REVIEW

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Treatment and Follow-up of Non-stress Adrenal Insufficiency

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Abstract

Adrenal insufficiency (AI) is defined as the inability of the adrenal cortex to produce adequate amounts of glucocorticoids and/or mineralocorticoids. As these hormones have important roles in water-salt balance and energy homeostasis, AI is a serious and potentially life-threatening condition. Glucocorticoid replacement therapy is vital in all cases of AI. In children with primary AI (PAI), it is recommended to start glucocorticoid replacement therapy with three or four doses of hydrocortisone and adjust according to individual need. Long-acting glucocorticoids such as prednisolone and dexamethasone are not recommended in children with AI. Mineralocorticoid and salt replacement therapy is also necessary in PAI with aldosterone deficiency. In childhood, it is recommended that patients are monitored at least every three to four months with clinical evaluation including weight gain, growth rate, blood pressure and general well-being of the patient. To prevent adrenal crisis in patients with PAI, glucocorticoid dose adjustment is recommended to patients and/or their families according to the magnitude and severity of the stress situation. This education should include recognition of conditions leading to adrenal crisis, signs of adrenal crisis and how to respond to an impending adrenal crisis. With long-term use of glucocorticoids, the lowest possible dose should be maintained to control the disease to avoid possible side effects. Here, members of the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes' present an evidence-based review with good practice points and recommendations for the diagnosis and follow-up of non-stress AI.

Keywords: Adrenal insufficiency, adrenal crisis, glucocorticoid, family education

Introduction

Adrenal insufficiency (AI) is defined as the inability to produce adequate amounts of glucocorticoids and/or mineralocorticoids from the adrenal cortex. Non-stress AI impairs critical functions, such as energy homeostasis, electrolyte balance and immune regulation, leading to symptoms including chronic fatigue, hypotension and increased susceptibility to other illnesses. Effective management of this condition requires early diagnosis and appropriate hormone replacement therapy to prevent serious complications (1).

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for 'treatment and follow-up of non-stress AI' in childhood and adolescence. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

1. Glucocorticoid Treatment in Adrenal Insufficiency

The basis of treatment in AI is glucocorticoid replacement. The main goals of treatment are to reduce the signs and symptoms of AI, to prevent the development of adrenal crisis by ensuring normal physical and pubertal growth, and also to prevent long-term complications (2,3). Inadequate treatment (in terms of dose or duration) may cause signs

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of AI. Overtreatment is associated with iatrogenic Cushing syndrome (ICS), growth suppression (not necessarily with Cushingoid signs), osteoporosis, increased risk of cardiovascular disease and poor metabolic control (3). Both under- and overtreatment have a negative effect on growth and development in children (4,5).

Long-term glucocorticoid replacement therapy is given in all cases of AI. If aldosterone deficiency is also present in primary AI (PAI), mineralocorticoid and sodium chloride therapy is also needed. Anti-inflammatory and growth suppressive effects of the preparation, mineralocorticoid activity, plasma and biological half-life and route of administration are the key features of the glucocorticoid when choosing which treatment to give (6). Hydrocortisone is the synthetic form of natural cortisol with high oral bioavailability (7), short half-life and less growth suppressive effect (2). It is also the glucocorticoid preparation of choice in childhood because it has fewer side effects compared to synthetic prednisolone and dexamethasone (1,2). Due to the half-life of hydrocortisone of approximately 90 minutes, three or four doses per day are recommended to mimic physiologic cortisol release (1). In addition, hydrocortisone can be titrated more easily than more potent, long-acting glucocorticoids, which reduces the potential for long-term side effects (1).

Hydrocortisone, the first choice glucocorticoid in children, is generally administered orally at a dose of 7.5-15 mg/m^2/day in three or four doses. Hydrocortisone has a high protein binding capacity and its clearance increases at high doses. Hydrocortisone clearance is 26% lower in the evening than in the morning (8). However, it is recommended that the first and highest dose should be given in the morning after waking up, the second dose should be given after lunch and the third dose should be given at least 4-6 hours before sleep and at the lowest dose in order to be compatible with the circadian rhythm and not to disrupt sleep quality and insulin sensitivity (1,9,10). It may also be recommended to divide the total daily dose into three doses, with half the total given in the morning and the other half divided between midday and the evening (1).

