ACTH:

If basal cortisol is >500nmol/l, significant deficiency is unlikely. If serum cortisol <100nmol/l then ACTH deficiency is present (unless patient taking exogenous steroid). With intermediate values the adequacy of the hypothalamo-pituitary axis must be evaluated by a stimulation test (eg ITT). ACTH deficiency will usually lead to an impaired response on a short Synacthen test but this cannot exclude mild or recent deficiency.

SENSITIVITY AND SPECIFICITY

Dependent on assay used

REFERENCES

Stewart PM et al. *Lancet* 1 1208-1210 (1988).

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ANTERIOR PITUITARY STIMULATION TESTS

INSULIN TOLERANCE TEST (ITT)

INDICATIONS

Assessment of ACTH and cortisol reserve.
Assessment of GH reserve in children with definite growth retardation
GH response in adults (see also GH protocols)
Differentiation of Cushing's syndrome from depression (rarely needed).

CONTRAINDICATIONS

Ischaemic heart disease
Epilepsy or unexplained blackouts
Untreated hypothyroidism (impairs GH and cortisol response).
Severe longstanding hypoadrenalism (liver glycogen stores are depleted, causing severe hypoglycaemia during the ITT) / Serum cortisol <100nmol/L
Glycogen storage disease

PRECAUTIONS

ECG must be normal
Serum cortisol (9am) must be >100nmol/l (ACTH deficiency is unlikely if serum cortisol 400-500nmol/l or more)
Serum T4 must be normal (replace first if low)
If abnormal, or if in doubt, perform glucagon test instead
Side effects include: sweating, palpitations, loss of consciousness and occasionally convulsions.

PREPARATION

Fast overnight (water permitted); perform test recumbent.
Discontinue hydrocortisone 24 hours (or at least prior 2 doses)
Medications can be given after completion of the test ie by lunchtime.
In peri-pubertal children (bone age > 10 years) priming is needed

Males:	100 mg testosterone enanthate i.m. (single injection) 3 days before test
Females:	100 mcg ethinyloestradiol p.o. each for three days before the test.

Calculate Actrapid Insulin dose:

Usual dose	0.15 U/kg
Acromegaly, type 2diabetes, Cushing's	0.3 U/kg

50mls 50% dextrose must be available for immediate administration (but only use if persistent severe hypoglycaemia). If this is required, CONTINUE SAMPLING!

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PROCEDURE

- At all times a doctor or nurse must be in attendance.
- Site indwelling cannula. At 0 minutes, take baseline bloods and then inject insulin i.v.
- Take samples for GH, cortisol and glucose (check glucose on glucometer with each sample) at 0, 30, 45, 60, 90, and 120 mins, flushing the cannula with saline between samples.
- At 30 minutes check whole blood glucose with Glucometer and repeat the insulin dose if not hypoglycaemic (this will mean prolonging sampling by 30 min).
- If insulin dose repeated: restart the clock and collect at t= 0, 30, 45, 60, 75, 90, 120, 150 mins.
- Adequate hypoglycaemia (≤2.2mmol/l) necessary. Record symptoms in the notes.
- There must be at least 2 specimens following adequate hypoglycaemia. Patient need not be hypoglycaemic throughout. Lowest glucose level following IV insulin is usually at 20-30 minutes, with spontaneous resolution. Obtain specimen for glucose before reversal.
- If needed, reverse hypoglycaemia orally (juice/Lucozade). If severe/patient unrousable consider i.v. 20% dextrose (10-15 ml) or 1 mg i.m. glucagon (1 amp), and continue sampling.
- If patient has a hypoadrenal crisis give i.v. 0.9% saline and hydrocortisone 100 mg.
- Once test completed, give supervised meal. Patient should not drive for 2 hours after the test.

INTERPRETATION

- The test cannot be interpreted unless hypoglycaemia (≤2.2mmol/l) is achieved.
- Adequate cortisol response is defined as a rise to above 500 nmol/l.
- Patients with normal cortisol response (as defined above) can withstand major surgery without steroid replacement.
- Patients with satisfactory basal values (>250nmol/L) but subnormal stimulated values require cover for major illnesses and surgery and carry a steroid card and/or MedicAlert bracelet.
- All other patients with subnormal responses require hydrocortisone replacement
- Adequate GH response is a rise >6ng/ml.
- In children a rise to greater than 12 ng/ml is considered normal.

SENSITIVITY AND SPECIFICITY

- If adequate hypoglycaemia is not achieved then deficiency cannot be diagnosed.
- 5-15% of 'normals' will show a suboptimal response.
- 20% of patients with Cushing's syndrome will show a rise greater than 170nmol/l but a rise of less than this is rare in depression or alcoholic pseudo-Cushing's.
- GH responses are reduced in 20% of normal children and some small children whose peak GH is 3-6ng/ml may benefit from GH replacement.
- See section on adult GH replacement for further information on GH replacement

REFERENCES

Plumpton et al., Br. J. Surg. 56, 21 (1969).
Greenwood et al., J. Clin. Invest. 45, 429 (1965).
Hurel SJ et al. *Clin.Endocrinol.(Oxf)* 44 141-146 (1996)
Jones SL et al. *Clin Endocrinol (Oxf)* 41 123-128 (1994)

GLUCAGON TEST

INDICATIONS

Assessment of growth hormone and ACTH/cortisol reserve especially when insulin-induced-hypoglycaemia is contra indicated.

CONTRAINDICATIONS

Phaeochromocytoma or insulinoma (may provoke an attack)

Severe hypocortisolaemia (09.00h level <100 nmol/l)

Thyroxine deficiency may reduce GH and cortisol response.

