Adrenal insufficiency
A timely diagnosis and treatment plan count

MARK S. COOPER BM BCh, PhD, FRCP(London), FRACP

Typical features of adrenal insufficiency can be nonspecific and the diagnosis is often missed or delayed. Prompt treatment, both in the acute setting and long term, is required to avoid a potentially catastrophic adrenal crisis.

Key points

- **Adrenal crises are common in people with adrenal insufficiency and the effects can be catastrophic.**
- **Early administration of parenteral hydrocortisone is a crucial part of the management of patients undergoing a crisis.**
- **Healthcare providers are often too slow to give parenteral hydrocortisone because of inappropriate concerns regarding the risks of glucocorticoid use.**
- **Education and empowerment of individuals with adrenal insufficiency is key to long-term management.**

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Professor Cooper is Head of the Discipline of Medicine at Concord Clinical School, The University of Sydney, Sydney, NSW.

Adrenal insufficiency (also known as hypoadrenalism) is a relatively uncommon endocrine disorder that is associated with considerable mortality if unrecognised. The condition develops gradually and patients often have several encounters with primary care physicians before the diagnosis is made. Primary adrenal insufficiency (PAI; also known as Addison's disease) is due to intrinsic problems with the adrenal glands that lead to their destruction. Secondary adrenal insufficiency (SAI) is caused by diseases of the pituitary or hypothalamus that lead to failure to regulate the adrenal glands. Compared with PAI, SAI is caused by a more diverse range of pathologies and is often associated with abnormal levels of several pituitary hormones. The focus of this review will be on PAI.

Pathophysiology

Adrenal insufficiency refers to deficiency in the levels of one or more of the main hormones made by the adrenal cortex (i.e. cortisol and aldosterone). In patients with PAI, the secretion of both cortisol and aldosterone is deficient. In patients with SAI, the production of cortisol is deficient because of low levels of adrenocorticotropic hormone (ACTH), which is secreted by the pituitary and regulates cortisol synthesis; however, aldosterone production is maintained because it is regulated primarily by the renin–angiotensin system.

In Australia, the most common cause of PAI in adults is autoimmune adrenalitis but other causes include tuberculosis, other infections (e.g. HIV, cytomegalovirus, histoplasmosis), bilateral tumours or haemorrhage, and genetic conditions. PAI has a prevalence of about one in 10,000 and an incidence of four per million.[1] Although rare, PAI can be catastrophic if it is not recognised and treated in a timely manner.

Clinical presentation

The typical features experienced by patients with PAI are anorexia, weight loss, lethargy and nausea (see the case scenario in the Box). As these are nonspecific, the presence of PAI can be missed for considerable periods of time. A relatively specific feature is salt cravings but this is not always present and is usually only asked about once the condition becomes obvious.

Increased skin pigmentation is a characteristic and helpful clinical sign in patients with PAI. This is due to the activation of melanocortin receptors in the skin by high levels of ACTH (and possibly other pituitary-derived peptides). Such skin pigmentation is not seen in patients with SAI. Decreasing insulin requirements in an individual with type 1 diabetes should raise the possibility of PAI.

Without treatment, or in response to intercurrent illness, an adrenal (Addisonian) crisis is likely to develop in patients with PAI. This is characterised by circulatory collapse (often with rapid development) and more marked abnormalities in biochemistry, with significant hyponatraemia and hyperkalaemia. In children in particular, hypoglycaemia can also be a significant feature.

Hyponatraemia is a common but not universal finding in patients with adrenal insufficiency. Hyperkalaemia is a common feature of PAI but not SAI because it reflects aldosterone deficiency. In patients in advanced states of PAI, serum urea levels are often increased due to volume depletion. A common finding in patients with adrenal insufficiency is a mild increase in the level of thyroid-stimulating hormone with normal levels of free thyroxine. Although this may suggest there is associated autoimmune hypothyroidism, it is usually just a sign of glucocorticoid deficiency. Giving the patient thyroxine in this situation without glucocorticoids can precipitate an adrenal crisis. Thyroid function tests (and thyroid antibody levels) should be checked six to eight weeks after starting glucocorticoids and only then should a decision be made regarding thyroxine treatment.

Diagnosis

The appropriate approach in the diagnosis of PAI depends on the clinical context. In a patient presenting with an adrenal crisis, any delay in treatment could have serious consequences. Blood samples should be therefore taken to check the levels of cortisol and ACTH and then treatment started immediately.

When a patient is not in an adrenal crisis the preferred test is a tetracosactrin (ACTH [1-24]) stimulation test. This test involves measurement of cortisol and ACTH levels at baseline and cortisol levels 30 minutes after intravenous or intramuscular administration of 250 µg of synthetic ACTH (1 to 24 amino acid sequence). Although assay-dependent, a typical normal response to the test is a rise in cortisol levels to above 500 nmol/L. In individuals who fail to achieve such a rise, a diagnosis of adrenal insufficiency is likely, with a raised ACTH level at baseline (e.g. greater than double the upper limit of normal) indicating the presence of PAI whereas a low or low–normal ACTH level suggests SAI.

