Peri-operative Pituitary Management

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Disclosures

• Received honoraria from Ipsen, Novartis, Servier, Bristol-Myers Squibb/AstraZenica

• Served on medical advisory boards for Ipsen and Novartis
Outline

- Pre-operative assessment
- Post-operative management
  - Hypothalamic-pituitary-adrenal axis
  - Diabetes insipidus
  - Remaining anterior pituitary function
  - Cushing’s disease
  - Acromegaly
Pre-Operative Assessment Of Pituitary Axes

• Two main questions to answer regarding pituitary tumour:
  
  1. Functioning or non-functioning?
     
     and
  
  2. Compromising normal pituitary function?

  (Clinical anatomical effects – optic chiasm, cavernous sinus invasion)
Pre-Operative Screening Tests

- Adrenal (ACTH)
  - Morning cortisol
  - Synacthen Stimulation Test?
  - Screening for Cushing’s Disease?

- Thyroid (TSH)
  - FT4 and TSH

- Gonadal (LH, FSH)
  - LH, FSH and oestradiol / testosterone

- Growth hormone (GH)
  - IGF-1
  - GTT for GH suppression

- Prolactin
  - Serum prolactin
  - (Macroprolactin)
Pre-operative Assessment

- Non-functioning microadenomas rarely cause hypopituitarism
- Macroadenomas commonly cause hypopituitarism
  - Tumour size can significantly influence pre-operative hypopituitarism and post-operative recovery

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>Number of patients (n)</th>
<th>Preoperative hypopituitarism</th>
<th>Partial or complete recovery of pituitary function following surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mm</td>
<td>22</td>
<td>16 (72.7%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>10–20 mm</td>
<td>221</td>
<td>217 (71%)</td>
<td>137 (72.6%)</td>
</tr>
<tr>
<td>20–30 mm</td>
<td>334</td>
<td>298 (89.2%)</td>
<td>164 (55%)</td>
</tr>
<tr>
<td>30–40 mm</td>
<td>106</td>
<td>103 (97.1%)</td>
<td>25 (24.2%)</td>
</tr>
<tr>
<td>&gt;40 mm</td>
<td>38</td>
<td>38 (100%)</td>
<td>4 (10.5%)</td>
</tr>
</tbody>
</table>

Pre-operative Assessment

- Macroadenomas commonly cause hypopituitarism

  - **Mechanism** –
    - Compression of portal vessels in pituitary stalk
    - Expanding tumour mass
      - ? dependant on direction and rate of expansion
    - Increasing intrasellar pressure

Arafah et al. J Clin Endocrinol Metab 2000;85:1789-93
Pre-operative Assessment

<table>
<thead>
<tr>
<th>Patients with hypopituitarism (n = 33)</th>
<th>Patients without hypopituitarism (n = 16)</th>
<th>P value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Range</strong></td>
</tr>
<tr>
<td>MISP (mm Hg)</td>
<td>12–56</td>
<td>7–32</td>
</tr>
<tr>
<td>PRL (ug/L)</td>
<td>13–41</td>
<td>4–20</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>1.3–4.5</td>
<td>0.8–3.5</td>
</tr>
</tbody>
</table>

$^a$ Respective statistical differences between data of patients with and those without hypopituitarism.

Arafah et al. J Clin Endocrinol Metab 2000;85:1789-93
Pre-operative Assessment

- Recovery of pituitary function post-operatively (reduced pressure on portal vessels)
  - Depends on cell viability
    - Viability often persists despite raised ISP due to additional arterial blood supply to the anterior pituitary (not purely portal supply)
    - Focal pituitary necrosis – no recovery

Arafah et al. J Clin Endocrinol Metab 2000;85:1789-93
FIG. 3. Inferior view of the pituitary gland and its arterial capsular rete. Type I acrylic injection.
Transsphenoidal Surgery

- The pituitary is accessed through the nasal floor
- The tumour is identified and dissected from the normal tissue
- The technique preserves the remaining normal pituitary tissue
Post-operative Recovery of Pituitary Function

- Nearly half of initial pituitary hypofunctions normalise after transphenoidal adenomectomy\(^1\)
  - Usually within 2-3 months but can be up to 12 months\(^2\)
  - Important to reassess after surgery without substitution therapy