There are no published randomized control studies on different treatment regimens in children with PAI (1). The first aim of treatment is to use the lowest dose of glucocorticoid that allows adequate growth and pubertal development and controls the signs of AI. Another aim is to mimic the physiologic release of cortisol and to prevent the side effects of high doses. To better plan the dose of GC, the endogenous cortisol production rate is taken as a basis. A few studies have shown that the physiologic cortisol production rate is 6-8 mg/m^2/day in older children and adults (11,12), but there is insufficient data in children under 5 years of age. While an initial hydrocortisone dose of 8 mg/m^2/day is thought to be sufficient for replacement therapy in non-congenital adrenal hyperplasia (CAH) patients with PAI, supraphysiologic doses of 10-15 mg/m^2/day are needed to suppress adrenocorticotropic hormone (ACTH) secretion, since there is an additional risk of increased adrenal androgen production due to ACTH in patients with CAH.

Children treated with hydrocortisone experience several spikes in cortisol concentrations during the day, often reaching supraphysiologic levels. This is followed by prolonged periods of hypocortisolemia between doses. Therefore, new technologies are being developed to provide more physiologic glucocorticoid replacement therapy, including new glucocorticoid formulations, subcutaneous hydrocortisone pump and some adjuvant therapies (13).

When hydrocortisone is not available and after the epiphyses have closed, glucocorticoid preparations such as prednisone, prednisolone, methylprednisolone, or dexamethasone may be used. As an alternative to hydrocortisone, prednisone may be preferred in adolescents and adults with closed epiphyses with poor treatment compliance (1,14). However, dexamethasone is not preferred because of the high risk of Cushingoid side effects (1). Meta-analyses comparing hydrocortisone and prednisolone treatments have found no significant difference between the treatment groups in terms of 17-hydroxyprogesterone (17-OHP) levels in most studies. Prednisolone treatment has been associated with higher hydrocortisone-equivalent doses and has been found to significantly reduce final height compared to hydrocortisone. Studies comparing hydrocortisone and prednisolone have shown that, despite similar hydrocortisone-equivalent doses, prednisolone is associated with higher values for cardiovascular and metabolic risk markers, including body mass index (BMI), waist-hip ratio, serum insulin during oral glucose tolerance testing, total fat mass, and trunkal fat mass. Prednisolone has also been shown to be associated with higher rates of osteoporosis and fractures. In studies comparing dexamethasone with hydrocortisone/prednisolone, dexamethasone was found to cause significantly more adrenal suppression and was associated with higher values for cardiovascular and metabolic risk markers and lower bone mineral density (BMD), making its use not recommended in children (15,16).

The use of hydrocortisone in three or four doses per day may make it difficult for the patient to comply with treatment. A new generation of long-acting, slow-release, modified hydrocortisone preparations that better mimic physiologic cortisol release and continuous subcutaneous hydrocortisone infusion with a pump are being studied.

There are two modified hydrocortisone formulations; Plenadren® and Chronocort®. Plenadren®, a dual-release hydrocortisone preparation, was designed for single dose use, but failed to provide adequate replacement effect and required an additional glucocorticoid dose in the evening. Studies in adults show that it provided a better cortisol exposure duration profile compared to conventional hydrocortisone formulations, resulting in better metabolic outcomes and quality of life for patients. It is approved for use in adults, but not yet in children (3). Chronocort®, a delayed-release hydrocortisone given in two doses daily, has been reported to be successful in mimicking physiologic cortisol release and controlling androgen synthesis (3).

Continuous subcutaneous hydrocortisone infusion with a pump has been reported to be successful in achieving more normal morning ACTH and cortisol values and 24-hour salivary cortisol curves more in line with circadian rhythm in non-CAH PAI patients. However, in cases with complete glucocorticoid deficiency, the risk of adrenal crisis is high due to the risk of pump malfunction. Moreover, there are high costs, the need for training, and local skin sensitivity. These therapies may be an alternative treatment in cases where classical treatment is not well tolerated (17).

Good practice points:

1. Glucocorticoid replacement therapy is vital in all cases of AI. In PAI accompanied by aldosterone deficiency, mineralocorticoid and salt replacement therapy are also required (1⊕⊕⊕O).

2. In children with PAI other than because of CAH (non-CAH PAI), it is recommended to start glucocorticoid replacement therapy with hydrocortisone, with an initial dose of 8 mg/m^2/day, in three or four doses, and adjust it according to individual needs (2⊕⊕OO).