Case scenario

A 25-year-old woman was seen by her GP over several months with nausea and weight loss. The nausea varied in extent with bouts of vomiting but there was a progressive increase in severity over time.

Routine biochemical tests were unremarkable. She was referred to a gastroenterologist, and on investigation endoscopy was normal and coeliac disease was excluded. A diagnosis of cyclical vomiting was considered.

Additional tests to determine whether she had thyrotoxicosis showed a mildly raised level of thyroid-stimulating hormone (TSH) with normal levels of free thyroxine. She was treated with thyroxine to correct the high TSH level. Shortly after, her condition deteriorated with increased abdominal pain and vomiting, and she was unable to stand without feeling dizzy.

On admission to hospital her blood pressure was 80/40 mmHg when lying down. She was noted to have deeply pigmented skin even in areas that had not been exposed to the sun. A diagnosis of primary adrenal insufficiency was suspected and a blood test was taken to confirm the diagnosis. She was treated immediately with intravenous hydrocortisone and normal saline.

Management of patients with adrenal insufficiency

Acute management

Delays in initiating treatment for an adrenal crisis are a significant contributor to mortality in patients with PAI. It is important to emphasise that treatment will normally be needed before the results of diagnostic tests are available. The treatment of individuals who subsequently turn out not to have adrenal insufficiency is unlikely to be harmful.

Acute treatment of patients with a suspected adrenal crisis is initially with 50 mg hydrocortisone stat intramuscular or intravenous. Hydrocortisone is a direct replacement for the cortisol the adrenal gland is unable to make, hydrocortisone being the name used for cortisol when it is used as a medication. Intravenous normal saline is also given because affected individuals usually have a large deficit in both sodium and water. Subsequently, about 75 to 150 mg/day hydrocortisone is given in divided doses; for example, 25 mg every eight hours in patients with moderate illness or 50 mg every eight hours in those with critical illness.

Depending on clinical response, the dose of hydrocortisone can gradually be reduced over several days and eventually changed to oral dosing; for example, 20 mg in the morning and 10 mg in the early evening. When the total daily dose of hydrocortisone drops below 50 mg, fludrocortisone 100 µg should be added in those people suspected of having PAI. Fludrocortisone is given to replace the mineralocorticoid (aldosterone) that is deficient in patients with PAI.

The underlying cause of PAI should always be determined. The presence of adrenal antibodies indicates an autoimmune basis. If these antibiotics are not present, then more detailed evaluation is warranted, including adrenal imaging and specialised blood tests (e.g. to rule out adrenoleukodystrophy).

Table. Glucocorticoid replacement doses for patients with primary adrenal insufficiency and intercurrent illness

Severity of illness	Increase in glucocorticoid dose	Management plan
Mild illness (e.g. nonfebrile cough or cold, dental extraction under local anaesthetic)	No need for increase	–
Moderate illness (e.g. fever, minor trauma, minor surgery)	Triple the replacement dose, e.g. increase hydrocortisone dose from 20 mg/day to 60 mg/day	Continue for at least three days and return to normal dose 24 hours after resolution of illness
Severe illness (e.g. major surgery, major trauma, critical illness)	Increase dose to 25 to 50 mg hydrocortisone intramuscular or intravenous every six hours	Taper dose to normal by decreasing by 50% per day

Long-term management

The long-term management of patients with adrenal insufficiency is crucial and was discussed in depth in a previous article in this journal.[2] Long-term management is based on trying to mimic through replacement the normal diurnal and illness-related changes in circulating cortisol levels. Under normal nonstressed conditions cortisol production is high in the early morning and very low at midnight. Therefore, patients typically take a higher dose of hydrocortisone first thing in the morning followed by further smaller dose(s) later in the day. Hydrocortisone should be taken in two to three divided doses through the day and it is not necessary to take it with food. The first dose should be taken as soon as possible after waking. The later dose for a twice-daily regimen should be given at 2 to 3 pm, and in a three times a day regimen doses should be taken at midday and 4 to 5 pm. Glucocorticoids should not be administered after 5 pm for routine maintenance therapy in patients with PAI as glucocorticoid levels are normally low in the late evening.

