GLUCOCORTICOID THERAPY AND ADRENAL SUPPRESSION

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ABSTRACT

Glucocorticoids are steroid hormones produced by the adrenal cortex. They have pleiotropic effects and contribute substantially to the maintenance of resting and stress-related homeostasis. Although the molecular mechanisms of their actions are not fully understood, most of glucocorticoid effects are mediated by a ubiquitously expressed transcription factor, the glucocorticoid receptor. The latter influences the transcription rate of several glucocorticoid-target genes or interact physically with other transcription factors regulating their transcriptional activity in a positive or negative fashion. We present the molecular mechanisms of glucocorticoid action, and we discuss glucocorticoid treatment in endocrine and non-endocrine disorders, the side effects of glucocorticoids, their concomitant use and interactions with other drugs, and the risk factors for adrenal suppression. We suggest regimens for weaning patients from long-term glucocorticoid therapy, describe the glucocorticoid withdrawal syndrome, and provide some future perspectives on glucocorticoid treatment. For complete coverage of all related areas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

Glucocorticoids are steroid hormones produced by the *zona fasciculata* of the adrenal cortex. These molecules are secreted into the peripheral blood under the control of the hypothalamic-pituitary-adrenal (HPA) axis in an ultradian, circadian and stress-related fashion (1). Glucocorticoids influence a myriad of physiologic functions contributing substantially to the maintenance of resting and stress-related homeostasis. At the cellular level, glucocorticoids regulate proliferation, differentiation and programmed cell death (apoptosis) of various cell types and may change the methylation status of cytosine-guanine dinucleotides (CpG) located in the regulatory regions of many genes, leading to important epigenetic alterations (1, 2).

Although glucocorticoids have been introduced in the treatment of rheumatoid arthritis since 1949, their molecular mechanisms of actions remain an evolving field of molecular and cellular endocrinology. Their anti-inflammatory and immunosuppressive effects are mediated mostly by their cognate receptor, the glucocorticoid receptor (GR), a transcription factor that belongs to the steroid receptor subfamily of the nuclear receptor superfamily (3). The therapeutic applications of synthetic glucocorticoids have been greatly broadened to encompass a large number of non-endocrine and endocrine diseases. Indeed, the prevalence of long-term glucocorticoid use worldwide is estimated at between 1% and 3% of adults (4).

When glucocorticoids are used at supraphysiologic doses, glucocorticoid-induced Hypothalamic-pituitary-adrenal (HPA) axis suppression renders the adrenal glands unable to generate sufficient cortisol if glucocorticoid treatment is abruptly stopped. In addition to adrenal suppression, a growing list of glucocorticoid adverse effects have been documented.

Glucocorticoid resistance has become another limitation in the therapeutic use of glucocorticoids. Our ever-increasing and deeper understanding of the molecular mechanisms of glucocorticoid actions might provide the basis for designing selective GR agonists that will optimize the therapeutic outcome, while minimizing undesired side effects.

MOLECULAR MECHANISMS OF GLUCOCORTICOID ACTION

Within the glucocorticoid target cell, the human (h) GR interacts with heat shock proteins (HSP90, HSP70) and immunophillins (FKBP51 and FKBP52), forming a multiprotein complex. Upon glucocorticoid-binding, the hGR dissociates from its protein partners, translocates into the nucleus, and forms homo- or hetero-dimers that bind to specific DNA sequences, termed “glucocorticoid response elements” (“GREs”), influencing the transcription of several glucocorticoid target genes in a positive or negative fashion (3, 5). For additional information please see the Endotext chapter on Glucocorticoid receptors (6). Many anti-inflammatory genes are trans-activated by glucocorticoids, while pro-inflammatory genes are trans-repressed by these hormones. Aside from the genomic actions, accumulating evidence suggests that glucocorticoids may exert some effects in a very short time frame, independently of gene transcription and/or translation (7). These nongenomic glucocorticoid effects are believed to be mediated by membrane-bound hGRs that trigger specific kinase signaling pathways (8).

In addition to the above-mentioned actions, glucocorticoids can influence gene expression independently of hGR binding to DNA. These actions are mediated by physical interaction between the monomeric hGR with other transcription factors, such as the nuclear factor κB (NF-κB), the activator protein 1 (AP-1), and the signal transducers and activators of transcription (STATs), influencing the transcription rate of target genes of the latter (3, 5, 6).

SYNTHETIC GLUCOCORTICOIDS

Since the introduction of glucocorticoids (GCs) in the treatment of rheumatoid arthritis in 1949, intense efforts have been made by science and industry to maximize the beneficial effects and minimize the side effects of glucocorticoids. Thus, many synthetic compounds with glucocorticoid activity were manufactured and tested (9). The pharmacologic differences among these chemicals result from structural alterations of their basic steroid nucleus and its side groups. These changes may affect the bioavailability of these compounds - including their gastrointestinal or parenteral absorption, plasma half-life, and metabolism in the liver, fat, or target tissues - and their abilities to interact with the glucocorticoid receptor and to modulate the transcription of glucocorticoid - responsive genes (10, 11). In addition, structural modifications diminish the natural cross-reactivity of glucocorticoids with the mineralocorticoid receptor, eliminating their undesirable salt-retaining activity. Other modifications increase glucocorticoids' water solubility for parenteral administration or decrease their water solubility to enhance topical potency (11).