3. Long-acting glucocorticoids, such as prednisolone and dexamethasone, are not recommended in children with AI (2⊕⊕OO).

2. Mineralocorticoid Treatment in Adrenal Insufficiency

In neonates with proven aldosterone deficiency, fludrocortisone is usually used orally at an initial dose of 100 µg, divided into one or two doses per day. Dose adjustment should be made according to the needs of the patients during follow-up. In children older than 1 year, 50-100 µg/day is usually sufficient. In severely affected patients, mineralocorticoid replacement is provided intravenously with hydrocortisone and sodium chloride (1).

In infants, additional sodium chloride is needed due to mineralocorticoid resistance in immature renal tubules and low sodium content in breast milk and formula. Typically, 1-2 g/day of sodium chloride (17-34 mmol/day) is required in newborns and this need for support may continue for the first 12 months of life (1). The ideal is to use a standard salt solution prepared in the pharmacy or standard sodium chloride tablets (18). Increased secretion of vasopressin and ACTH is prevented by correction of hypovolemia with fludrocortisone and sodium chloride in infancy. Thus, less need for glucocorticoid doses and normal growth may be achieved in cases of CAH-related PAI (15,18).

Up to 20 mg of hydrocortisone used in standard AI treatment has mineralocorticoid activity equivalent to approximately 100 µg of fludrocortisone, 100 µg of fludrocortisone has glucocorticoid activity equivalent to approximately 1-1.5 mg of hydrocortisone (19). Since glucocorticoid absorption and clearance show individual differences, individualization of dose adjustment according to need, with intermittent monitoring after initial doses would be the most appropriate approach (2,3,14).

Good practice point:

1. In all cases with aldosterone deficiency, fludrocortisone is recommended at an initial dose of 100 µg/day, and sodium chloride supplementation is recommended for infants throughout the neonatal period and until the age of 12 months (1⊕⊕⊕O).

3. Treatment of Adrenal Androgen Deficiency

Patients with PAI frequently have adrenal androgen deficit, which can have serious consequences for female patients in particular while they are transitioning from youth to adulthood. Adrenal androgens, including androstenedione and dehydroepiandrosterone (DHEA), are essential for preserving androgen-dependent hair development, bone health, and general wellness. These androgens may also support sexual function and libido in females (20,21).

3.1. Recommendations for Androgen Replacement in Women

It is advised to take into account DHEA replacement medication for female patients who are entering adulthood from adolescence, especially if they are exhibiting signs of adrenal androgen deficit, such as poor energy, decreased libido, and lower quality of life. The initial recommended dose is 25-50 mg/day, which can be changed based on the clinical response and blood androgen levels. Monitoring should be done every six to twelve months, with a focus on

weighing the advantages of a higher quality of life against any possible drawbacks, such as hirsutism or acne (20,21).

Recommendations for Androgen Replacement in Men

Adrenal androgens often have a minor role in men with PAI because gonadal testosterone production is present. Thus, it is not advised to replace DHEA on a regular basis unless there is proof of a combined adrenal and testicular androgen insufficiency. In these situations, testosterone replacement treatment is recommended, with dosage and monitoring in line with accepted practices for the treatment of hypogonadism (1,3).

Men should only think about androgen replacement therapy if symptoms like diminished quality of life, low libido, or decreased muscle mass are evident and low androgen levels are proven (1,3).

Good practice points:

1. While transitioning to adulthood, women with PAI may consider DHEA treatment (25-50 mg/day), especially if they are experiencing symptoms of poor energy or decreased sexual interest (2⊕⊕OO).

2. It is not advised for men with PAI to get regular DHEA medication unless a concomitant testicular androgen deficit has been verified (2⊕⊕OO).

4. Transition from Adolescence to Adulthood

For individuals with AI, the shift from pediatric to adult endocrinology treatment is very important. The dosages of glucocorticoids and mineralocorticoids need to be reviewed and modified in accordance with adult dosing standards during this phase. The particular requirements of this age group, such as bone health, metabolic state, and mental health, should get extra consideration (1).

Glucocorticoid Dosing

Hydrocortisone should be administered at a physiological replacement dose, with modifications to take into consideration changes in body weight and the completion of growth. Adults are usually administered 15-25 mg/day of hydrocortisone in two or three doses (1).

