Anaesthesia and adrenocortical disease

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Key points

Adrenocortical disease results in disturbances of body water volume and electrolyte concentrations; intra-cellular electrolyte defects may be severe.

Preoperative assessment is of crucial importance in identifying the endocrine disease process and the severity of its effects.

Preoperative preparation involves correction of volume deficit and electrolyte disturbances, and replacement of deficient hormones.

Cardiovascular disturbance and instability are particularly common and invasive cardiovascular monitoring should be considered.

Postoperative mineralocorticoid and glucocorticoid supplementation should be considered in Addison’s disease and in steroid-induced hypoadrenalism.

Physiology

The adrenal glands lie on the superior aspect of the kidneys and consist of two endocrine organs: the inner adrenal medulla and the outer adrenal cortex. The adrenal cortex and medulla have distinct embryological origins. The medullary portion consists of chromaffin cells derived from the ectodermal cells of the neural crest. The cortex is of mesodermal origin. The adrenal glands are densely vascularized, the arterial blood supply reaching them from branches of the renal and phrenic arteries and the aorta. The medulla receives blood rich in corticosteroids from the cortex; this regulates the synthesis of the enzymes that convert noradrenaline into adrenaline. Venous drainage is via a single adrenal vein into the renal vein on the left and the inferior vena cava on the right.

Adrenal medulla

The adrenal medulla is a modified sympathetic ganglion comprising 30% of the adrenal gland. Pre-ganglionic, cholinergic, sympathetic nerve fibres richly innervate it. Approximately 90% of cells are epinephrine secreting, while the remainder are norepinephrine secreting. It is unclear which types of cells secrete dopamine. Medullary tissue is also located at extra-adrenal sites along the course of the abdominal aorta. The adrenal medulla and the catecholamines that it secretes are not discussed further as they are beyond the scope of this review, which focuses on the adrenocortical function.

Adrenal cortex

The adrenal cortex is responsible for the secretion of three classes of steroids, glucocorticoids, mineralocorticoids and androgens (sex hormones). Glucocorticoids affect the metabolism of carbohydrates, fats and proteins and are important in mediating the response to fasting and stress. Mineralocorticoids are essential for electrolyte and fluid balance.

Histologically, the adrenal cortex comprises three distinct layers: (i) outer zona glomerulosa; (ii) middle zona fasciculata, which is the largest layer; and (iii) inner zona reticularis. The cells of all three zones secrete corticosterone, but the enzymes responsible for aldosterone production occur only in the zona glomerulosa. The enzymatic mechanism for synthesizing cortisol (hydrocortisone) and androgens exists mainly in the two inner zones.

Synthesis and release of glucocorticoids and mineralocorticoids

All of the adrenocortical hormones are derived from cholesterol. This can be synthesized in the gland but is mostly taken up from the circulation. The mineralocorticoids and glucocorticoids are termed C21 steroids because they have 21 carbon atoms in their structure. The sex hormones are C19 steroids.

Adrenocorticotropic hormone (ACTH) releases cholesterol from lipid droplets in the cytoplasm of cells. It acts via G-protein-linked membrane receptors, which increase intracellular cAMP (and thus protein kinase-A) activity. Cholesterol is converted in the mitochondria to pregnenolone, which is transferred to the smooth endoplasmic reticulum where it undergoes further modification to the three main classes of steroids. The steroids secreted in clinically significant amounts are aldosterone, the glucocorticoids cortisol and corticosterone and the androgens dehydroepiandrosterone (DHEA) and androstenedione.

The corticosteroids in the circulation are mainly bound to plasma proteins such as transcortin (also called corticosteroid-binding globulin) and, to a much lesser degree, albumin. However, aldosterone has minimal protein binding. Inactivation of both cortisol and aldosterone occurs mainly in the liver where they are conjugated with glucuronide and excreted in the urine.

Actions of glucocorticoids

The actions of glucocorticoids are summarized in Table 1; they have catabolic, cardiovascular and anti-inflammatory effects and promote glycogen storage in the liver.
Cortisol promotes protein catabolism and liver gluconeogenesis ensuring normal blood glucose concentrations during fasting. It also antagonizes the action of insulin. Glucocorticoids are essential for the normal cardiovascular response to stress—without them, the cardiovascular system becomes unresponsive to catecholamines and the vascular endothelium becomes more permeable.

Cortisol also has some mineralocorticoid activity, which is particularly significant when it is produced in excess. Other effects observed during excessive production of glucocorticoids are immunosuppression, inhibition of the healing process in tissues and decreased growth hormone secretion by the anterior pituitary.