- New hypopituitarism can develop following TSS
  - Macroadenoma > microadenoma\(^1\)

\(^1\)Webb et al. J Clin Endocrinol Metab 1999;84:3696-700
Peri-operative Pituitary Management

- Two main management issues for Endocrinologists:
  - Glucocorticoid replacement and assessing the HPA axis
  - Diagnosis and management of diabetes insipidus
Peri-operative Glucocorticoid Therapy

- General agreement that stress-dose glucocorticoids should be prescribed to all patients with pre-operative ACTH deficiency
- Less consensus on the need for glucocorticoids in patients with an intact HPA axis pre-operatively
  - Reported prevalence of new ACTH deficiency after pituitary surgery 27%¹
  - Potential for adrenal insufficiency cf the adverse effects of glucocorticoids:
    - Transient diabetes insipidus
    - Hyperglycaemia

¹Webb et al. J Clin Endocrinol Metab 1999;84:3696-700
Two common approaches to post-op HPA axis Mx

- Empirical administration of glucocorticoid with HPA axis function assessment at ~ 6 weeks
  - Safe
  - Some will have unnecessary exposure to glucocorticoids
  - Non-suppressive replacement dose

- Early post-op assessment of cortisol
  - Selective administration of cortisol replacement
  - Risk of incorrect assessment and hypoadrenalism
  - Patient must be well informed
  - Additional patient monitoring?
Peri-operative Glucocorticoid Therapy

• Issues surrounding post-op cortisol assessment
  – ACTH deficiency may be transient, with subsequent normalisation of HPA function
  – Strategies for peri-operative assessment and replacement vary considerably between institutions
  – No universally accepted method regarding timing, assessment and replacement strategy in post-operative period when normal pre-operative HPA function
Peri-operative Glucocorticoid Therapy

- Questionnaire sent to a senior Endocrinologist in 18 Australasian hospitals that perform pituitary surgery¹

- Patient with pre-operative ACTH deficiency
  - 18/18 Endocrinologists prescribe stress glucocorticoid doses

- Patient with intact ACTH axis
  - 2/18 prescribe no glucocorticoids
  - 1/18 prescribe one hydrocortisone dose at start of surgery
  - 15/18 prescribe stress glucocorticoid doses for ≥48 hours

Peri-operative Glucocorticoid Therapy

- 17/18 assess HPA axis pre-operatively with early morning cortisol or SST

- Peri-operative glucocorticoid
  - 15/18 hydrocortisone equivalent
  - 3/18 dexamethasone

- Glucocorticoid dosing varied widely

- Pre-op evaluation influenced glucocorticoid prescribing in 10 centres
  - 16/18 prescribed glucocorticoids for all patients with macroadenoma (8 used higher dose if pre-op ACTH deficiency)
  - 2/18 would not prescribe glucocorticoids for macroadenoma with pre-operative intact HPA axis

Peri-operative Glucocorticoid Therapy

- Tumour size influenced prescribing at 7/18 centres
  - Lower dose or no glucocorticoid for microadenoma

- 14/18 measured early am cortisol post-op to stratify patients for definitive HPA axis testing
  - Cut-off choice varied (300-580 nmol/L)
Limitation Of Cortisol Thresholds

- Cortisol concentrations are assay dependent\(^1\)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Males</th>
<th>Non-OCP females</th>
<th>P-value*</th>
<th>OCP females</th>
<th>P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC-MS</td>
<td>274 (131–575)</td>
<td>254 (139–463)</td>
<td>0.193</td>
<td>542 (318–922)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Centaur</td>
<td>298 (158–565)(^\dagger)</td>
<td>257 (138–477)(^\dagger)</td>
<td>0.023</td>
<td>488 (323–738)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Architect</td>
<td>289 (151–556)(^\dagger)</td>
<td>247 (134–455)(^$)</td>
<td>0.018</td>
<td>465 (301–718)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E170</td>
<td>370 (182–750)(^\dagger)</td>
<td>292 (147–581)(^\dagger)</td>
<td>0.001</td>
<td>646 (383–1090)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immulite (2000)</td>
<td>316 (165–604)(^\dagger)</td>
<td>267 (144–495)(^\dagger)</td>
<td>0.003</td>
<td>510 (330–788)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Access</td>
<td>293 (160–538)(^\dagger)</td>
<td>252 (143–444)(^$)</td>
<td>0.011</td>
<td>429 (286–643)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results are expressed as geometric mean (2.5th–97.5th percentile) in nm.
*P-value for difference between genders.
\(^\dagger\)P-value for difference between women taking an oral contraceptive pill and those who were not.
\(^\dagger\)P-value for immunoassay vs GC-MS < 0.005.
\(^\$\)P-value 0.95 and 0.21 for Architect and Access assays vs GC-MS respectively.