Mineralocorticoid Replacement

To maintain normal blood pressure and serum electrolyte balance in individuals with aldosterone deficit, fludrocortisone should be adjusted. Adult dosage typically varies between 50 and 100 µg/day, split into one or two doses (1).

Support for Transition

To help the patient manage their condition on their own throughout the transition phase, a systematic strategy should be created. This include making sure that the patient is aware of stress dosage, the significance of sticking to their prescription schedule, and emergency response techniques. The patient and family should have a special session on managing adrenal crises, encompassing the following topics:

- Identification of adrenal crisis symptoms.

- The appropriate usage of hydrocortisone injections.

- When to seek medical attention in an emergency.

All things considered, to guarantee the best possible management of AI during the transition from youth to adulthood, meticulous planning and customized therapy modifications are required (1,3).

Good practice points:

1. For glucocorticoid dosing, hydrocortisone should be continued at a physiological replacement dose, with adjustments to account for growth completion and changes in body weight. In adults, hydrocortisone is typically given at 15-25 mg/day divided into two or three doses (1⊕⊕⊕O).

2. For mineralocorticoid replacement in patients with aldosterone deficiency, fludrocortisone should be adjusted to maintain normal blood pressure and serum electrolyte balance. Typical adult dosing ranges from 50-100 µg/day, divided into one or two doses and without restriction of salt intake (1⊕⊕⊕O).

5. Follow-up in Cases of Adrenal Insufficiency

Dose adjustment in glucocorticoid and mineralocorticoid replacement therapy should be adjusted not only according to normal laboratory values but also clinical findings, blood pressure, and serum sodium and potassium values (22). Although dose adjustment is not made according to a single parameter, the most important parameters in dose adjustment are growth rate of height, weight changes and evaluation of general well-being, which should be evaluated at each visit in patients with PAI (1).

Symptoms of cortisol deficiency, such as inadequate weight gain, fatigue, nausea, loss of appetite, hyperpigmentation and headache, indicate that the dose should be increased (1). Doses above 8 mg/m^2/day, which is above physiological

release, may suppress growth. Decreased growth rate with weight gain or other cushingoid findings indicate excessive glucocorticoid use. In addition, weight gain, insomnia and peripheral edema are also signs of glucocorticoid excess. Questioning the daily habits, energy status, mental concentration power, daytime sleepiness, frequency and degree of decreases in energy status of the patients may help in better adjustment of the glucocorticoid dose (1).

The ideal glucocorticoid dose in a growing child is the lowest dose that achieves the desired therapeutic goals (6).

Fludrocortisone treatment monitoring is recommended to be performed primarily according to clinical evaluation and serum electrolyte (sodium and potassium) measurements (1). Inadequate weight gain, salt cravings, dehydration, hyponatremia accompanied by hyperkalemia, and increased renin activity or level indicate inadequate fludrocortisone intake (1). Blood pressure should be routinely monitored, and blood pressure monitoring is especially important because mineralocorticoid sensitivity increases in the first year of life (1). Plasma renin measurement is recommended in case of dose modification and when there is thought to be a problem with treatment compliance (1).

Patients with PAI of unknown autoimmune origin may be evaluated annually in terms of conditions, such as diabetes mellitus, premature ovarian failure, vitamin B12 deficiency due to autoimmune gastritis, and especially thyroid disease, which may be associated with autoimmune diseases (1).

Good practice points:

1. In childhood, it is recommended to evaluate cases at a maximum interval of 3-4 months (ungraded best practice statement).

2. It is recommended that glucocorticoid therapy should be monitored by clinical assessment, including weight gain, growth rate, blood pressure and general well-being of the patient (ungraded best practice statement).

6. Long-term Risks in Treatment

Even if glucocorticoid therapy is optimal, normal circadian rhythm and pulsatile secretion cannot be achieved. Despite adequate glucocorticoid and mineralocorticoid treatment, a significant number of patients continue to have objective or subjective complaints (1). These complaints may be related with decreased function, decreased general perception, feeling unwell, etc., and may be related with under- or overdose of glucocorticoids. Studies into the effects of PAI and long-term glucocorticoid use are generally related to adult CAH cases. Metabolic, cardiovascular, and bone metabolism complications may be observed. It has also been shown that catecholamines and neuropeptides are impaired in PAI (23) and this is associated with cardiovascular variability, hypoglycemia and physical activity in CAH-related PAI (24).

