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CLINICAL QUESTION

What is the best long-term management strategy for patients with primary adrenal insufficiency?

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Summary

Primary adrenal insufficiency is treated with glucocorticoid and mineralocorticoid replacement therapy. Recent data revealed that health-related quality of life in adrenal insufficiency is impaired in many patients and that patients with adrenal insufficiency are also threatened by an increased mortality and morbidity. This may be caused by inadequate glucocortiocid therapy and adrenal crisis. Therefore, the optimization of hormone replacement therapy remains one of the most challenging tasks in endocrinology because it is largely based on clinical grounds because of the lack of objective assessment tools. This article provides answers to the important daily clinical questions, such as correct dose finding, dose adaptation in special situations, e g, pregnancy, improvement of quality of life and measures for protection from adrenal crisis. Other important aspects discussed are side effects of glucocortiocid replacement therapy and interactions with other drugs.

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Finding the correct dose

How can I control quality of replacement?

Individual dose adaptation and monitoring of glucocorticoid replacement remains challenging as cortisol production is highly variable during the day and further influenced by many factors that activate stress responses like physical activity, pain, infections, psychological stress, low blood glucose, etc. Recommended daily hydrocortisone doses in primary adrenal insufficiency (PAI) are lower than estimated before ranging between 10 and 20 mg.[1,2] However, this reflects a mean need during the day and may not cover the need induced by additional stressors. Therefore, patients need to learn how to adapt their dose according to daily needs in a more flexible manner. Furthermore, comedication has to be taken into account as, e. g., inductors of CYP3A4 increase cortisol clearance which may necessitate a dose increase up to doubling the dose (see section 'Are there any interactions with other drugs?'). Some authors recommend weight-adjusted hydrocortisone dosing, thrice daily before food, leading to a reduction of intervals with excess cortisol exposure during the day and to reduced interindividual variability of cortisol profiles.[3] This might be helpful when newly starting hydrocortisone replacement. However, other authors showed that there was no correlation of a clinical score assessing quality of replacement therapy with total or body weight-adjusted glucocorticoid dose.[4] This demonstrates that dose finding has to be individually adapted and also requires patient education enabling the patient to correctly and autonomously adapt the hydrocortisone dose. Because of the nonphysiological cortisol profiles achieved by current replacement regimes, to date no reliable laboratory parameter exists for correct assessment of replacement quality. Even the serum cortisol day curves suggested by some authors only give a rough estimate and help to identify largely over- or underreplaced patients but are of limited value in the standard monitoring of glucocorticoid replacement.[4] Treatment surveillance is mainly guided by clinical judgment assessing daily performance, subjective health status and signs and symptoms of glucocorticoid over-replacement (weight gain, skin alterations) or underreplacement (fatigue, nausea, myalgia and joint stiffness). Fatigue is, however, a common complaint also under apparently optimized standard replacement conditions. Therefore, an increase in hydrocortisone should timely be reevaluated to avoid overdosing.

Fludrocortisone is used for mineralocorticoid replacement as a single morning dose of 0·05–0·20 mg. Electrolytes within the normal range, normal blood pressure without evidence of postural hypotension, and a plasma renin concentration in the upper normal range indicate adequate mineralocorticoid replacement.

How to adapt for daily life?

In addition to the circadian profile, cortisol levels increase in response to stressful stimuli (strong physical stress and strong

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and prolonged psychological stressors). In cases of defined strong and prolonged physical activity (e.g. intensive fitness training or running for several hours), an additional hydrocortisone dose of 5–10 mg is recommended. In contrast, short physical activity does not seem to require additional doses.[5] An additional dose of hydrocortisone might also be considered in situations of severe and prolonged psychological stress (e.g. death of a relative, acute depression) as such conditions have also been reported to cause adrenal crisis.[6] Ideally, the additional dose should be given well before – not at the time of – the expected stress; however, this is often difficult to foresee. It is important to timely reduce the hydrocortisone dose back to the standard dose to avoid over-replacement. Short lasting stressors usually do not routinely require dose adaptation. Shift work leads to adaptation of cortisol profiles in healthy subjects according to their sleep-wake cycles. Patients on shift work usually report better performance when they adapt their hydrocortisone dose according to the time of awakeness.