Starvation >48 hours / glycogen storage diseases (hypoglycaemia from inability to mobilise glycogen)

PRECAUTIONS

Serum cortisol must be >100nmol/l

Serum T4 must be normal (replace first for several weeks if low)

Patient must be supervised at all times

Children <4 need to be admitted the previous day

Side effects include nausea (in 30%) and occasional vomiting.

PREPARATION

Fasting from midnight.

Calculate glucagon dose:

Adults: 1 mg (1.5mg if > 90kg)

Children: 15µg/kg

PROCEDURE

- Continuous observation less important than for ITT as no hypoglycaemia provoked.
- Insert an indwelling cannula and take basal samples for glucose, cortisol and GH.
- Administer i.m. glucagon and take further samples at 90, 120, 150, 180, 210 and 240 minutes.
- Observe for 2hours and allow to go home if BM >4mmol/l.

INTERPRETATION

- Blood glucose usually falls to a peak around 90minutes and then falls.
- Adequate cortisol response is defined as a rise to above 550nmol/l. Adequate GH response is a rise to a value greater than 6ng/ml.

SENSITIVITY AND SPECIFICITY

Slightly less reliable test of somatotroph and corticotroph function than the ITT.

However, it is an excellent alternative in patients who cannot tolerate hypoglycaemia because of epilepsy or ischaemic heart disease.

REFERENCES

Rao R.H. et al., Metabolism 36, 658-663 (1987).
Mitchell ML et al. *N.Engl.J.Med.* 282 539-541 (1987).

THYROTROPHIN RELEASING HORMONE (TRH) TEST

INDICATIONS

- Seldom clinically useful – does not provide any additional information for the diagnosis of secondary hypothyroidism or predicting a risk of developing TSH deficiency.
- Diagnosis of thyroid hormone resistance
- Diagnosis of TSHoma

CONTRAINDICATIONS

Allergy (rare)

PRECAUTIONS

- Patients should be warned that they may have transient side effects after the injection: metallic taste in the mouth, flushing and mild nausea, desire to micturate.
- TRH significantly increases blood pressure.
- Very rarely, pituitary tumour haemorrhage or infarction has been described, with severe headache.
- TRH could precipitate pituitary apoplexy in pituitary macroadenoma.

PREPARATION

Stop thyroxine for 3 weeks prior to test so this test (therefore rarely used in people on thyroxine.)

Overnight fast not necessary.

Dose of TRH: 200 μg TRH at 9am.

PROCEDURE

- Patient should be supine
- Site indwelling cannula and take baseline bloods for TSH and thyroxine.
- Inject TRH slowly i.v. over 2 minutes at 9am then flush with saline.
- Take samples for TSH at t = 0, 20 mins and 60 mins.

INTERPRETATION

- The normal result is a TSH rises by more than 2 mU/l to greater than 3.4 mU/l. The 20 min value is higher than 60 min value.
- If the 60 min sample exceeds the 20 min value then this usually indicates primary hypothalamic disease, but may sometimes be seen in pituitary disease or primary hypothyroidism.
- In hyperthyroidism, and in euthyroid Graves' opthalmopathy, the TSH remains suppressed and fails to respond to TRH.
- In hypothyroidism there is an exaggerated response. With the current sensitive TSH assays basal levels are now adequate and dynamic testing is not usually needed to diagnose hyperthyroidism.
- Thyroid hormone resistance is associated with a normal or exaggerated response.
- In TSHoma, there is no response to TRH.

SENSITIVITY AND SPECIFICITY

Inadequate TSH rise is not an indication for thyroxine replacement unless free T4 is reduced.

REFERENCE

Hall et al., Lancet i: 759-63 (1972).
Yoshino A et al. *Acta Neurochir.(Wien.)* 149 557-565 (2007)
Brucker-Davis F et al. *J.Clin.Endocrinol.Metab* 84 476-486 (1999)

GONADOTROPHIN RELEASING HORMONE [GnRH/LHRH] TEST

INDICATIONS

Principal use is to confirm precocious puberty.
Rarely required to further investigate possible gonadotrophin deficiency.

CONTRAINDICATIONS

Allergy

PRECAUTIONS

Basal tests frequently sufficient to diagnose gonadotrophin deficiency therefore consider carefully if dynamic testing indicated

PREPARATION

Overnight fast not necessary unless combined with ITT.
Where menstrual cycle is normal perform the test in the follicular phase (day 3-7 of the cycle).
Larger dose or priming with GnRH if suspected of hypogonadism may be necessary.
(N.B. Do not prime with sex steroids if test is being carried out to confirm precocious puberty)
Dose required: 100 mcg GnHRH (Gonadorelin).

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PROCEDURE

- Site indwelling cannula and take baseline bloods: LH, FSH and testosterone (M) or oestradiol (F).
- Inject GnRH intravenously and flush cannula with saline.
- Take samples for LH and FSH at t = 30 and 60 mins.

INTERPRETATION

The normal peaks can occur at either 30 or 60 minutes. LH should exceed 10 U/l and FSH should exceed 2 U/l. An inadequate response may be an early indication of hypopituitarism.

Normal ranges:

	Serum LH (mU/l)		**Serum FSH (mU/l)**	
	20 min	60 min	20 min	60 min
Female	15-42	12-35	1-11	1-25
Male	13-58	11-48	1-7	1-5

Pre-pubertal children should have no response of LH or FSH to LHRH. If sex steroids are present (i.e. the patient is undergoing precocious puberty), the pituitary will be "primed" and will therefore respond to LHRH. Do NOT prime with steroids before this test. Note that the test cannot readily discriminate delayed puberty from gonadotrophin deficiency.

SENSITIVITY AND SPECIFICITY

This test does not diagnose gonadotrophin deficiency but rather the level of reserve of LH/FSH secretion.

In a male hypogonadotrophic hypogonadism is diagnosed on the basis of a low serum testosterone without elevation of basal gonadotrophins.