6.1. Growth Suppression and Bone Health

Long-term glucocorticoid usage, especially at supraphysiologic levels, might affect linear development in children and adolescents and may contribute to lower final adult height. In addition, low BMD, an increased risk of osteoporosis, and bone fractures can result because of long-term high-dose glucocorticoid usage. Patients with CAH who are prescribed larger dosages of glucocorticoids to control their adrenal androgen production are at higher risk. Glucocorticoids, which also have a direct resorptive effect on bone, create a negative calcium balance by decreasing calcium absorption from the intestines and increasing calcium excretion from the kidneys. It is important to keep the steroid dose within physiologic limits to ensure normal growth and bone health in children. However, daily glucocorticoid use tends to be higher than total daily endogenous cortisol secretion in healthy people. Most studies of BMD in patients with CAH are limited by small patient numbers, heterogeneous populations and methods, such as age and glucocorticoid regimen. In children and adolescents using glucocorticoids for CAH, there was no evidence of a decrease in height-adjusted BMD measurements regardless of the type of steroid used, duration of use, serum androgen and 17-OHP levels (2,25,26). In a recent cross-sectional randomized controlled study conducted in adults, BMDs of women with CAH and non-CAH PAI were compared after 2 years of glucocorticoid treatment, and it was shown that BMD was lower in those with higher glucocorticoid doses and that glucocorticoid replacement should be performed at the lowest possible dose to maintain bone health (27). Despite the differences between studies, patients with CAH are at risk for osteoporosis at later ages. In adult patients with CAH, it is recommended that BMD measurement be performed in case of higher than average glucocorticoid dose use or non-traumatic bone fracture and then BMD should be measured at 2-5-year intervals (2). To preserve normal development and bone health, it is important to use the lowest effective dose. In high-risk patients, routine monitoring of growth parameters and evaluations of bone health using techniques such as dual-energy X-ray absorptiometry scans may be necessary (1).

6.2. Cardiovascular and Metabolic Risks

Individuals on long-term glucocorticoid medication may experience increased central obesity, dyslipidemia, and

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hypertension, all of which raise the risk of cardiovascular disease. Studies in individuals with CAH have indicated an increased incidence of cardiovascular risk factors, such as high blood pressure and unfavorable lipid profiles, which may contribute to long-term morbidity. In a study including metabolic evaluation, abdominal adiposity was observed in adolescents and young people with CAH in long-term follow-up with a higher rate of proinflammatory visceral adipose tissue increase compared to subcutaneous adipose tissue when compared with age-, gender- and BMI-matched controls (3,28). In a meta-analysis, a higher homeostasis model assessment-insulin resistance (HOMA-IR) value was found in CAH patients compared to controls. However, no significant difference was found in serum fasting blood glucose, insulin levels or lipid levels (3,29). In the same meta-analysis, systolic and diastolic blood pressure were slightly increased (3,29). Although it is difficult to evaluate cardiovascular (CVS) mortality and morbidity in patients, there are a few studies conducted in patients over the age of 50 years (3,30). While normal left ventricular morphology was evaluated in adolescent and adult patients with CAH, mild diastolic dysfunction and impaired exercise performance were found. More studies are needed to evaluate CVS and metabolic side effects (3,31,32).

In the follow-up of patients with PAI, routine monitoring of blood pressure, serum lipid levels, and markers of IR (HOMA-IR and fasting glucose) is advised. To lower these risks, lifestyle interventions including exercise and food adjustments should be promoted.

6.3. Psychological and Cognitive Effects

Long-term exposure to glucocorticoids can affect one's quality of life, mood, and cognitive abilities. Patients on long-term steroid treatment have reported experiencing symptoms such as anxiety, deptression, and trouble concentrating. Although the effects on mental health are frequently underappreciated, they can have a major impact on general wellbeing (3,30). Regular follow-up of patients who have AI should include mental health examination. To treat these symptoms, psychological assistance and, if necessary, pharmaceutical intervention should be taken into account.

6.4. Risk of Adrenal Crisis

The main goal in long-term treatment monitoring should be to use the lowest effective dose of glucocorticoids that prevents adrenal crises, allows adequate growth and adolescent development, and minimizes long-term hazards. Long-term care for children and adolescents with AI should include supportive therapy, customized dose modifications and routine follow-up assessments (3,26).