\(^1\)El-Farhan et al. Clin Endocrinol 2013:78:673-80
Limitation Of Cortisol Thresholds

- Cortisol concentrations are assay dependent\(^1\)

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\(^1\)El-Farhan et al. Clin Endocrinol 2013:78:673-80
Limitation Of Cortisol Thresholds

- Cortisol concentrations are assay dependent\(^1\)

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Fig. 1 Baseline serum cortisol as a predictor of SST outcome in three cortisol immunoassay. Baseline serum cortisol is graphed against the % likelihood of passing (specificity: continuous line) or failing (sensitivity: dashed line) the SST.

\(^1\)Sbardella et al. Clin Endocrinol 2017:86:177-84
Limitation Of Cortisol Thresholds

- Ultradian\(^1\) and diurnal\(^2\) rhythms

\(^2\)Brown et al. Under Review Clin Endocrinol 2017
Peri-operative Glucocorticoid Therapy

Pituitary adenoma for surgery

0800h cortisol + ACTH 1-24 test

- normal
  - No perioperative glucocorticoids
  - Assess 0800h cortisol day 1-3

- abnormal
  - 48 hours hydrocortisone or dexamethasone
  - Assess 0800h cortisol day 3-5

Peri-operative Glucocorticoid Therapy
Peri-operative Glucocorticoid Therapy

- Royal Melbourne study\(^1\) evaluated safety of not prescribing glucocorticoids in 44 patients having transsphenoidal hypophysectomy and considered low risk of post-op hypocortisolism
  - Intact HPA axis pre-operatively
  - No pituitary apoplexy

- 2/44 patients developed ACTH deficiency and treated with glucocorticoids long-term (despite post-op cortisol > 250 nmol/L)

- No adrenal crises / major morbidity and reduced length of hospital stay

Peri-operative Glucocorticoid Therapy

• Endocrine Society Clinical Practice Guidelines¹

• “We recommend using stress doses of steroid in AI before surgery and tapered doses after surgery before repeat testing

• In patients with normal preoperative adrenal function, we suggest an individualised clinical approach for post-operative GC administration until the HPA axis can be evaluated”

¹Fleseriu et al. JCEM 2016;101;3888-3921
Peri-operative Glucocorticoid Therapy

- Questionnaire sent to a senior Endocrinologist in 18 Australasian hospitals that perform pituitary surgery¹

- For definitive post-operative testing of HPA axis
  - 8/18 insulin tolerance test (44%)
  - 4/18 250 µg synacthen test (22%)
  - 1/18 1 µg synacthen test (6%)
  - 2/18 metyrapone test (11%)
  - 3/18 early morning cortisol (17%)

Peri-operative Glucocorticoid Therapy

• Prospective evaluation of a week one overnight metyrapone test with subsequent dynamic assessments of HPA axis after pituitary surgery

  • Morning cortisol day 3-4
  • OMT day 5-7 and week 6
  • 250 mcg SST week 6
  • ITT week 7

• OMT within first week no better than early morning cortisol level at predicting glucocorticoid requirement at 6 months

• OMT at 6 weeks demonstrated HPA recovery in substantial proportion (37%) of patients who failed earlier assessments – definitive testing should be delayed until 6 weeks post-op

• SST at 6 weeks had poor sensitivity compared to ITT and glucocorticoid requirement at 6 months

  • ? Adrenal atrophy not yet developed

Peri-operative Glucocorticoid Therapy

- SST

- Recovery of HPA axis has been demonstrated up to a year post-operatively¹
  - Reassessment of glucocorticoid requirements beyond 6 weeks may be clinically indicated.