In case of hot climate or strong perspiration, it is necessary to increase the fludrocortisone dose (0·1–0·2 mg/day) and/or the salt intake.

What do I have to consider when the patient is pregnant?

According to the analyses from Norwegian and Swedish registries, number of births in women being diagnosed with PAI is reduced.[7,8] The vast majority of women with PAI have uneventful pregnancies with normal pregnancy outcome. However, an increased risk of preterm delivery has been noted.[7] Some authors state that an increase in hydrocortisone dose by 50% during the last trimester may be necessary,[9,10] because of an increase in cortisol-binding globulin (CBG), total cortisol and also free cortisol. Single cases of adrenal crisis because of missing dose adaptation have been observed.[6] In summary, the need for an increase in hydrocortisone dose during the last trimester is still controversial. We recommend close clinical supervision during the last trimester and dose adaptation according to clinical judgement. Because of the anti-mineralocorticoid effect of progesterone, the fludrocortisone dose needs to be increased depending on serum potassium levels and blood pressure. Plasma active renin concentrations are not informative during pregnancy.[11] At delivery, hydrocortisone 100–150 mg/day intravenously during the first 24–48 h is recommended followed by rapid tapering and oral administration.

Can/should I modify the replacement dose in hypertension?

In hypertensive patients, the hydrocortisone dose is usually maintained. The fludrocortisone dose may, however, be reduced under supervision of serum potassium levels.

No data exists in patients with adrenal insufficiency using antihypertensive medication that influences the renin-angiotensin system, however, plasma renin concentrations should be interpreted with caution for monitoring the fludrocortisone dose.

Improve quality of life

How can I improve quality of life?

It has been shown that despite standard replacement therapy, some patients with adrenal insufficiency still suffer from impaired well-being. This has been partly associated with nonphysiological cortisol profiles achieved by current regimens that restore neither the circadian nor the ultradian pattern of physiological cortisol secretion. Preclinical studies however indicate that ultradian cortisol patterns may be of further clinical relevance.[12,13] New delayed-release hydrocortisone preparations are under development, which result in a more physiological cortisol profile.[2,14] However, the superiority of such a hydrocortisone preparation remains to be demonstrated. Circulating epinephrine levels are decreased in Addison's disease [15] which may contribute to the observed fatigue, limited glucose response to exercise and neuroglycopenic symptoms reported by some patients.[5,16] No replacement strategy for epinephrine deficiency is available. However, it might perhaps be helpful to combine hydrocortisone with a small carbohydrate-rich meal before exercising.[16]

Which patient benefits from DHEA substitution?

DHEA and DHEA-S are highly abundant adrenal steroids, but their physiological role is still not fully elucidated and both steroids are not crucial for survival. DHEA is converted into sex steroids and represents the main source of androgen production in women. DHEA replacement in women with PAI leads to restoration of pubic and axillary hair and sebum production. A recent meta-analysis on the effects of DHEA replacement revealed some beneficial effects on general quality of life, however, the overall evidence does currently not support routine use of DHEA in PAI.[17] DHEA (12·5–50 mg/day) may be beneficial in selected patients (mainly women) with PAI and complaints related to androgen deficiency like decreased libido, dry skin or depressive symptoms.