Patients with AI are nevertheless susceptible to adrenal crisis, even with proper glucocorticoid and mineralocorticoid medication, especially during times of elevated physiological stress, such as illness or surgery. It is important to recognize and treat this potentially fatal situation. It is imperative that patients and caregivers get ongoing education and training on the prevention and management of adrenal crises. In order to notify medical personnel in an emergency, patients should always wear medical identification and patients or their families should be provided with an emergency injection kit (33,34).

Good practice points:

1. In long-term glucocorticoid use, the lowest dose possible to control the disease should be maintained to avoid possible side effects. For bone health, age-appropriate calcium and vitamin D intake and weight-bearing exercises may be recommended in children (ungraded good clinical statement).

2. Chronic use of high-dose glucocorticoids can also lead to bone health complications such as decreased BMD, increased risk of osteoporosis, and bone fractures (2⊕⊕OO).

3. Patients receiving long-term glucocorticoid therapy are at risk for cardiovascular complications, including hypertension, dyslipidemia, and increased central obesity, which may elevate the risk of cardiovascular disease (2⊕⊕OO).

4. Symptoms such as anxiety, depression, and difficulty concentrating have been reported in patients on long-term steroid therapy. The impact on mental health is often under recognized but can significantly affect overall well-being (2⊕⊕OO).

7. Management of Recovery from Adrenal Suppression in Long-term Steroid Use

Synthetic glucocorticoids are widely used in clinical practice for their anti-inflammatory and immunosuppressive effects. One of the possible undesirable side effects of glucocorticoid therapy is the suppression of the hypothalamic-pituitary-adrenal (HPA) axis, corticotrope-releasing hormone (CRH) and ACTH, which may lead to AI. Factors affecting the risk of glucocorticoid-induced AI include the duration, route of administration, dose and strength of glucocorticoid therapy, concomitant drug use affecting metabolism, individual sensitivity and pharmacokinetics of the preparation used. In patients using exogenous glucocorticoids, Cushing syndrome and subsequent glucocorticoid withdrawal syndrome may develop when treatment is reduced (35).

Steroid-related side effects usually require tapering as soon as the disease being treated is under control. To safely terminate long-term steroid therapy, physicians must consider both the recovery of normal cortisol secretion and potential withdrawal symptoms. A careful approach and appropriate patient counseling are necessary during steroid therapy to avoid both recurrent activity of the underlying disease and possible cortisol deficiency due to suppression of the HPA axis. Glucocorticoid therapy should not be completely discontinued until adrenal function is restored. Since it is mainly regulated by the renin-angiotensin system, adrenal glomerulosa function remains normal and salt loss does not occur (35).

The duration of steroid treatment is a critical factor when considering glucocorticoid withdrawal. A few months of treatment will completely suppress the HPA axis but does not cause adrenal atrophy. Years of treatment may result in almost complete atrophy of the adrenal fasciculata/reticularis layers and therefore may cause a withdrawal syndrome lasting months (6).

While adrenal function usually improves rapidly in short-term (< 1 week) high-dose glucocorticoid use, cases of AI have been reported in use lasting more than 7-14 days (36).

Despite the widespread use of steroids, the literature guiding the management of steroid-dependent AI originate from studies that are very heterogeneous in design, patient population, sample size, types and regimens of glucocorticoids used, and assessment of adrenal function. Therefore, the level of evidence is low, leading to differences in management between different centers and physicians (35,36,37,38,39).

Glucocorticoids that enter the systemic circulation directly or survive first-pass metabolism after gastrointestinal absorption cause a negative feedback effect on CRH-producing neurons and corticotrope cells in the pituitary. This leads to decreased adrenal cortisol production and adrenal cortical hypoplasia and atrophy after long-term exposure (35).

Systemic steroids, especially those with longer half-life and higher potency, are more likely to cause AI than other routes of administration due to direct feedback suppression of CRH and ACTH on the HPA axis. Treatment with bedtime glucocorticoid administration and multiple divided doses are more likely to cause AI by affecting circadian ACTH release. The administration of glucocorticoid therapy every other day carries a lower risk of AI than daily high-dose therapy.

A recent analysis of medical records from primary and secondary care in the UK reported an increased incidence of AI and ICS among chronic oral glucocorticoid users (mainly prednisolone) with higher daily and cumulative doses. Although these data provide a good population-based estimate of the risk of ICS associated with glucocorticoid use, it is difficult to determine this risk at the individual level (35,36,37,38). Some studies have suggested a direct relationship between the dose and duration of systemic glucocorticoid treatment and the likelihood of AI, but the evidence has been reported to be limited (36,39).