Peri-operative Glucocorticoid Therapy

- HPA axis recovery may occur up to 12 months post-operatively\(^1\)
  - 36 patients
  - ITT at 3 months and 12 months post-TSS for macroadenomas
  - 3-months: 20/36 (56%) ACTH insufficient
  - 12 months: 16/36 (44%) ACTH insufficient

Peri-operative Glucocorticoid Therapy

- Subnormal peak cortisol response to stimulation testing does not predict a subnormal cortisol production rate\(^1\)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Other hormone deficiencies and replacement therapy</th>
<th>Age (yr)</th>
<th>BMI (kg/m(^2))</th>
<th>Baseline cortisol (mmol/liter)</th>
<th>Peak cortisol (mmol/liter)</th>
<th>24-h urinary cortisol production (nmol/liter)</th>
<th>CPR (mg/d)</th>
<th>CPR/BSA (mg/d/m(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Prolactinoma</td>
<td>GHD on GH</td>
<td>54</td>
<td>23.4</td>
<td>320</td>
<td>492</td>
<td>20.54</td>
<td>7</td>
<td>4.29</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Prolactinoma</td>
<td>None</td>
<td>47</td>
<td>36.3</td>
<td>233</td>
<td>470</td>
<td>37.31</td>
<td>10</td>
<td>4.93</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Prolactinoma</td>
<td>GHD—no pituitary replacement</td>
<td>50</td>
<td>45.5</td>
<td>323</td>
<td>366</td>
<td>105.13</td>
<td>8.95</td>
<td>3.82</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Nonfunctioning pituitary adenoma</td>
<td>GHD on GH</td>
<td>45</td>
<td>30.1</td>
<td>257</td>
<td>490</td>
<td>88.96</td>
<td>29.3</td>
<td>15.10</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Optic nerve glioma</td>
<td>GH, LH, and FSH deficiency on GH and estrogen</td>
<td>21</td>
<td>36.9</td>
<td>299</td>
<td>477</td>
<td>136.50</td>
<td>7.97</td>
<td>4.11</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Acromegaly</td>
<td>None</td>
<td>38</td>
<td>31.3</td>
<td>164</td>
<td>494</td>
<td>157.28</td>
<td>16.8</td>
<td>5.79</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Acromegaly</td>
<td>None</td>
<td>57</td>
<td>34.1</td>
<td>313</td>
<td>480</td>
<td>114.46</td>
<td>11.6</td>
<td>5.13</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Medulloblastoma</td>
<td>None</td>
<td>37</td>
<td>18.9</td>
<td>198</td>
<td>403</td>
<td>118.62</td>
<td>4.17</td>
<td>2.94</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Multiple pituitary hormone deficit—traumatic brain injury</td>
<td>GH, LH, and FSH deficiency on GH and testosterone</td>
<td>28</td>
<td>22.2</td>
<td>293</td>
<td>419</td>
<td>265.89</td>
<td>6.18</td>
<td>3.51</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Nasopharyngeal carcinoma</td>
<td>None</td>
<td>63</td>
<td>17.7</td>
<td>275</td>
<td>443</td>
<td>200.62</td>
<td>7.81</td>
<td>5.10</td>
</tr>
</tbody>
</table>

Basal unstressed CPR reference range (2.1 – 12 mg/d.m\(^2\))

\(^1\)Paisley et al. J Clin Endocrinol Metab 2009:94:1757-60
Peri-Operative Management Of Diabetes Insipidus

• Up to 30% of patients undergoing pituitary surgery develop transient diabetes insipidus¹

• Characterized by the combination of:
  • Urine volume >250 mL/hour for ≥ 2 hours
  • Urine osmolality <200 mOsm/kg H₂O or specific gravity <1.005

• Negative fluid balance increases serum osmolality and hypernatraemia develops

• Consider causes of polyuria other than DI
  • Excessive IV fluids peri-operatively
  • Hyperglycaemia (diabetes mellitus may be unmasked by high dose glucocorticoids)

Factors found to increase risk of post-operative DI

- Young age
- Male sex
- Large intrasellar mass
- CSF leak
- Certain tumours – craniopharyngioma, Rathke’s cleft cyst, ACTH-secreting