In a female hypogonadotrophic hypogonadism is diagnosed on the basis of amenorrhoea, low serum oestradiol without elevated gonadotrophins and no LH/FSH response to clomiphene.

The response on the GnRH test may be subnormal (particularly in primary pituitary disease), normal or even exaggerated (especially in patients with hypothalamic disease).

REFERENCE

Mortimer et al., BMJ, 3: 267-271.

Corticotrophin releasing hormone test (CRH TEST)

INDICATION

Additional information in the differential diagnosis of Cushing's Syndrome (see also Cushing's protocols)

CONTRAINDICATIONS

None specific

PRECAUTIONS

None specific

CRH causes flushing in many patients

PREPARATION

Fast from midnight and perform the test after overnight recumbency

PROCEDURE

Take two baseline samples at t=–15 mins (8.45 am) and t=0 mins (9am) for ACTH and Cortisol.

Administer 100 micrograms human CRF intravenously at t=0 (or 1μg/kg in children).

Further blood samples samples at 15, 30, 45, 60, 90 and 120 mins (final sample 11am: for ACTH and cortisol at all timepoints.).

INTERPRETATION.

A rise in **cortisol** from basal to peak of >20% suggests a pituitary source.

A rise in **ACTH** from basal to peak of > 50% suggests a pituitary source.

A small proportion of patients with true Cushing's syndrome have a flat response to CRH.

A peak cortisol >900 nmol/l plus a rise >20% is strongly suggestive of Cushing's disease.

SENSITIVITY AND SPECIFICITY

ovine (oCRH) was used in most studies. Human (hCRH) appears less potent, so smaller rises may still be suggestive of Cushing's disease.

REFERENCES

Kaye and Crappo (1990). Ann Intern Med. 112: 434-444

Nieman etal (1993). JCEM 77: 1308-1312.

Growth hormone releasing hormone (GHRH) TEST (SECOND-LINE TEST OF GH RESERVE)

INDICATIONS

Differential diagnosis of isolated GH deficiency

CONTRAINDICATIONS

Allergy

PRECAUTIONS

Patients should be warned that flushing is likely.

Marked transient hypotension may occur.

PREPARATION

Fast from midnight.

Patient to remain recumbent until 9am (and fasted).

PROCEDURE

- IV cannula at 8.30 am and take basal cortisol and ACTH at 8.30am.
- Take two further baseline samples at –15 mins (8.45 am) and 0 mins (9am) for GH
- Administer 100 micrograms $GHRH_{(1-29)}$amide iv at t=0 (children's dose 1µg/kg.

Then sample at 15, 30, 45, 60, 90 and 120 mins for GH at all timepoints.

INTERPRETATION.

Patients with isolated GH deficiency, including after radiotherapy, frequently show a GH response to GHRH within normal limits (>4 ng/ml), implying hypothalamic GHRH deficiency. The test cannot be used to show normality of GH secretion.

REFERENCES

Grossman et al (1984) Clin Endo 21:321

Ross et al (1987) Lancet i:5

CLONIDINE TEST (SECOND-LINE TEST OF GH RESERVE)

INDICATIONS

Assessment of GH reserve when ITT contraindicated.

Limited clinical value; occasionally used as part of a research protocol

CONTRAINDICATIONS

None

PRECAUTIONS

Systolic BP falls by 20-25mmHg in all subjects

Patient should lie down for 2 hours after the test or until blood pressure is satisfactory.

PREPARATION

Fast from midnight.

PROCEDURE

- IV cannula at 8.30 am and take basal GH at 8.30am.
- Clonidine 0.15mg/m^2 orally at 9am
- Measure blood pressure every 30 minutes
- Take further samples at 30, 45, 60, 90, 120 and 150 mins for GH at all timepoints.

INTERPRETATION

If the GH rises above 10 ng/ml, the GH reserve is probably normal.

SENSITIVITY AND SPECIFICITY

Since the mechanism and locus of action of the test is uncertain, interpretation is of uncertain significance. The test is more accurate in children, and can be highly sedative.

REFERENCES

Milner, Burns (1982) Arch Dis Child 57: 944

ARGININE INFUSION [SECOND-LINE TEST OF GH RESERVE]

INDICATIONS

Assessment of GH reserve when ITT contraindicated, but of limited clinical value

Used in a child with definite growth retardation and a subnormal physiological growth hormone (GH) stimulation test (i.e. GH < 5.7 ng/ml).

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CONTRAINDICATIONS

None

PRECAUTIONS

None

PREPARATION

Fast from midnight.

If performed in a child and the child's bone age is >10 years, the test should be done after sex steroid hormone priming as described for Insulin Tolerance Test.

PROCEDURE

- Two IV cannulae (each arm) at 8.30 am and take basal blood glucose and GH at 8.30am.
- Arginine 0.5g/kg (max 30g) in 100ml normal saline infused over 30 minutes commencing at t=0 (9am)
- Take further samples for blood glucose and GH at 30, 45, 60, 90, 120 and 150 mins for GH at all timepoints.

INTERPRETATION

If the GH rises to 40mU/l or above, the GH reserve is probably normal.

For the test in a child, a normal GH response of >5.7 ng/ml excludes GH deficiency.

- A GH response of 2.7-5.7 ng/ml may indicate partial GH deficiency and should be investigated by a second formal stimulation test.
- A GH response of <<2.7 ng/ml should also generally be confirmed by a second test. However, if there are other compatible clinical and auxiliary findings, the child may be directly considered for GH replacement therapy.
- A child with pubertal growth delay may show a subnormal GH response if the test is performed without sex hormone priming. However, there should be a normal response after priming.

SENSITIVITY AND SPECIFICITY

A child with GH deficiency will not respond to this test.