Protection from adrenal crisis

Patients with PAI need to adjust their glucocorticoid dose adequately in case of stress to cover the increased demand in adrenal steroids. Adrenal crises occur in PAI with a frequency of about 6·6 adrenal crises per 100 patient years.[6] Precipitating causes are mainly gastrointestinal infection and fever (45%), but also other stressful events (major pain, surgery, emotional distress, heat, pregnancy).[6] Especially patients with additional comorbidities are at a higher risk.[18] One of the major problems is the inadequate training of patients and their relatives how to react in situations with stress and illnesses. Only a very small proportion of patients possesses a glucocorticoid emergency kit.[6,18] In addition, the unawareness and lack of knowledge of physicians result in diminishing the dose or even stopping glucocorticoid replacement therapy.[6] As particularly infectious disease is one of the major causes of adrenal crises, physicians should be aware that an early aggressive treatment of infectious diseases combined with sufficiently increased glucocorticoid

doses is mandatory. The establishment of an emergency hotline for both patients and attending physicians should be considered to minimize hospitalization for adrenal crisis.[6] In the recent years, new guidelines for the management of pre-hospital adrenal crisis were established for all ambulance services in Great Britain. The use of hydrocortisone in the pre-hospital management for patients who are steroid-dependent in addition to an extensive training for paramedics have been successful: patients are 'flagged' on ambulance systems so crews have prior warning when attending a patient with adrenal insufficiency, patients feel safer and paramedics are more able to manage adrenal crisis successfully.

Patient's education

All patients with adrenal insufficiency must receive a structured crisis prevention education together with their partners or relatives. This should be given at the time of first diagnosis. In addition, each visit (every 3 or 6 months) the patient should be trained in recognizing typical stressful situations (fever, infection, stress, surgery or trauma) and symptoms of acute adrenal insufficiency, and instructed on glucocorticoid dose adjustment in these situations. In case of minor physical stress (infectious diseases with fever, stress, surgery under local anaesthesia) or major and prolonged psychic stress, the daily hydrocortisone replacement dose should be doubled or tripled to approximately 40-50 mg/day. When prednisolone is used as glucocorticoid replacement, standard substitution of 5 mg prednisolone daily should be increased to 10–15 mg/day. Under conditions of medium or major physical stress (trauma, surgery with general anaesthesia, delivery) and in case of diarrhoea/vomiting, hydrocortisone needs to be substituted intravenously (100–250 mg/24 h). As high doses of hydrocortisone have a mineralocorticoid effect, adjustment of fludrocortisone during these stressful events is not required.

All patients with adrenal insufficiency must receive a steroid emergency card that gives information on the underlying cause, the current replacement regime and the responsible endocrinologist. Alternatively, the patient should wear a Medic-Alert bracelet, necklace or anklet providing an emergency phone number to access the patient's clinical details.

Emergency set

A glucocorticoid emergency kit should be provided to every patient. This may contain rectal suppositories [prednisolone-suppository (Rectodelt®)], which are easily administered and should be carried by every patient, especially on travels. One suppository contains 100 mg prednisolone (equals 400 mg hydrocortisone). However, in the case of diarrhoea, rectal administration is not regarded as sufficient. A hydrocortisone emergency kit (e.g. 100 mg hydrocortisone-21-hydrogensuccinate for intramuscular injection) is furthermore prescribed, and patients (together with relatives) are educated in self-administration of hydrocortisone as intramuscular injection in emergency situations.

Treatment of adrenal crisis

An Addison's crisis requires substitution of 100 mg hydrocortisone as intravenous bolus and then 150 mg hydrocortisone as a continuous infusion over 24 h. Furthermore, an adequate fluid replacement with physiological saline solution (NaCl 0·9% intravenously initially 1 l/h) under continuous cardiac monitoring is necessary. If the reason for the patient's condition is adrenal insufficiency, improvement in response to glucocorticoids is usually seen within 12 h. Depending on the clinical condition of the patient, the steroid dosage may be reduced the following day and then tapered to the patient's individual daily dose.[19]

Avoid side effects of therapy

Is there any risk of osteoporosis?