**Regulation of glucocorticoid activity**

The hypothalamus, anterior lobe of the pituitary and adrenal cortex are involved in a negative feedback system. In the healthy individual, the secretion of cortisol from the adrenals follows a diurnal rhythm following that of ACTH release from the pituitary. Plasma ACTH and cortisol concentrations rise during sleep to reach their highest levels in the morning soon after waking. Hypothalamic release of corticotrophin-releasing hormone (CRH) into the hypophysal portal blood regulates ACTH release. Cortisol exerts a negative feedback on both CRH and ACTH release.

**Actions of mineralocorticoids**

The actions of mineralocorticoids are summarized in Table 1. The principle effect of aldosterone is to stimulate sodium reabsorption from the distal convoluted tubule of the kidney (at the expense of potassium and hydrogen ions, which are lost in the urine); this results in expansion of the extracellular fluid.

**Regulation of aldosterone secretion**

The factors affecting aldosterone secretion are the renin–angiotensin system, direct effects of a fall in plasma sodium or a rise in plasma potassium and ACTH release from the pituitary. The epithelioïd juxtaglomerular cells secrete renin into the afferent arterioles as they enter the glomeruli. Renin secretion is directly stimulated by a decrease in afferent arteriolar pressure (this may be attributed to a generalized fall in blood pressure or decrease in blood volume), sympathetic renal nerve stimulation, increased circulating catecholamines and increased circulating prostaglandins (especially prostacyclin). Renin release is also influenced by sodium load to the distal tubule via a modified region of the tubular epithelium called the macula densa. A reduction in sodium load (which may be attributable to a reduction in extracellular fluid volume) is detected by the macula densa and results in an increase in renin secretion. Renin cleaves angiotensin-I from angiotensinogen. Angiotensin-I is converted to angiotensin-II in the lungs by angiotensin-converting enzyme (ACE). Angiotensin-II binds to receptors in the zona glomerulosa and acts via G-protein to activate phospholipase-C. It facilitates the conversion of cholesterol to pregnenolone and the conversion of corticosterone to aldosterone.

**Disorders of adrenocortical function**

The common disorders of adrenocortical function are summarized in Table 2.

### Table 1 The major actions of glucocorticoids and mineralocorticoids

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>Cardiovascular</th>
<th>Kidney</th>
<th>Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Protein catabolism</td>
<td>Maintenance of responsiveness to catecholamines</td>
<td>Weak mineralocorticoid activity</td>
<td>Immunosuppression and slowed healing</td>
</tr>
<tr>
<td>Mineralocorticoids</td>
<td>Gluconeogenesis None</td>
<td>None</td>
<td>Sodium reabsorption</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potassium and H⁺ excretion</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Common disorders of adrenocortical function

<table>
<thead>
<tr>
<th></th>
<th>Aldosterone ↑</th>
<th>Hypertension, hypokalaemia, alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conn’s (primary hyperaldosteronism)</td>
<td>Cortisol ↑ or (depending on aetiology)</td>
<td>Altered appearance, bruisings, muscle wasting, hypertension, diabetes, hypokalaemia</td>
</tr>
<tr>
<td>Secondary hyperaldosteronism</td>
<td>Renin ↑</td>
<td></td>
</tr>
<tr>
<td>Cushing’s</td>
<td>Cortisol ↑ or ↓</td>
<td>Hypoglycaemia, hyponaetraemia, hyperkalaemia and raised urea</td>
</tr>
<tr>
<td>Addison’s</td>
<td>Aldosterone ↑ or ↓</td>
<td>Acute: abdominal pain, vomiting, dehydration and hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic: fatigue, pigmentation, anorexia, weight loss and postural hypotension</td>
</tr>
</tbody>
</table>

### Hyperaldosteronism

In primary hyperaldosteronism (Conn’s syndrome), there is excess secretion of aldosterone from an adrenal adenoma (60%), bilateral adrenal hyperplasia (30%) or, rarely, carcinoma. Patients with secondary hyperaldosteronism have high plasma concentrations of renin and aldosterone. Causes include congestive cardiac failure and liver cirrhosis.

### Clinical features and investigations

Hypertension is the usual presenting sign. Conn, describing the disease, stated that he believed this was almost entirely

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attributable to an increase in extracellular fluid volume and, therefore, would not result in serious hypertension. However, malignant hypertension is known to occur, and this may be centrally mediated or may be caused by aldosterone-induced vasoconstriction via a direct effect on vascular endothelium.6 Conn’s syndrome should be suspected in cases of refractory hypertension.

Hypokalaemia is often severe and may be exacerbated by treatment of hypertension with diuretics. Because 98% of body potassium is located intracellularly, large potassium deficits are present in patients with chronically low plasma concentrations. Conn’s syndrome should be suspected in cases of spontaneous hypokalaemia (<3.5 mmol litre$^{-1}$) or moderately severe hypokalaemia (<3.0 mmol litre$^{-1}$) during diuretic therapy, despite oral potassium supplementation.6 Metabolic alkalosis is sometimes present due to hydrogen ion loss.

