Pituitary hormone replacement

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Abstract

Hypopituitarism is associated with increased morbidity and mortality. Hormone replacement therapies are available for effective treatment of anterior pituitary deficiencies of growth hormone, adrenocorticotropic hormone, thyroid-stimulating hormone, luteinizing hormone and follicle-stimulating hormone secretion. The posterior pituitary antidiuretic hormone can also be replaced. The aim of replacement therapy is to mimic as far as possible the normal physiology of the hormone and to avoid over-treatment. Currently available hormone preparations and their advantages and disadvantages are discussed.

Keywords adrenocorticotropic hormone; dehydroepiandrosterone; growth hormone; hydrocortisone; hypopituitary; oestrogen; testosterone; thyroxine

Hypopituitarism is associated with increased morbidity and mortality, and endocrine replacement therapy should aim to mimic the normal hormonal milieu as far as possible, thereby improving symptoms while avoiding over-treatment. Replacement therapy is available for corticotropin, thyrotropin, gonadotropin, growth hormone (GH) and antidiuretic hormone (ADH) deficiencies.

Adrenocorticotropic hormone deficiency

Hydrocortisone is pharmaceutically manufactured cortisol and is the logical choice for glucocorticoid replacement therapy because it directly replaces the missing hormone, cortisol, and its serum concentration can be monitored. Alternatives include cortisone acetate, which is metabolized to cortisol and can therefore be monitored in the same manner as hydrocortisone. Cortisone acetate's onset of action is slower than that of cortisol, but its duration of activity is longer. Cortisol is predominantly a glucocorticoid but has some mineralocorticoid action, as opposed to various synthetic glucocorticoids, such as prednisolone and dexamethasone, which are potent, pure glucocorticoids that are more difficult to dose titrate or monitor.

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What's new?

- Modified-release formulations of hydrocortisone for reduced frequency of dosing
- Testosterone replacement with gel preparations or 3-monthly injection should aim for testosterone concentrations in the mid-normal range
- Thyroxine replacement in central hypothyroidism may require titration to suppress thyroid-stimulating hormone
- Good-quality long-term surveillance of growth hormone replacement is required

The aims of hydrocortisone replacement are to replicate normal circadian rhythm and to avoid over-dosing, which can lead to features of Cushing's syndrome, including increased bone turnover and reduced insulin sensitivity.

However, it is impossible completely to mimic normal physiology with the preparations of hydrocortisone currently available.[1] The plasma half-life of cortisol is less than 2 hours and twice-daily regimens are associated with plasma concentrations that are high and non-physiological post-dose and very low in the late afternoon, when they are associated with lower quality-of-life scores than in patients taking more frequent doses.[2] Three-times-daily regimens (on rising, at noon and in the early evening (before 6pm)) are therefore recommended, although it is best to avoid large doses of glucocorticoid in the evening.

The total dose of hydrocortisone used in traditional regimens is supra-physiological for most patients. Recent evidence shows that cortisol production rates in normal individuals are significantly lower than previously believed. A total daily dose of 15—20 mg (10 mg in the morning, 5 mg at noon and 5 mg in the evening) is held to be the 'best-guess' starting dose.[3]

Monitoring of therapy is based mainly on clinical assessment of symptoms of over- or under-replacement, as there is no biochemical gold standard. However, most patients will undergo an 8-hour hydrocortisone day-curve or a modified three-point day-curve, aiming to place serum cortisol concentrations within the physiological range. Such monitoring may allow detection of minor degrees of over-replacement or under-replacement that are unlikely to be clinically obvious.

Formulations of modified-release oral hydrocortisone are now becoming available that allow less frequent dosing, with the aim of improving adherence.[4]

Patient education is crucial, so that patients understand the need to increase their hydrocortisone dose whenever they suffer an intercurrent illness or undergo a minor procedure; under these circumstances, the dose must be increased two- to threefold. The possibility of vomiting means that all patients should be advised to carry an emergency hydrocortisone pack containing hydrocortisone for intramuscular administration. In addition, patients should carry a steroid card or *MedicAlert* bracelet.