Limited data are available regarding long-term side effects of glucocorticoid replacement therapy.[20] A series of small studies in PAI have shown inconsistent correlation between bone mineral density (BMD) and disease duration, glucocorticoid type and dose.[4,21–26] The most recent and largest study by Lovas *et al.* [27] showed that BMD at the femoral neck and lumbar spine is reduced in PAI suggesting undesirable effects of the replacement therapy. Nowadays it is believed that bone loss is not influenced by duration or type of steroid treatment,[23,26] but rather by the glucocorticoid dose.[22] The current studies support the recommendation that daily hydrocortisone dose should not exceed 20 mg. Patients with higher doses, additional risks for osteoporosis (family history, bone fractures, hypogonadism and postmenopausal women) or longer disease duration (who probably received higher glucocorticoid doses in the past) should be evaluated by DXA scan. Additionally, vitamin D insufficiency should be treated.

What about the metabolic risk profile?

A physiological 24-h cortisol rhythmicity is partly responsible for the normal diurnal variation in glucose tolerance. Patients with secondary adrenal insufficiency seem to have higher cholesterol levels, hypertriglyceridaemia and an increased prevalence of hyperglycaemia and/or diabetes mellitus compared with hypopituitary patients without glucocorticoid replacement therapy.[28] Another study showed that those patients had a dose-related increase in body mass index, triglycerides, low-density lipoprotein cholesterol and total cholesterol levels,[29] suggesting that glucocorticoid replacement therapy is associated with some, but not all features of the metabolic syndrome. In patients with PAI receiving different hydrocortisone dose regimens or dexamethasone 0·1 mg/15 kg body weight at breakfast over a 4-week observation period, no significant difference was observed in fasting plasma insulin, insulin resistance or beta-cell function.[30] Taken together, these scarce data suggest that lower levels of glucocorticoids have fewer adverse effects and support the view that recent glucocorticoid doses were slightly too high [29] and that even a modest increase in the dosage above the average daily hydrocortisone production rate might cause an adverse metabolic profile.[2] It is recommended that

patients on higher glucocorticoid doses or coexisting metabolic symptoms should be checked on a regular basis.

How can I estimate the risk of additional autoimmune diseases for the patient and its relatives?

In large series of patients with Addison's disease, concomitant autoimmune disease was detected in about two-thirds of the patients.[31,32] As several autoimmune diseases are preceded by a long-term pre-clinical period prior clinical manifestation, detection of autoantibodies might help to predict further autoimmunity. As antibody-measurements become better available, this might be helpful in future for risk assessment, however, currently no consensus on a general screening of patients with Addison's disease exists. In patients with autoimmune PAI, thyroid function should be controlled on a regular basis. Patients should further be screened for possible gastrointestinal malabsorption (e.g. vitamin B12 and gliadin-antibodies) and for blood glucose/HbA1c to early discover diabetes mellitus. Relatives of those patients have an increased risk to develop autoimmune adrenal insufficiency and should be evaluated for symptoms of hypocortisolism.

Are there any interactions with other drugs?

Rifampicin increases cortisol clearance [33,34] and glucocorticoid replacement should be doubled during rifampicin treatment. Other drugs such as antifungal therapies (e.g., ketoconazole), hypnotic agents (e.g. etomidate, barbiturates), thyrosine kinase inhibitors (e.g. sunitinib), phenytoin, carbamazepine and many more are known to interfere with glucocorticoid synthesis and metabolism (acceleration of CYP3A4 metabolism) and may cause or aggravate adrenal insufficiency.[35] Other drugs such as ritonavir, fluoxetine, diltiazem and cimetidine are known to inhibit CYP3A4 metabolism and might result in increased hydrocortisone levels.[2]

Mitotane (o,p'DDD) is a strong CYP3A4 inducer and increases CBG. Therefore, standard glucocorticoid replacement doses should be at least doubled to tripled during chronic mitotane treatment, e.g., in adrenal cortical carcinoma.[36] Estrogens are known to increase CBG and total cortisol levels. However, if it is necessary to increase the hydrocortisone dose in at least some Addison's women on contraceptive medication needs to be investigated in further studies.

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