**Diagnosis**

The aldosterone to renin ratio helps eliminate other factors such as posture, time of day and salt loading. A ratio greater than 400 (ng dl$^{-1}$)/(ng ml$^{-1}$ h$^{-1}$) is consistent with Conn’s syndrome. MRI scan of adrenals, bilateral adrenal vein catheterization or adrenals scintigraphy with $^{131}$I-labelled or $^{99m}$Tc-labelled precursors of aldosterone assist in differentiating between an adenoma and hyperplasia. Such differentiation is important because treatment differs according to the diagnosis.4

**Treatment**

Bilateral hyperplasia is usually treated medically with spironolactone (aldosterone antagonist), often with an ACE inhibitor. Adrenal adenoma often requires surgical treatment with laparoscopic or open removal after medical optimization.

**Cushing’s syndrome**

Cushing’s syndrome is caused by excessive levels of glucocorticoids. These may be secreted by the adrenal cortex or may be exogenously administered. Excessive secretion of cortisol is most commonly secondary to excess ACTH secretion from an anterior pituitary adenoma (Cushing’s disease) resulting in bilateral adrenal hyperplasia. In 20–30% of patients, the cause is an adrenal adenoma or carcinoma. More rarely, Cushing’s syndrome is secondary to ectopic ACTH secretion; this is most commonly from oat cell carcinoma of the lung.

**Clinical features and investigations**

These include moon face, central obesity with buffalo hump, thin skin that bruises easily and purple striae on abdomen and thighs. Proximal muscle wasting, osteoporosis, hypertension and left ventricular hypertrophy may be present. Impaired glucose tolerance and frank diabetes mellitus (type II) occur, owing to the counter-regulatory effects of cortisol on insulin action. Hypokalaemia may occur, owing to the weak mineralocorticoid effect of cortisol causing sodium retention and potassium loss.

**Screening tests**

- **24 h Urinary free cortisol**: elevated cortisol levels confirm a pathological cause (normal 450–700 nmol litre$^{-1}$).
- **Short dexamethasone suppression test**: dexamethasone 1 mg is given orally at midnight. Normal individuals show suppression of 9 a.m. serum cortisol.

**Establishing the cause**

- **High-dose dexamethasone-suppression test**: eight doses of dexamethasone 2 mg are given orally over 48 h. There is suppression of serum cortisol in pituitary dependent Cushing’s disease but not in adrenal Cushing’s or ectopic ACTH secretion.
- **Serum ACTH concentrations**: elevated concentrations are seen in Addison’s disease, adrenoleukodystrophy, Cushing’s disease, ectopic production of ACTH and Nelson’s syndrome. Low concentrations are seen in Cushing’s syndrome related to an adrenal tumour, exogenous Cushing’s syndrome and pituitary insufficiency.
- **MRI scan of pituitary fossa and CT/MRI of adrenal glands**: radiological investigations should only be performed after biochemical tests have suggested a likely source.
- **Inferior petrosal venous sampling after CRH stimulation** is the definitive test for pituitary Cushing’s disease.4

**Treatment**

Trans-sphenoidal surgical removal and occasionally radiotherapy is indicated for pituitary-dependent Cushing’s disease. Adrenal adenoma/carcinoma requires surgical removal of the affected gland. Treatment of the underlying cause is required in cases of ectopic ACTH production. Metyrapone (inhibitor of cortisol synthesis) may be useful in cases not amenable to surgery.4

**Adrenocortical insufficiency (Addison’s disease)**

Addison’s disease is characterized by reduced or absent secretion of glucocorticoids, usually associated with deficient mineralocorticoid activity. Destruction of the adrenal cortex by autoantibodies is the cause of primary hypoadrenalism in 80% of cases; other causes include tuberculosis, metastatic carcinoma, bilateral adrenalectomy and haemorrhage (e.g. meningococcal sepsis).1 Secondary hypoadrenalism results from prolonged corticosteroid therapy and hypopituitarism. Aldosterone secretion is maintained and the fluid and electrolyte disturbances are less marked.2

**Clinical features and investigations**

Those presenting with the acute condition (Addisonian crisis) may have abdominal pain, vomiting, dehydration and hypotension (particularly postural). The chronic condition has an insidious onset with fatigue, anorexia, weight loss and postural hypotension (salt and water loss). There is increased pigmentation; especially of exposed areas, palmar creases and the buccal mucosa. This occurs because high plasma concentrations of ACTH mimic melanocyte-stimulating hormone.4 There is often hypoglycaemia, hyponatraemia, hyperkalaemia and a raised serum urate. Autoimmune
Addison’s disease may be associated with other autoimmune disease such as pernicious anaemia and Grave’s disease.  

