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, adrenocorticotrophic 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 overtreatment. Currently available hormone preparations and their advantages and disadvantages are discussed.

Keywords Adrenocorticotrophic hormone; dehydroepiandrosterone; growth hormone; hydrocortisone; MRCP; oestrogen; testosterone; thyroxine

Key points

- The dose of hydrocortisone replacement is typically 15—20 mg per day. Initiating thyroxine and growth hormone (GH) replacement in unreplaced adrenocorticotrophic hormone-deficient patients can be dangerous and potentially induce hypoadrenalism
- Refer to the SfE Emergency guidelines for advice about emergency hydrocortisone replacement and how to amend doses at times of illness; intercurrent illness in a patient with hypopituitarism can be fatal if the hydrocortisone dose is not increased appropriately
- During thyroxine replacement in central hypothyroidism, dose titration should aim to place free thyroxine concentrations in the upper half of the reference range, depending on the symptoms
- Testosterone deficiency in men and oestrogen deficiency in women <50 years of age should be treated with hormone replacement if there are no contraindications
- Fertility is achievable in males and females with hypopituitarism with appropriate hormonal regimens
- GH replacement in adults with severe GH deficiency can significantly improve quality of life, body composition and lipid profile
- Desmopressin treatment for diabetes insipidus should not be stopped without expert advice

Introduction

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 overtreatment. Replacement therapy is available for corticotrophin, thyrotrophin, gonadotrophin, growth hormone (GH) and antidiuretic hormone (ADH) deficiencies.

Adrenocorticotrophic hormone (ACTH) deficiency

The management of acute hypoadrenalism is beyond the scope of this article, but it is essential that it is recognized as a medical emergency requiring urgent treatment.[1]

Hydrocortisone is pharmaceutically manufactured cortisol. It is the logical choice for glucocorticoid replacement therapy because it directly replaces the missing hormone, cortisol, and 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.

The aims of hydrocortisone replacement are to replicate normal circadian rhythm and avoid overdosing, which can lead to features of Cushing's syndrome, including bone loss and insulin resistance.

It is impossible to completely mimic normal physiology with the preparations of hydrocortisone currently available. The plasma half-life of cortisol is <2 hours, and twice-daily regimens are associated with non-physiological peaks and troughs. Three-times-daily regimens (on rising, at noon, in the early evening (before 6 p.m.)) are therefore recommended, although compliance can be a problem and it is best to avoid large doses of glucocorticoid in the evening.

In patients with ACTH deficiency, a total daily hydrocortisone dose of 15—20 mg (10 mg in the morning, 5 mg at noon, 5 mg in the evening) is held to be the 'best-guess' starting dose; however,

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the dose required can vary dependent on severity of ACTH deficiency and endogenous cortisol secretion.

Monitoring of therapy is based mainly on clinical assessment of symptoms of over- or under-replacement such as blood pressure and weight, as there is no biochemical gold standard. However, most patients 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 can allow detection of minor degrees of over-replacement or under-replacement that are unlikely to be clinically obvious.

A modified-release oral hydrocortisone is now available that allows less frequent dosing, with the aim of improving adherence; however, it is expensive and long-term benefits remain to be seen.

There is increasing interest in prednisolone as a potentially effective alternative to hydrocortisone as an inexpensive once-daily preparation with an appropriate pharmacokinetic profile. It is difficult to monitor therapy, although plasma concentrations can be measured by mass spectrometry.

Patients should be taught to increase their hydrocortisone or alternative glucocorticoid dose with intercurrent illness or minor procedures; in these circumstances, the dose must be increased 2- to 3-fold.[1] Patients should be advised to carry an emergency hydrocortisone pack containing hydrocortisone for intramuscular administration in case of vomiting, diarrhoea or an acute hypoadrenal crisis. In addition, patients should carry a corticosteroid card or wear a MedicAlert bracelet.[1]

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 replacement is generally indicated if thyroxine (T4) levels start to fall; it is not necessary to wait until T4 is below the reference range. 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 micrograms daily (1.6–1.8 micrograms/kg per day). In patients who are elderly and have evidence of ischaemic heart disease, therapy should start at lower doses (25–50 micrograms daily or even on alternate days).

Measurement of serum TSH is unhelpful for monitoring T4 replacement therapy in central hypothyroidism. 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 micrograms increments. For the most accurate interpretation of serum concentrations, thyroid function tests should be taken before administering levothyroxine. Over-replacement with T4 over time can be associated with reduced bone mineral density, increased risk of osteoporotic fracture and increased 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 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.[2]

Although it is much discussed in the literature and occasionally used in clinical practice, there is currently no good evidence for the use of liothyronine as monotherapy or in combination with levothyroxine although this can be warranted in individual cases.

Gonadotrophin deficiency

Patients who do not desire fertility

In both sexes, sex steroid replacement therapy is important to maintain well-being, normal body composition, bone mineral density and sexual function.

Women: oestrogen therapy with cyclical progesterone to replicate a normal menstrual cycle is the usual method of replacing sex steroids in women with hypopituitarism. Progesterone must be given cyclically or continuously in all women with a uterus in order to prevent adverse effects of unopposed oestrogen on the endometrium (dysfunctional bleeding, endometrial cancer); if given cyclically, a minimum of three or four bleeds per year is recommended. Progesterone can be delivered orally, transdermally or via a local intrauterine contraceptive device. Oestrogen can be delivered as a tablet, transdermal patch or gel. A transdermal delivery of oestradiol combined with micronized progesterone is probably the most physiological form of replacement and associated with the lowest risk of venous thromboembolism and stroke.[3]

Hormone replacement therapy (HRT) improves vasomotor, urogenital and sexual symptoms, and minimizes the risk of osteoporosis. The long-term effects on the cardiovascular system and breast cancer risk in women <50 years of age are incompletely understood, but available data do not suggest increased risk of cardiovascular disease or breast cancer. If HRT, rather than an oral contraceptive pill, is used, it should be recognized that this is not an effective contraceptive. Treatment should be continued until the typical age of menopause (about 51 years), and the decision to treat for longer should be based on the principles guiding HRT in all postmenopausal women.[3]

Men: androgen replacement therapy for men with gonadotrophin deficiency is available in many modalities. The choice of preparation depends on local availability and the patient's wishes. Intramuscular injection of testosterone esters every 2–3 weeks has traditionally been most commonly used, but this leads to significant variations in the peak and trough plasma testosterone concentrations; it 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 the most popular form of testosterone replacement. They have the advantage of maintaining stable physiological testosterone profiles and are easy to administer, but have to be applied daily. They can cause local irritation, and care must be taken to avoid testosterone transfer to other people, particularly pregnant women and children. Most gels are available in 50 mg sachets, but a gel dispenser system allows more careful titration