Common patterns:

- Transient
- Permanent
- Tri-phasic

Peri-Operative Management Of Diabetes Insipidus

Tri-phases of central diabetes insipidus

Inhibition of ADH release

Stored ADH depleted

ADH (Antidiuretic Hormone)

Polyuric phase

Antiuretic phase

24 hours

4-5 days

6-11 days

Time

Peri-Operative Management Of Diabetes Insipidus
Peri-Operative Management Of Diabetes Insipidus

Expectant monitoring
- Accurate recording of fluid intake and output
- Measurement of urine osmolality or specific gravity every 4–6 h, until resolution or stabilization
- Measurement of serum sodium levels every 4–6 h, until resolution or stabilization

Antidiuretic hormone therapy
- Desmopressin given intravenously or subcutaneously at an initial dose of 1–2 μg
- Repeat the desmopressin dose when urine output is 200–250 ml/h for ≥2 h with urine specific gravity <1.005 or urine osmolality <200 mOsm/kg H₂O

Maintenance of fluid balance
- Allow the patient to drink according to their thirst
- Supplement with hypotonic intravenous fluids—5% dextrose in water, followed by 5% dextrose in 0.45% (half-normal) saline—if the patient is unable to maintain normal plasma osmolality and serum sodium levels through drinking

Monitor for resolution of transient diabetes insipidus or triphasic response
- Positive daily fluid balance >2 l suggests inappropriate antidiuresis
- Antidiuretic hormone therapy should be suspended and fluids restricted to maintain serum sodium levels within the normal range

Manage anterior pituitary insufficiency
- Administer stress-dose corticosteroids (hydrocortisone 100 mg intravenously every 8 h, tapered to an oral dose of 15–30 mg daily) until anterior pituitary function can be fully evaluated

Peri-Operative Management Of Diabetes Insipidus

- Aqueous vasopressin (Pitressin – 5 units)
  - SC or IM, duration of anti-diuretic effect variable 2-8 hours
  - May cause contraction of smooth muscle of GI tract or vasculature (IV)

- Desmopressin (DDAVP - 1 µg SC)
  - Selectively binds to AVP V2 receptor to reduce polyuria
  - Avoids AVP V1 receptor-mediated pressor effects
  - Longer half-life

- Majority of cases desmopressin only needs to be given once or twice, therefore needs to be administered with care and close monitoring of fluid balance
# Peri-Operative Management Of Diabetes Insipidus

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose form</th>
<th>Sponsor</th>
<th>Shortage dates</th>
<th>Shortage details</th>
</tr>
</thead>
</table>
Other Axes

• Other axes can be assessed ~6 weeks after surgery
  • TSH
    • FT₄ and TSH
  • Gonadal
    • LH, FSH and oestradiol / testosterone
  • Growth hormone
    • IGF-1
    • GH reserve by ITT if used in HPA axis assessment or patient considering GH replacement
  • Prolactin
    • Serum prolactin if prolactinoma
Peri-operative Management in Cushing’s Disease
Peri-operative Management in Cushing’s Disease

- Peri-operative fluid balance
  - Higher rates of DI\(^1\)
    - Longer intra-op manipulation to localise small microadenomas
    - Closer to posterior pituitary
- VTE prophylaxis
  - CD is a hypercoagulable state\(^2\)
- Peri-operative glucocorticoids and HPA assessment
  - Suppression of normal corticotrophs due to negative feedback

\(^1\)Aulinas et al, Pituitary 2012; 15:380-5
\(^2\)Barbot et al, Pituitary 2015;18:487-93
A – Pre-treatment
B – Remission and reduction in cortisol and adrenal hyperplasia
C – Residual adenoma
D - Remission

Czepielewski et al, Arq Bras Endocrinol Metab 2007;51:1362-72
Peri-operative Management in Cushing’s Disease

- **Issues**
  - Early assessment of cure
  - Criteria for early and sustained remission
  - Glucocorticoid withdrawal syndrome
    - Complete resection of adenoma is followed by development of ACTH deficiency as normal corticotrophs are suppressed by pre-existing hypercortisolaemia
    - Rationale for using glucocorticoids during and immediately after TSS
Peri-operative Management in Cushing’s Disease