**Diagnosis**

*Short Synacthen test*: tetracosactrin 250 μg is given via the i.v. or intramuscular route. Serum cortisol concentrations are measured before the tetracosactrin and then 30 and 60 min after administration. A low initial cortisol concentration with an inadequate response suggests adrenocortical insufficiency. Serum cortisol concentration >580 nmol litre⁻¹ excludes the diagnosis.  

Adrenal antibodies and radiological imaging may be useful in determining the cause.

**Treatment**

Treatment comprises the replacement of steroids and mineralocorticoids. A typical starting regime would be hydrocortisone 20 mg in the morning and 10 mg at night with fludrocortisone 50–100 μg daily.

**Acute Addisonian crisis**

Treatment is with high-dose i.v. hydrocortisone. An initial dose of 200 mg is followed by 100 mg every 6 h until oral supplements can be taken. Fluid resuscitation is required, and dextrose may be necessary to treat hypoglycaemia. Invasive monitoring and high-dependency care should be considered.

**Relative adrenal insufficiency in the critically ill**

Relative hypoadrenalism in intensive care patients is well described and quite common. There may be an inadequate response during the short Synacthen test; this carries a poor prognosis. Low-dose replacement steroids should be considered (e.g. i.v. hydrocortisone 50 mg every 6 h).

**Anaesthetic management**

Anaesthetic management should primarily focus on preoperative assessment and optimisation. This may involve the direct effects of excess steroids such as hypertension and end organ damage. Preoperative assessment will also include recognition of associated disease such as pernicious anaemia. Intraoperatively, these patients are particularly at risk of cardiovascular instability and appropriate monitoring should be considered. Postoperative management will include adequate pain control and hormone replacement therapy.

**Conn’s syndrome**

Most anaesthetic problems relate to potassium depletion and hypertension. Hypokalaemia and metabolic alkalosis should be corrected preoperatively. As Conn noted, it may be impossible to restore serum potassium concentrations to normal. Hypokalaemia theoretically prolongs the action of non-depolarizing neuromuscular blocking agents. Low serum potassium is also known to suppress baroreceptor tone, so hypovolaemia should be treated aggressively. Spironolactone, given in doses up to 400 mg day⁻¹, moderates the metabolic and electrolytic effects; it also assists restoration of normovolaemia. Hypertension may be well controlled with spironolactone or may require additional therapy (e.g. ACE inhibitors). Features of end-organ damage secondary to hypertension (e.g. left ventricular hypertrophy) should be excluded.

Unilateral or bilateral adrenalectomy may be performed to treat Conn’s syndrome depending on the pathology. This may be performed laparoscopically or via an open laparotomy. An appropriate method of analgesia should be discussed at the preoperative visit. Manipulation of the adrenal gland during tumour removal may cause cardiovascular instability due to the secretion of catecholamines although this is not as severe as with phaeochromocytoma. It is useful to have a short-acting α-blocker available (e.g. phenolamine). Replacement corticosteroid and mineralocorticoid therapy is required for all patients undergoing bilateral adrenalectomy and occasionally in those undergoing unilateral adrenalectomy. Hydrocortisone is given i.v. from the time of operation until oral medications can be administered, whereupon oral fludrocortisone and hydrocortisone are given.

**Cushing’s syndrome**

Many of these patients have poorly controlled hypertension and evidence of end-organ damage should be sought. Electrocardiographic abnormalities may suggest ischaemic heart disease (e.g. high voltage QRS, inverted T-waves) but these may be related to the Cushing’s disease itself and may revert to normal after curative surgery. Further problems may be encountered because of patients’ obesity; they may have sleep apnoea, giving a history of snoring and experience daytime somnolence. Impaired glucose tolerance and diabetes mellitus are common; appropriate measures should be taken (e.g. sliding scale insulin). Gastroesophageal reflux is also common and this group often require preoperative acid suppression therapy and rapid sequence induction. Extra care should be taken with positioning because there is susceptibility to pressure sores and fractures because of fragile skin and osteoporosis. If the Cushing’s syndrome is iatrogenic, an additional dose of steroids may be required preoperatively.

**Addison’s disease**

These patients should be given all their routine medication on the morning of surgery. Serum potassium and glucose concentrations should be checked preoperatively and re-checked regularly during the post-operative period. For major surgery, blood glucose should be checked every 4 h and electrolytes should be measured daily. I.V. hydrocortisone 25 mg should be given at induction. For minor surgery, the above regimen is sufficient. For intermediate surgery, such as hysterectomy, four doses of i.v. hydrocortisone 25 mg should be given over the first 24 h after surgery. For major surgery, 200 mg of i.v. hydrocortisone should be administered...
each 24 h until the patient can be re-started on maintenance therapy. In these cases, it is advisable to consult and share the patient's care with an endocrinologist.

References

3. Farling PA, McBrien ME, Breslin D. Endocrine physiology. World anesthesia 2002; 14

See multiple choice questions 91–95.