The percentage of children who are not GH deficient and who show a normal response varies from 45 – 93%. Generally, 20% of normal children fail to respond to a formal test and this is the reason for doing 2 tests before proceeding to GH therapy. For example, 71% of normals will respond to both insulin tolerance and arginine stimulation tests. However, the others will respond to at least one test: 13% to insulin, 16% to arginine.

REFERENCES

Merimee et al (1969) NEJM 280: 1434

Raiti et al., Lancet 1183 (1967).

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POSTERIOR PITUITARY FUNCTION

BASAL INVESTIGATIONS

Plasma (P) and urine (U) osmolalities obtained simultaneously on rising or as soon as possible thereafter in outpatients.
Other useful corroborative evidence includes plasma sodium level and urine volumes (day and overnight)

Interpretation
In a normal individual, plasma osmolality will be in the range 280-295 mosm/kg and urine will be concentrated. U:P ratio is usually more than 2:1, this excludes significant diabetes insipidus (DI) as long as the plasma osmolality is not raised above 295 mosm/kg.

In diabetes insipidus the plasma osmolality is usually raised and the urine is not appropriately concentrated (ie U:P < 2.0), although urine osmolality may be a little higher than plasma in mild cases.

WATER DEPRIVATION TEST

INDICATION
Diagnosis of diabetes insipidus.
Used in differential diagnosis of polyuria, separating Cranial Diabetes Insipidus (CDI), Nephrogenic Diabetes Insipidus (NDI) and Psychogenic Polydipsia/Compulsive Water Drinking (PP).
If in the basal state plasma osmolality > 295 mosmol/kg, plasma Na > 145 mmol/l and urine is hypotonic (< 300 mosmol/kg), go straight to trial of DDAVP without water deprivation.

CONTRAINDICATIONS
Exclude other causes of polyuria: diuretics, chronic renal failure, hypercalcaemia, hypokalaemia, hyperglycaemia.
Results cannot be interpreted in anterior pituitary hormone deficiency (eg. steroid and thyroxine deficiencies impair excretion of a free water load.)
In the fully hydrated patient, no other contraindications.

PRECAUTIONS
Care in patients with potentially severe clinical DI who may become dehydrated.
Test requires supervision from a doctor.
If true CDI or NDI, risk of excessive dehydration.

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PREPARATION

No tobacco/alcohol for 24 hrs before the test

Stop interfering medication (eg: diuretics).

DDAVP stopped for at least 24 hours before the test.

Give normal steroid replacement before the test.

Light breakfast (do not fast or limit fluids overnight).

PROCEDURE

Stage 1 (exclusion of Psychogenic polydipsia): 0730 – 1630

- No fluid allowed but dry food permitted (e.g. toast)
- Weigh patient at time 0 and calculate weight 97% of patient's weight. Document on chart. Weight should be measured at 4,6,7,and 8 hours: stop test if >3% weight loss (positive test)
- Urine passed and discarded at time 0; urine then passed hourly and hourly volume estimated
- Urine specimen taken for osmolality from the total hourly sample passed, over the following intervals: 7.30 – 8.30hrs (U1), 10.30 – 11.30 (U2), 13.30 – 14.30 (U3), 14.30 – 15.30 (U4), 15.30-16.30 (U5).
- Blood taken for osmolality and plasma sodium at 8.00hrs (P1), 11.00 (P2), 14.00 (P3), 15.30 (P4), 16.30 (P5).
- Note down urine volumes in chart (see below) (U1-U5).
- If the patient loses more than 3% of body weight then supervising doctor to review: measure plasma osmolality urgently. If >305mosm/kg then give DDAVP (desmopressin 2µg im) and allow patient to drink. If osmolality lower than this then patient may have been fluid overloaded before the test.
- After 8 hours, supervising doctor to review the test (and arrange for osmolalities if necessary). If the urine output has not decreased and / or the U:P ratio is less than 2 but the plasma osmolality has not become concentrated to >295 mosm/kg, continue water deprivation for a further hour and measure P5 and U5. At the end of the water deprivation test give DDAVP as per protocol.

Stage 2 (differential diagnosis CDI from NDI): 16.30 – 20.30 hrs

- Patient may now eat and drink freely
- At 16.30 hrs, administer DDAVP: 2 µg i.m.
- Continue to measure hourly urine volumes and take samples for osmolality from each hourly sample. There is no point measuring plasma samples (or taking any blood), as the patient are now eating and drinking freely.
- Note down urine volumes in chart as shown below (U6-U9).

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Time	Hours	Urine sample	Weight	Plasma Samples	Other instructions
0730	0	Discard	Yes		
0800		-	-	P1	
0830	1	U1	-		
1030	3	Discard	-		
1100		-	-	P2	
1130	4	U2	Yes		
1330	6	Discard	Yes		
1400		-	-	P3	
1430	7	U3	Yes		
1530	8	U4	Yes	P4	review by Doctor
1630	9	U5	Yes	P5	
Give DDAVP 2µg IM if no loss more than 3% body weight and Plasma Osmol > 305mosmol/kg					
1730	9	U6		-	allow free fluid
1830	10	U7		-	allow free fluid
1930	11	U8		-	allow free fluid
2030	12	U9		-	allow free fluid

INTERPRETATION

1) Normal response

Urine osmolality rises and urine volume and free water clearance fall progressively with water deprivation. U:P ratio should be 2 or more at the end of the test. Plasma osmolality rises but remains below 295 mosm/kg.

2) Medullary washout due to overdrinking, or partial DI

Start with a low plasma osmolality, which concentrates to normal during stage 1. Urine concentrates, though may be subnormal response (see below).

3) Cranial DI

Patient excessively concentrates plasma to >295 mosmol/kg with inappropriately hypotonic urine (U3:P3 or U4:P4 = <2).