In a meta-analysis of 10 studies including 298 children with acute lymphoblastic leukemia, it was shown that AI occurred in almost all patients treated with high-dose systemic glucocorticoid therapy for less than two months. In most children, adrenal function returned within a few weeks, but it was reported that AI persisted in 11% of those who underwent ACTH stimulation testing at 12 to 34 weeks (40).

The duration of steroid treatment is critical in the development of glucocorticoid withdrawal syndrome. When tapering pharmacologic doses of steroids, rapidly reducing the dose to "physiologic" maintenance doses can cause problems. Even with physiologic replacement, patients receiving pharmacologic doses of glucocorticoids will experience steroid withdrawal syndrome. Long-term steroid therapy inhibits glucocorticoid receptor synthesis and thus may cause steroid withdrawal syndrome, with a subphysiologic cellular response, even at physiologic concentrations of glucocorticoids. It is therefore necessary to gradually reduce the dose of the drug from the outset. A very important point to be considered is that AI is not clinically significant in patients who do not show obvious signs and symptoms of cortisol deficiency (6,35,37).

In a study evaluating the risk of AI in glucocorticoid users, symptoms consistent with AI were reported in only 2% of patients, but an inadequate cortisol response was obtained in 19% of patients with dynamic testing. Notably, although symptom assessment was not standardized in this study, these data suggest that patients with symptoms are only the tip of the iceberg. Furthermore, patients with AI can often present with non-specific signs and symptoms that can be attributed to other causes. More importantly, in an undiagnosed and untreated patient with AI, events such as infection and surgery may trigger a life-threatening adrenal crisis due to the inability to generate an adequate stress response (41).

Cases of symptomatic glucocorticoid-dependent AI and ICS have also been associated with inhaled glucocorticoids. Most cases have been reported in patients treated with ≥500 µg/day of fluticasone propionate. A retrospective

cohort study in Canada reported 392 hospitalizations for AI over a 15-year period among adults treated with inhaled glucocorticoids. Patients with higher daily doses (≥1000 µg/day) or cumulatively high doses of steroids (>157000 µg/year) were found to have almost twice the risk of hospitalization compared to those with lower exposures (42). In a cohort of 2.4 million people in a review of national medical records in the United Kingdom, only 31 cases of AI associated with inhaled glucocorticoids were identified. Given the widespread use of inhaled glucocorticoids, the low rates of AI observed in these studies suggest that this problem is largely unrecognized or underreported (43).

Steroid tapering protocols are empirical. Their success is determined by the duration and pattern of treatment and individual patient responses. Steroid therapy may be more easily discontinued in patients receiving every other day treatment than in those receiving a long-acting and potent glucocorticoid, particularly dexamethasone, on a daily basis. In patients on long-standing treatment, a 25% reduction, usually weekly, is recommended and a taper protocol of 8 to 10 weeks may be needed. An appropriate tapering scheme should be made based on the size of the tablets available, and treatment should be discontinued after reduction to a dose equivalent to 5 mg/day of hydrocortisone, and adrenal function assessed. In a patient undergoing glucocorticoid taper, the approach is to treat with equivalent hydrocortisone doses of 5 mg for at least 1 to 4 weeks, then discontinue for 24 hours and assess the HPA axis. This assessment is done by measuring morning cortisol levels, synthetic ACTH stimulation tests and, less commonly used, nocturnal metyrapone testing and insulin tolerance tests. Even after successful cessation of treatment, the HPA axis is not completely normal. As in patients successfully treated for Cushing's disease, the HPA axis may fail to respond to severe stress for 6 to 12 months after discontinuation of long-term, high-dose glucocorticoid therapy (6,35).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (44).

Good practice point:

1. In steroid use for more than 14 days due to systemic disease, it is recommended to taper and discontinue the drug (2⊕⊕OO).

Footnotes

Authorship Contributions

Design: Fuat Buğrul, Nurhan Özcan Murat, Data Collection or Processing: Fuat Buğrul, Nurhan Özcan Murat, Analysis or Interpretation: Fuat Buğrul, Nurhan Özcan Murat, Literature Search: Fuat Buğrul, Nurhan Özcan Murat, Writing: Fuat Buğrul, Nurhan Özcan Murat.

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