Thyroid-stimulating hormone deficiency

Diagnosing thyroid-stimulating hormone (TSH) deficiency and knowing when to start replacement therapy is a challenge; in pituitary disease, TSH is of little diagnostic value and to wait

until thyroxine (T4) is below the lower limit of a reference range is to wait too long. Secondary hypothyroidism is treated in the same manner as primary hypothyroidism: with T4 replacement therapy. The normal starting dose in young patients without evidence of cardiac disease is 75—100 μg daily. In the elderly and those with evidence of ischaemic heart disease, therapy should start at lower doses (25—50 μg daily or even on alternate days).

Measurement of serum TSH has traditionally been considered unhelpful in the monitoring of T4 replacement therapy, although it has recently been suggested that the finding of an unsuppressed TSH value in these patients may be indicative that they are undertreated with thyroxine. It is also generally accepted that the aim should be to restore the serum free T4 concentration to the middle/upper end of the normal range by titrating the dosage of levothyroxine in 25 μg increments. Thyroid function tests should be taken before administration of levothyroxine for the most accurate interpretation of serum concentrations.[5] Over-replacement with T4 over long periods of time may be associated with reduced bone mineral density (BMD), increased risk of osteoporotic fracture and an increase in the rate of development of atrial fibrillation; excessive doses of T4 should therefore be avoided. In patients with suspected hypopituitarism, T4 therapy should be delayed until adrenocorticotropic hormone (ACTH) deficiency has been excluded or treated because there is a risk of worsening the features of cortisol deficiency. Patients taking oestrogen or GH replacement therapies may require increased doses of levothyroxine as a result of effects on binding globulins and deiodinase activity.

Although it is much discussed in the literature and occasionally used in clinical practice, there is currently no good evidence for the addition of liothyronine (L-T3) to the thyroid replacement regimen.[6]

Gonadotropin deficiency

Patients who do not desire fertility

In both sexes, sex steroid replacement therapy is important for the maintenance of well-being, normal body composition, BMD and sexual function.

Women: sex steroids can be provided by many standard hormone replacement therapy preparations. Progesterone must be given cyclically or continuously in all women with a uterus in order to prevent the possible effects of unopposed oestrogen on the endometrium (dysfunctional bleeding, endometrial cancer). Oestrogen can be delivered as a tablet, a patch, a gel or an implant. Oestrogen replacement therapy can minimize the risk of osteoporosis when started early, but its long-term effects on the cardiovascular system and breast cancer risk in women below the age of 50 remain understudied. Treatment should be continued until the typical age of the menopause (about 51 years of age) and the decision to treat for longer should be based on the principles guiding hormone replacement therapy in all postmenopausal women (Table 1).

Men: androgen replacement therapy for men with gonadotropin deficiency is available in many modalities. The choice of preparation depends on local availability and the wishes of the patient. Intramuscular injection of testosterone esters every 2—3 weeks has traditionally been the most commonly used method, but this leads to significant variations in the peak and trough plasma testosterone concentrations and has been largely abandoned in favour of transdermal or longer-acting intramuscular preparations, which generate more stable plasma concentrations.

Transdermal preparations in the form of gels are now the most popular forms of testosterone replacement. They have the advantage of maintaining stable physiological testosterone

Hormone replacement therapy

Hormone deficiency	Replacement	Usual daily dose
Growth hormone	Growth hormone	0.3—1 mg subcutaneously in the evening
Gonadotropins		
• Women	Oestradiol valerate	1—2 mg daily orally
	or	
	Conjugated equine oestrogens	0.625—1.25 mg daily orally
	plus	
	Progesterone	Dose depends on preparation used Sex steroids may be administered transdermally (oestradiol, 25—100 μg/24 hours)
• Men	Intramuscular (IM)	
	• Testosterone ester (*Sustanon*®) (testosterone propionate, phenylpropionate and isocaproate)	250 mg IM every 2 or 3 weeks (limited availability)
	• Testosterone undecanoate (*Nebido*®)	1000 mg/12 weeks
	Transdermal	
	• Gel sachet	50 mg/5 g sachet/24 hours
	• Gel dispenser	10 mg/0.5 g dispensed
	Buccal	30 mg/12 hours
Thyroid-stimulating hormone	Levothyroxine	75—150 μg daily
Adrenocorticotropic hormone	Hydrocortisone	10 mg morning, 5 mg noon, 5 mg evening
Prolactin	Nil	—
Antidiuretic hormone	Desmopressin	10—40 μg daily intranasally in two or three divided doses 300—600 μg daily orally in two or three divided doses

Table 1