After DDAVP: CDI patient, deficient in ADH, is still able to concentrate urine to >150% of previous highest level. In NDI, patient is unable to respond to ADH or DDAVP, and concentrates urine to <150% of previous highest value.

Diagnosis	**After dehydration***	**After DDAVP***
Normal	>750	>750
PP or partial CDI	300-750	<750
CDI	<300	>750
NDI	<300	<300

*Urine osmolality (mosmol/kg)

Many patients fall in the range 300-750 following water deprivation and it is often difficult to differentiate between PP and partial DI, especially following pituitary-surgery. In this instance, the plasma sodium may be helpful, since in PP, this is often low at the start of the test.

If there is a partial response, this test does not reliably differentiate between PP and partial CDI or NDI because the response to dehydration and DDAVP may be very similar:

- Polyuria of any origin (e.g. PP or CDI) washes out medullary concentration gradient, blunting maximal urinary concentration
- CDI may increase renal sensitivity to very low levels of AVP. If patient has only a partial deficiency of AVP, dehydration may therefore rapidly increase urine osmolality to maximum of which they are capable.
- Some patients with NDI can concentrate urine if plasma AVP increases to supra-physiological levels, e.g. with exogenous DDAVP.
- With PP patients avoid excess water/fluid at discharge as there is a small chance that following ddAVP and subsequent excess water intake of developing hyponatraemia.

If there is a partial response proceed to Prolonged Water Deprivation Test (modified Miller and Moses)

SENSITIVITY AND SPECIFICITY

When well performed, the WDT has a sensitivity and specificity of 95% for diagnosing and differentiating severe CDI and NDI. The incidence of false positive and false negative results for PP or partial CDI/NDI is 30-40% (investigate further).

REFERENCES

Dashe et al (1963) JAMA 185:699
Vokes et al., Endo. Metab. Clin. N. Amer. 17(2), 281 (1988).

PROLONGED WATER DEPRIVATION TEST (MILLER AND MOSES)

INDICATION

Differential diagnosis of mild central DI from primary polydipsia and other causes of thirst / polyuria

CONTRAINDICATIONS

Severe clinical DI

PRECAUTIONS

Unless symptoms are very mild (objectively 24 hour urine volume <4l) and DI clinically unlikely, a routine 8 hour water deprivation test should be performed first.
This test to be performed if results of 8 hour water deprivation test equivocal.
Adrenal and thyroid function must be normal, or replaced

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PROCEDURE

The patient must be nil by mouth from 18:00 the day before the test and arrive on Clinical Investigation Unit by 7:45.

Weigh patient at time 0 and calculate weight 97% of patient's weight. Weight should be measured at hourly intervals: stop test if >3% weight loss (positive test)

IV cannula

General management as for routine water deprivation test

Collect urine for osmolality hourly

Collect plasma for osmolality every 2 hours

Weigh patient every 2 hours. If patient loses >3% of body weight, supervising doctor to review. In this event, measure plasma osmolality urgently; if above 305 mosm/kg patient has DI – give DDAVP and allow to drink. If osmolality is <275 mosm/kg the patient has been fluid overloaded before the test.

All osmolalities should be measured immediately

Water deprivation should be continued until three consecutive urine osmolalities show <30mosm/kg increase (ie has reached a plateau).

When a plateau has been reached, give 2µg im DDAVP. Patient is then allowed to drink.

Time	Hours	Urine Osm	Plasma Osm	Weight
08:00	**0**	**U1**	**P1**	**yes**
09:00	**1**	**U2**	**-**	
10:00	**2**	**U3**	**P3**	**yes**
11:00	**3**	**U4**	**-**	
12:00	**4**	**U5**	**05**	**yes**
etc	**etc**	**etc**	**etc**	**etc**

After DDAVP 2µg im and collect urine hourly for 4 hours

INTERPRETATION

1). **Normal response**: urine osmolality rises to reach a plateau and does not increase further in response to ddAVP. Plasma osmolality is maintained within the normal range. U:P >2 at the end of dehydration.

2). **Primary psychogenic polydipsia***:* before DDAVP urine maximum osmolality >290mOsm/kg with no further rise in urine osmolality after DDAVP. Baseline plasma osmolality is usually low.

3) **Partial cranial DI**: a rise in urine osmolality of 9% or more after ddAVP suggests partial cranial DI ie endogenous maximal AVP secretion is insufficient to maximally concentrate the urine.

SENSITIVITY AND SPECIFICITY

REF:

Miller et al (1970) Ann Int Med 73: 721

THERAPEUTIC TRIAL OF DDAVP (adapted from Hammersmith hospital practice)

INDICATION

Used when partial response to water deprivation test to differentially diagnose Psychogenic Polydipsia (PP) and partial Cranial Diabetes Insipidus (CDI) or Nephrogenic Diabetes Insipidus (NDI).

SIDE EFFECTS

Water intoxication in PP

PROCEDURE

- Admit to hospital
- Monitor daily: fluid input and output, body weight, U+Es and urine osmolality.
- Observe patient for 2 days and then 10 mcg DDAVP given intranasally od for at least 2-3 days.

INTERPRETATION

Partial CDI: prompt improvement in thirst and polyuria
NDI: no effect; can be treated for further 2–3 days with a 10 fold increased dose to see if defect partial or complete
PP: decreased polyuria with no change in polydipsia. Causes weight gain, increased urine osmolality and progressive dilutional hyponatraemia, which may develop rapidly and severely (hence need for hospitalisation)

SENSITIVITY AND SPECIFICITY

Small possibility of false diagnosis of PP as hyponatraemia may occur in 5% of CDI who continue to drink excessively on DDAVP because of associated abnormal thirst or prolonged habit.