Traditionally, the total recommended dose of glucocorticoid was about 30 mg/day but this amount is now considered to be excessive and most people manage with between 14 and 24 mg/day hydrocortisone (e.g. as 10 mg in the morning and 4 mg in the afternoon; or 14 mg in the morning, 4 mg at lunchtime and 4 mg in the afternoon). Dosing can also be calculated using body weight, with a morning dose of 0.12 mg/kg hydrocortisone, or body surface area, with a morning dose of 5.5 mg/m^2, and is more likely to result in cortisol levels within the normal healthy range than a fixed morning dose of 10 mg.[3]

An acceptable alternative medication to hydrocortisone is cortisone acetate. Cortisone acetate is a prodrug for hydrocortisone and is converted to hydrocortisone on the first pass through the liver. Prednisone/prednisolone are occasionally used under specialist supervision but dexamethasone is not appropriate as a replacement glucocorticoid in patients with adrenal insufficiency. Unfortunately, biochemical testing in an individual to determine the most appropriate glucocorticoid dose is not normally helpful, and dose adjustment is made primarily on the basis of the patient's energy levels and general wellbeing, changes in body composition and skin pigmentation. Fatigue, nausea and increased pigmentation are features of under-replacement and weight gain, insomnia and peripheral oedema are features of excessive replacement.

Fludrocortisone is given long term in patients with PAI. The typical dose is between 50 and 200 µg/day and is adjusted on the basis of blood pressure and serum electrolyte and renin levels.

Production of adrenal androgen dehydroepiandrosterone (DHEA) is also impaired in patients with PAI. This is not thought to have significant consequences for men. However, in women it is associated with reduced body hair; some studies have suggested that poor DHEA production can be associated with reduced libido and that some women could benefit from DHEA replacement.[4] This remains an area of controversy and use of DHEA replacement is not supported by findings from a systematic review and meta-analysis.[5] As such DHEA replacement is not routine.

A crucial aspect of corticosteroid replacement in patients with PAI is that the dose requires adjustment in the event of intercurrent illness. Where possible, individuals with PAI should be encouraged to make their own adjustments to their glucocorticoid replacement. Most experts are now moving to a three by three rule where the dose of glucocorticoid is increased by a factor of three for a minimum of three days.[2] For example, during a moderate illness, such as an upper respiratory or urinary tract infection associated with fever, a patient taking a total of 20 mg/day hydrocortisone should increase the dose to a total of 60 mg/day for at least three days and longer if the underlying problem has not resolved (Table). In situations where oral medication cannot be taken reliably, such as vomiting, then patients should be admitted to hospital unless intensive home support including parenteral administration of hydrocortisone can be arranged. To help patients manage in the interim between becoming unwell and being treated in hospital, they should have an intramuscular hydrocortisone injection kit available at home and be given appropriate training in its administration. In many parts of Australia, ambulance paramedics are able to administer this medication if patients or their relatives are unable to do so.

Patients should be advised to wear a medical alert bracelet or equivalent identification and to carry a 'steroid treatment card' outlining the nature of their corticosteroid replacement and emergency contact details. Despite patients taking these measures and even stating to medical staff in clear terms the

need for parenteral corticosteroid therapy, there continue to be delays in treatment in emergency departments of patients at risk of adrenal crisis. This appears to be due to a false belief that an adrenal crisis only develops slowly, whereas the reality is that it can develop rapidly due to a dramatic reduction in vascular tone.[6,7] Reinforcement of this message by both primary and secondary care practitioners to emergency services is important.

Role of primary and secondary care in patients with PAI

Current guidelines suggest that patients with PAI are reviewed by an endocrine specialist on at least an annual basis.[1] Patients should have an assessment of the adequacy of their current glucocorticoid replacement regimen. This will include taking a detailed history and measuring weight and blood pressure. Electrolyte levels and, where indicated, renin levels should be checked. Overtreatment with glucocorticoids could predispose patients to diabetes and osteoporosis;[8] it is therefore reasonable to check glycated haemoglobin levels and bone mineral densities on a periodic basis.

As patients with autoimmune adrenal insufficiency are at risk of developing other autoimmune conditions, such as thyrotoxicosis and pernicious anaemia, thyroid function tests, coeliac serology, vitamin B_{12} levels and a full blood count should be checked annually. Women should be made aware that the chance of premature ovarian failure is increased.

Advice for medical professionals and patient education is available through local endocrine nurse specialists and the Australian Addison's Disease Association (http://addisons.org.au). More detailed guidelines for the management of individuals with adrenal insufficiency are available and also deal with special situations such as management in pregnancy and childhood.[1,9]

Conclusion

Although rare, adrenal insufficiency can have catastrophic consequences if the diagnosis is missed. In the context of an actual or impending adrenal crisis, treatment should not be delayed and patients will often have a greater understanding of their needs than attending medical practitioners. Treatment of a suspected adrenal crisis is with intramuscular or intravenous hydrocortisone at a dose of 50 mg, followed by a normal saline infusion. Education of patients with PAI regarding self-adjustment of glucocorticoid treatment and management of crises and intercurrent illness is crucially important. Both the use of lower doses of glucocorticoids for replacement and patient self-management is encouraged. **ET**

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