- Approaches to early management post-TSS
  - Pre-empt severe adrenal insufficiency and steroid withdrawal syndrome with intra-operative/early post-operative glucocorticoid replacement
    - No consensus on choice of replacement glucocorticoid
  - Withhold glucocorticoid replacement until clinical signs and symptoms or biochemical confirmation of hypocortisolism
    - Requires vigilant monitoring to avert adverse haemodynamic consequences of hypocortisolaemia

Utz et al, Rev Endocrinol Metab Clin N Am 2005;34:459-78
Peri-operative Management in Cushing’s Disease

- Half-life of cortisol is 60-90 min
- Levels will start to decline after complete adenomectomy and would be expected to reach low levels (< 138 nmoL or < 5ug/dL) during the first 24-48 hours
- Therefore some centres avoid routine glucocorticoid use before, during and for several hours after surgery

AbdelMannan et al, Rev Endocr Metab Disord 2010;11:127-34
Peri-operative Management in Cushing’s Disease

• Factors limiting interpretation of cortisol levels in post-op period
  – Peri-operative administration of glucocorticoids
  – Factors influencing CBG levels (↑)
    • Oestrogens
    • Hepatitis
    • (Mitotane given pre-operatively)

  ➢ Change in serum cortisol levels post-operatively will be much slower (assay measures total cortisol)
Peri-operative Management in Cushing’s Disease

Postmenopausal woman receiving oestrogen therapy

ACTH

Cortisol

AbdelMannan et al, Rev Endocr Metab Disord 2010;11:127-34
Peri-operative Management in Cushing’s Disease

- Following surgical resection for CD there are 3 possible outcomes:
  - Complete and lasting remission/cure
  - Remission with future return of hypercortisolism
  - Persistent post-operative hypercortisolism
- No consensus concerning timing, choice of biochemical tests, or threshold values to define remission
Peri-operative Management in Cushing’s Disease

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Biochemical criteria for Cushing’s disease remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author, year (Ref. no.)</td>
<td>Timing of postoperative test</td>
</tr>
<tr>
<td>Hanly, 1992 [88]</td>
<td>ND</td>
</tr>
<tr>
<td>Fiddick, 1986 [82]</td>
<td>5-6 d</td>
</tr>
<tr>
<td>Chandler, 1987 [83]</td>
<td>Within 1 wk</td>
</tr>
<tr>
<td>Nakano, 1987 [84]</td>
<td>ND</td>
</tr>
<tr>
<td>Schori, 1987 [85]</td>
<td>7-10 d</td>
</tr>
<tr>
<td>Gualitine, 1988 [42]</td>
<td>3-6 mo</td>
</tr>
<tr>
<td>Monopulus, 1988 [86]</td>
<td>ND</td>
</tr>
<tr>
<td>Pitter, 1988 [44]</td>
<td>1 d</td>
</tr>
<tr>
<td>Annet, 1989 [43]</td>
<td>1-4 wk</td>
</tr>
<tr>
<td>Birk, 1990 [26]</td>
<td>4 wk</td>
</tr>
<tr>
<td>Tindall, 1999 [37]</td>
<td>1-26 wk</td>
</tr>
<tr>
<td>Ludiecke, 1991 [38]</td>
<td>6-6 h</td>
</tr>
<tr>
<td>Roland, 1991 [50]</td>
<td>ND</td>
</tr>
<tr>
<td>Lindholm, 1992 [90]</td>
<td>ND</td>
</tr>
<tr>
<td>Taitt, 1992 [44]</td>
<td>ND</td>
</tr>
<tr>
<td>McCarron, 1993 [49]</td>
<td>1-14 d</td>
</tr>
<tr>
<td>Tennyson, 1992 [42]</td>
<td>1 d</td>
</tr>
<tr>
<td>Kaus, 1994 [33]</td>
<td>ND</td>
</tr>
<tr>
<td>Bakos, 1986 [92]</td>
<td>ND</td>
</tr>
<tr>
<td>Knopp, 1989 [93]</td>
<td>ND</td>
</tr>
<tr>
<td>Sonnen, 1996 [44]</td>
<td>5-15 d</td>
</tr>
<tr>
<td>Stovin, 1989 [36]</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