REFERENCE

Vokes et al., Endo. Metab. Clin. N. Amer. 17(2), 281 (1988).

VISUAL FIELD TESTING (GOLDMANN or HUMPHREYS PERIMETRY)

INDICATIONS

Before and after pituitary surgery and before and during pregnancy in patients with macroprolactinomas/non-functioning adenomas. It is important to assess the entire visual pathway and patients will require assessment of:

Near and far visual acuity (using Snellen Charts)

Visual field testing (Humphrey or Goldmann Perimetry)

CONTRAINDICATIONS

None specific

PRECAUTIONS

Check acuity first

PROCEDURE

Humphrey perimetry assesses the central 24 degrees of vision.
Goldmann perimetry assesses the whole visual field.
Goldmann perimetry is carried out on Frances Fraser ward – if you would like to attend to observe or learn the process please contact the ward nursing staff directly to arrange this.

INTERPRETATION

Formal perimetry is highly accurate and reproducible. Field loss is always significant; it can occur as the result of the pituitary tumour or from the treatment of the tumour. If an increasing field loss is noted it is vital that the patient has imaging promptly.

PITUITARY HORMONE REPLACEMENT

ORAL GLUCOCORTICOID REPLACEMENT

First-line drug

Hydrocortisone

Usual dose

10mg on waking, 5mg at lunchtime, 5mg at tea time/early evening , but very variable.

Morning dose should be taken on waking (not with breakfast) – have tablets and water by the bedside.

Monitor by Hydrocortisone Day Curve (see below)

Patients should be warned of the need for extra replacement during illness or surgery and should carry a *Steroid Card* and wear a MedicAlert bracelet/necklace/anklet. Understanding of this should be checked at all clinic visits. Patients should have an ampoule of hydrocortisone ('emergency pack') suitable for injection and they and/or a relative should be trained to inject this.

Steroid cover for intercurrent illness:

- Mild cold or sore throat without fever – no change in dosage
- More severe pyrexial illness – double the replacement dose
- Severe illness, especially with vomiting or diarrhoea – parenteral therapy (100mg IM). First dose to be given by attending GP or patient or relative, assuming suitably trained.
- There is a patient instruction sheet available.

Steroid cover for surgical procedures:

The following always require corticosteroid replacement for surgery:

- Patients with Addison's disease or hypopituitarism on corticosteroid therapy (either hydrocortisone or similar).
- Patients receiving steroid therapy for other indications within the past month.
- Patients known to have a serum cortisol or <500nmol/l in response to an ITT or glucagon test, even if not on regular replacement.

Corticosteroid Equivalents:

Drug	Dose Equivalent (mg)
Hydrocortisone (cortisol)	20
Cortisone acetate	25
Prednisolone	5
Prednisone	5
Methylprednisolone	4
Triamcinolone	4
Dexamethasone	0.5
Betamethasone	0.5

ADDISON'S DISEASE (PRIMARY ADRENAL INSUFFICIENCY)

POTENTIALLY LIFE-THREATENING STEROID DEPENDENCY

GLUCOCORTICOID MEDICATION REQUIREMENTS FOR SURGERY AND DENTISTRY

ADDISON'S CLINICAL ADVISORY PANEL (ACAP)
These surgical guidelines have been prepared by Professor John Wass of the Churchill Hospital, Oxford, Dr Trevor Howlett of Leicester Royal Infirmary, Leicester, Dr Wiebke Arlt of University Hospital, Birmingham and Dr Simon Pearce of the Royal Victoria Infirmary, Newcastle.

ACAP is a group of endocrinologists with an interest in adrenal medicine. It advises the Addison's Disease Self-Help Group on clinical matters. Further information about ACAP is available on the ADSHG website at www.addisons.org.uk

ACAP has also issued emergency treatment guidance for hypoadrenalism and a patient education leaflet, available at www.addisons.org.uk/publications.

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Type of procedure	*Pre-operative and operative needs*	*Post-operative needs*
Lengthy, major surgery with long recovery time *eg. open heart surgery, major bowel surgery, procedures needing ITU*	100mg hydrocortisone i/m just before anaesthesia	Continue 100mg hydrocortisone i/m every 6 hours until able to eat & drink normally *(discharged from ITU)*. Then double oral dose for 48+ hours. Then taper the return to normal dose
Major surgery with rapid recovery *eg. caesarean section, joint replacement*	100mg hydrocortisone i/m just before anaesthesia	Continue 100mg hydrocortisone i/m every 6 hours for 24 - 48 hours *(or until eating & drinking normally)*. Then double oral dose for 24 - 48 hours. Then return to normal dose
Labour and vaginal birth	100mg hydrocortisone i/m at onset of labour	Double oral dose for for 24 - 48 hours after delivery. If well, then return to normal dose
Minor surgery *eg. cataract surgery, hernia repairs, laparoscopy with local anaesthetic*	100mg hydrocortisone i/m just before anaesthesia	Double dose oral medication for 24 hours. Then return to normal dose
Invasive bowel procedures requiring laxatives *eg. colonoscopy, barium enema*	Hospital admission overnight with i/v fluids and 100mg hydrocortisone i/m during preparation. 100mg hydrocortisone i/m just before commencing.	Double dose oral medication for 24 hours. Then return to normal dose
Other invasive procedures *eg. endoscopy, gastroscopy*	100mg hydrocortisone i/m just before commencing.	Double dose oral medication for 24 hours. Then return to normal dose
Minor procedure *eg. skin mole removal with local anaesthetic*	Not usually required.	An extra dose only where hypoadrenal symptoms occur afterwards
Major dental surgery *eg. dental extraction with general anaesthetic*	100mg hydrocortisone i/m just before anaesthesia.	Double dose oral medication for 24 hours. Then return to normal dose
Dental surgery *eg. root canal work with local anaesthetic*	Double dose *(up to 20mg hydrocortisone)* one hour prior to surgery.	Double dose oral medication for 24 hours. Then return to normal dose
Minor dental procedure *eg. replace filling*	Not usually required.	An extra dose only where hypoadrenal symptoms occur afterwards.

GENERAL NOTES

1. For any nil-by-mouth regimen, please arrange an intravenous saline infusion to prevent dehydration and maintain mineralcorticoid stability, eg. 1000ml every 8 hours if >50kg.

2. Intramuscular hydrocortisone is preferable to intravenous administration as it gives more sustained, stable cover. It may alternatively be given by infusion pump, eg. hydrocortisone 25mg bolus then 5mg per hour in glucose 5%.

3. Note that hydrocortisone acetate cannot be used due to its slow-release, microcrystalline formulation. Please use hydrocortisone sodium phosphate or hydrocortisone sodium succinate, 100mg.

4. Monitor electrolytes and blood pressure post-operatively for all procedures requiring injected steroid cover. If the patient becomes hypotensive, drowsy or peripherally shut down, administer 100mg hydrocortisone i/v or i/m immediately. Please administer bolus hydrocortisone over a minimum of 10 minutes to prevent vascular damage.

5. If any post-operative complications arise, eg. fever, delay the return to normal dose.

6. Please ensure back-up supplies of oral and injectable hydrocortisone are available for resuscitation before commencing surgery. Even at full steroid cover, post-operative resuscitation may occasionally be required.

ADDISON'S DISEASE Self Help Group — Addison's Clinical Advisory Panel

The Addison's Disease Self-Help Group works to support people with adrenal failure and promote better medical understanding of this rare condition.

Registered charity 1106791
www.addisons.org.uk

TTC, MD, ABG Jan 2009

HYDROCORTISONE INFUSION

INDICATIONS

For management of patient with adrenocortical insufficiency.

The aim is to establish a constant serum cortisol in adrenalectomised patients prior to investigation (eg ACTH venous sampling catheter) or when patients with adrenal insufficiency cannot take medications orally, or by intermittent IM route (for example if anticoagulated, or thrombocytopaenic). Due to the short half life, intermittent IV bolus administration is not a suitable mode of administration.

CONTRAINDICATIONS

None

PRECAUTIONS

None

PROCEDURE

Start hydrocortisone infusion 6 hours before the investigation.

Hydrocortisone 30mg in 60ml normal saline.

Infuse hydrocortisone 2mg (4ml) per hour.

This should result in a stable serum cortisol of 400-600nmol/l. Check level by sampling approx 4 hours into the infusion and adjusting rate as necessary.

HYDROCORTISONE DAY CURVE (HCDC)

INDICATION

To establish the correct dose and distribution of hydrocortisone replacement therapy throughout the day.

CONTRAINDICATIONS

None

PRECAUTIONS

None

PREPARATION

Stop all oestrogen therapy 6 weeks prior to test (because of interference by rise in CBG)

Fasting from midnight

Do not take first dose of hydrocortisone on waking.

PROCEDURE

- IV cannula at 0800. then take blood at t=0 minutes for cortisol
- Give morning dose of hydrocortisone
- Serum cortisol sampling at 30mins, 1hr, serve breakfast, sample at 2, 3 and 5hr, give lunch time dose of hydrocortisone (if applicable), sample at 7 and 9 hr, give the evening dose of hydrocortisone, sample at 9.5, 10 and 11 hour.

INTERPRETATION

Do not rely on the numbers : interpret in the light of clinical history and examination findings.

Aim for adequate cortisol levels throughout the day (peak <900 nmol/l, trough >100 nmol/l).

Usual values are approximately:

- morning peak cortisol 500 – 800
- lunchtime peak cortisol 400 – 500
- post evening dose 300 – 400

Once adequate levels are achieved, this rarely needs to be repeated, unless there is a significant change in other medication (eg. Starting HRT).

Minor departures do not necessarily need dose adjustment, especially if the patient is well.

Enzyme-inducing drugs (especially, phenytoin, carbamazepine and rifampicin) will increase metabolism of corticosteroids and should prompt an increment in replacement doses.

Initiation of GH treatment will also affect profile, decreasing levels slightly.

SENSITIVITY AND SPECIFICITY

Utility of HCDC debated, but may be useful to ensure levels not dropping <100nmol/L during day

REFERENCES

Peacey SR et *Clin Endocrinol (Oxf)* 46 255-261 (1997)

MINERALOCORTICOID REPLACEMENT

First-line drug

Fludrocortisone (NB Mineralocorticoid replacement is rarely necessary in ACTH deficiency.)

Usual dose

50-150µg once daily.

Dose may need modification in hot climate, on holiday, etc

Monitor by

Plasma renin activity. Should not be elevated or fully suppressed.

BARTS ENDOCRINE E-PROTOCOLS
PITUITARY FUNCTION

www.bartsendocrinology.co.uk

THYROID HORMONE REPLACEMENT

First-line drug

Thyroxine (T4)

Replacement in severe hypothyroidism usually started with small and increasing doses of T3

Usual dose

T4 100-200 µg once daily

(approximate requirement for T4 can be calculated by 0.6µg/kg daily

Monitor by

Serum T4 and T3 in secondary hypothyroidism; serum TSH and T4 in primary hypothyroidism

GONADAL AXIS REPLACEMENT

First-line drug

Various options and routes of administration (patches, tablets, topical, oral, injectable etc)

Refer to the treatment of hypogonadism section.

Usual dose

Dependent on formulation

GROWTH HORMONE REPLACEMENT

Refer to section on GH and acromegaly protocols

VASOPRESSIN REPLACEMENT (Cranial Diabetes Insipidus)

First-line drug

Desmopressin (DDAVP)

Usual dose

10-20µg prior to bed intranasally but may require additional doses during the day.