Table 2 (continued)

<table>
<thead>
<tr>
<th>First author, year (Ref. no.)</th>
<th>Timing of postoperative test</th>
<th>Biochemical tests</th>
<th>Remission cutoff value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitti, 1999 [20]</td>
<td>ND</td>
<td>UFC</td>
<td>Low/normal</td>
</tr>
<tr>
<td>Semple, 1999 [21]</td>
<td>ND</td>
<td>AM cortisol</td>
<td>Low/normal</td>
</tr>
<tr>
<td>Swearingen, 1999 [22]</td>
<td>1-10 d</td>
<td>AM ACTH</td>
<td>&lt; 138 nmol/L</td>
</tr>
<tr>
<td>Barbetta, 2001 [22]</td>
<td>1 mo</td>
<td>Cortisol</td>
<td>Normal</td>
</tr>
<tr>
<td>Cech, 2001 [39]</td>
<td>2 wk</td>
<td>UFC</td>
<td>Normal</td>
</tr>
<tr>
<td>Estrada, 2001 [38]</td>
<td>8-12 d</td>
<td>Cortisol every 6 hours</td>
<td>UFC</td>
</tr>
<tr>
<td>Rees, 2002 [37]</td>
<td>1-7 d</td>
<td>AM cortisol</td>
<td>&lt; 50 μg/dL</td>
</tr>
<tr>
<td>Shimmon, 2002 [94]</td>
<td>4-6 wk</td>
<td>UFC</td>
<td>Normal</td>
</tr>
<tr>
<td>Yap, 2002 [40]</td>
<td>3-4 d</td>
<td>AM cortisol</td>
<td>&lt; 50 μg/dL</td>
</tr>
<tr>
<td>Chen, 2002 [49]</td>
<td>2 d</td>
<td>LD-DST (1 mg)</td>
<td>&lt; 5 μg/dL</td>
</tr>
<tr>
<td>Perret, 2003 [53]</td>
<td>6 mo</td>
<td>LD-DST (2 mg)</td>
<td>&lt; 5 μg/dL</td>
</tr>
<tr>
<td>Hammer, 2004 [36]</td>
<td>1 wk</td>
<td>AM cortisol</td>
<td>&lt; 5 μg/dL</td>
</tr>
<tr>
<td>Rollin, 2004 [48]</td>
<td>1-12 d</td>
<td>LD-DST (1 mg)</td>
<td>&lt; 5 μg/dL</td>
</tr>
</tbody>
</table>
Peri-operative Management in Cushing’s Disease

- A lack of complete or near complete cortisol suppression in early post-operative period considered an indication of residual adenoma and absence of true remission
  (Estrada et al 2001, Trainer et al 1993)

- However, some patients have normal cortisol levels in early post-op period that remain stable with long-term follow-up
  (Pereira et al 2003, Toms et al 1993)
Peri-operative Management in Cushing’s Disease

- Duration of glucocorticoid replacement therapy is related inversely to risk of relapse (Bochicchio et al 1995)
  - 5 year risk of relapse:
    - 3% for > 1 year
    - 24% for < 1 year
    - 47% for no replacement

Peri-operative Management in Cushing’s Disease

- Late recurrence of Cushing’s disease after successful TSS

Peri-operative management in Acromegaly
• Post-operative assessment of cure
  
  • IGF-1 measurement after 12 weeks is recommended to assess need for other therapies\(^1\)
  
  • GH can be assessed as early as day 1 post-op however an elevated level may reflect surgical stress with normal somatotroph GH production\(^2\)
OGTT performed 1 week after pituitary surgery is reproducible over time and predictive of cure.

Individual IGF-1 profiles vary significantly until week 12 and in both cured and non-cured patients, patterns with early, intermediate and late stabilisation can be identified.
Summary

- Pituitary function must be carefully assessed pre- and post-operatively in patients undergoing pituitary surgery
- Lack of consensus on peri-operative glucocorticoid management
- Close monitoring of fluid balance – most common pattern of DI is transient
- Specific considerations for Cushing’s Syndrome and Acromegaly