OR 100µg desmopressin tablets split into 2 or 3 doses; usual dose 300-400µg/day.

Monitor by

Serum sodium.

PITUITARY TUMOURS

OPERATIVE MANAGEMENT OF PITUITARY TUMOURS

PRIOR TO ADMISSION

- Prior to surgery, ensure:
- Full endocrine assessment.
- Neurosurgical assessment.
- Neuro-ophthalmological assessment including Humphrey fields in previous 6/12
- Baseline investigations:
    - CT/MRI brain
    - Free T4, TSH, prolactin, oestradiol (females), testosterone (males), FSH, LH, cortisol, profile.
    - ECG and CXR if age >60 years.
    - IGF-1, GH, with oral GTT if clinically indicated
- If prolactinoma confirmed, treat with dopamine agonist drug (eg. cabergoline), then repeat CT/MRI scan (1-3 months after prolactin normalised or at minimum plateau). Surgery if tumour non-responsive.
- If patient is hypothyroid need short Synacthen test to exclude associated steroid dependency. Replace with T3 20 mcg tds for 4 days pre-op if surgery urgent, or thyroxine if surgery not imminent.
- Cushing's disease: start patient on cortisol-lowering medication titrating to mean cortisol level of 150–300 nmol/).

PRE-OPERATIVE MANAGMENT

- 'Stealth' CT organised for surgical team
- Visual fields documented and in notes
- For trans-sphenoidal surgery:

  Hydrocortisone 100 mg i.m. qds starting with pre-medication. (An IV infusion of 4.2 mg per hour (100 mg over 24 hours) is an alternative).

  Prophylactic antibiotics – amoxicillin 500mg tds and flucloxacillin 500 mg qds

BARTS ENDOCRINE E-PROTOCOLS
PITUITARY FUNCTION

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POST-OPERATIVE MANAGEMENT

1) STEROIDS

Continue parenteral steroid cover for:

24 hours: after selective removal of small microadenoma in patients with normal ACTH reserve preoperatively

72 hours: for all other adenomas without large suprasellar extension

7 days: For all cases with large suprasellar extension preoperatively big enough to compress hypothalamic structures or the chiasm

2) ANTERIOR PITUITARY FUNCTION

CORTISOL

- After the parenteral steroid cover period is completed, omit hydrocortisone after the early evening dose.
- Measure serum cortisol at 09:00 the next morning
- Replace in the light of the result
- If >100nmol/L may need ITT or glucagon test
- ACTH deficiency unlikely if serum cortisol 400-500nmol/L

THYROID AXIS

- Long plasma half life so no point to measure until 1 week postoperatively.
- Thereafter can measure weekly if an inpatient or arrange review at 2-3 weeks if discharged.

GONADAL AXIS

- In males measure serum 9am testosterone 1 week postoperatively, replace if low
- In females measure oestradiol but await the return of normal menstrual cyclicity

3) POSTERIOR PITUITARY FUNCTION

- Fluid balance charts should be kept. A spot urine osmolality is checked every 4 hours.
- If urine output >200ml per hr for 2 consecutive hours then consider DI. Check paired plasma and urine sodium and osmolarity. DI is confirmed by the presence of a high plasma osmolality (>295) in the presence of an inappropriately low urine osmolality (U:P ratio <2:1). Desmopressin (adult dose 0.5-1.0 mcg SC) could be given once diagnosis is confirmed.
- If the plasma osmolality is low the patient may be over-drinking due to a dry mouth. A low urine osmolality is appropriate.

BEFORE DISCHARGE FROM HOSPITAL

- If hydrocortisone replacement required, discharge on HC 10mg + 5mg + 5mg. Give steroid alert card and discuss 'sick day rules'. Patient should be discussed (with histology) at the next available pituitary MDT. The patient should be given and taught of the use of hydrocortisone emergency pack (IMI HC 100mg stat).
- **Acromegaly:** Assessment of HPA axis (ITT/glucagon stress test), assessment of GH burden via GH day curve and OGTT (see 'Post-operative assessment of acromegaly') performed 6 weeks post-op. Remind patients to omit their pm dose of hydrocortisone the day before their ITT/ glucagon stress test). Hydrocortisone to be resumed after test until results known.
- **Cushing's disease:** ALL patients with Cushing's disease must have a post-operative assessment at 4 weeks, 3-6 months and annually. At 4 weeks and 3-6 months post-operatively, this should include clinical assessment and a 5 point cortisol day curve (09:00, 12:00, 15:00, 18:00, 2030 mean cortisol should be 150-300nmol/L)
- ALL post-operative patients MUST have an endocrine OPD arranged on discharge to ensure revision of post-operative assessment occurs.
- Patients on hydrocortisone should be offered an ITT/glucagon stress test 2 years after surgery as there is a chance of recovery of corticotrophs (or recurrence).

REFERENCE
Biller *et al* Treatment of ACTH-dependent Cushing's syndrome: a consensus statement JCEM (2008) 93(7):2454-62

FOLLOW UP FOLLOWING PITUITARY SURGERY AND RADIOTHERAPY

Weekly visit to Frances Fraser ward for evaluation during external beam irradiation.

Following irradiation, endocrine testing should be performed on a yearly basis until failure of a cortisol response is apparent for at least 10 years, and then 5 yearly. Once failure is clear, the patient should be put on hydrocortisone replacement and further insulin tolerance tests are not required.

Patients who have undergone pituitary radiotherapy for acromegaly are often on somatostatin analogues following radiotherapy, and once it appears that the radiotherapy has worked, reassessment (OGTT + GH) off these analogues is essential.