Synthetic GCs' clinical efficacy depends on their pharmacokinetics and their pharmacodynamics. Pharmacokinetic parameters such as the elimination half-life and pharmacodynamic parameters such as the concentration producing the half-maximal effect determine the duration and intensity of GC effects (12). It is known that the presence of an 11β-hydroxyl group is essential for the anti-inflammatory and immunosuppressive effects of GCs and for the sodium retaining effects of the mineralocorticoids (MCs). The most important pharmacokinetic systems for GCs and MCs are the 11β- hydroxysteroid dehydrogenases (11β-HSDs) because they regulate the target cell adjustment between the active hydroxy- and the inactive oxo-form of a steroid (13, 14). 11β- hydroxysteroid dehydrogenase type 2 (11β-HSD2, oxidizing enzyme) catalyzes the conversion of cortisol to cortisone, the inactive metabolite, whereas 11β- hydroxysteroid dehydrogenase type 1 (11β-HSD1, reductase) converts cortisone to cortisol. Thus, 11β-HSD1, which is expressed in a wide range of tissues, mainly in the liver, facilitates GC hormone action whereas the major role of 11β-HSD2 is to prevent cortisol from gaining access to high-affinity MC receptors and, therefore, the enzyme is predominantly expressed in the MC responsive cells of the kidney and other MC target tissues (colon, salivary glands) and the placenta (13).

The main structural features determining GC potency are the size and the polarity of the substituent in position 6 or 16. A hydrophobic residue increases GC activity (statistically significant enhancement with 6-α methyl and 16-methylene substitution). The more polar 16-hydroxy substitution decreases GC potency. The 6α and 9α-fluorination (such as in 6α and 9α fluorocortisol respectively) leads to increased GC and MC activity and double fluorination in the same positions augments this shift. Moreover, the Δ1-dehydro-configuration (in prednisolone) enhances GC activity but opposite to that effect it attenuates MC potency. The same effect is observed with the 16-methylene, 16α-methyl (dexamethasone) and 16β-methyl (betamethasone) groups. Thus, the more selective GC transactivation activity of GCs with a 16α-methyl or 16β-methyl group and a Δ1-dehydro-configuration, results from a significantly decreased activity via the mineralocorticoid receptor (MR) and an enhanced activity via the glucocorticoid receptor (GR) (15). Moreover, whereas GC selectivity can be improved by hydrophobic substituents in position 16 and the Δ1-dehydro-configuration, maximal GC activity needs additional fluorination in position 9α (such as in dexamethasone) (16). Figure 1 presents the chemical structures of cortisol and the most commonly used synthetic GCs.

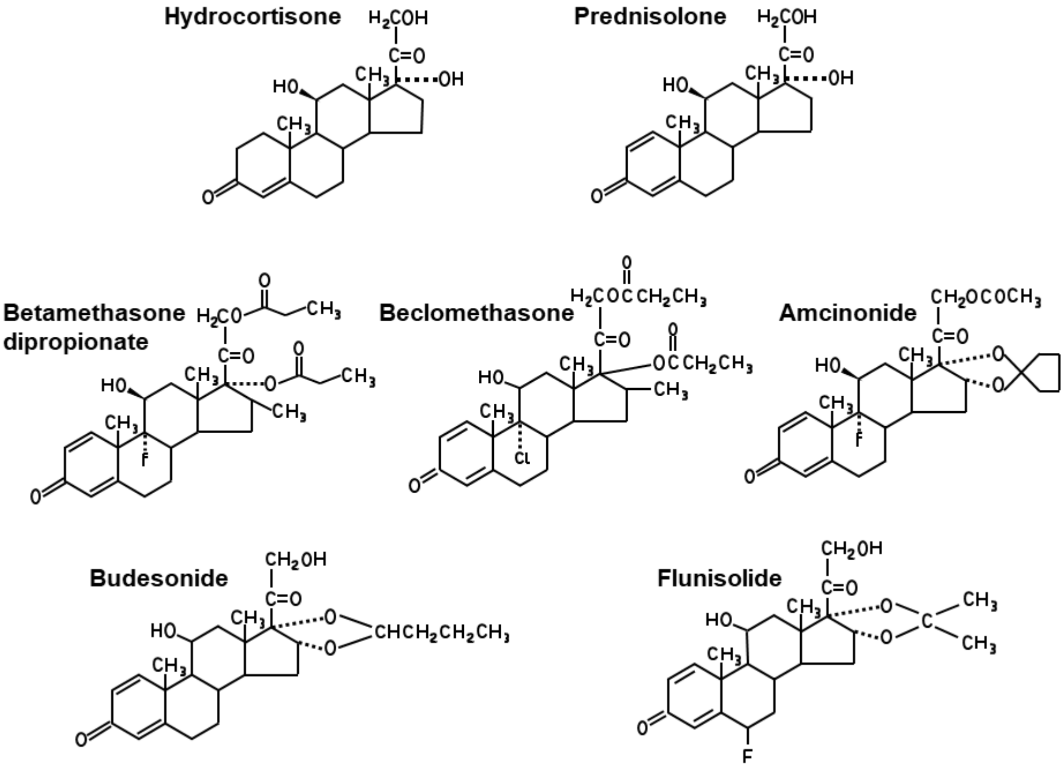

Figure 1: Chemical Structures of the Most Commonly Used Synthetic GCs.

Protein binding is another pharmacokinetic property that influences GCs biological activity because only the unbound GC fraction is biologically active (14). In humans, endogenous cortisol binding to cortisol binding globulin (CBG) ranges between 67% and 87%, whereas a further 7-19% of total cortisol is bound to albumin, leading to about 95% of cortisol being protein-bound in the plasma. Except for prednisolone, synthetic GCs bind predominantly to albumin and only marginally to CBG. Plasma binding e.g. of dexamethasone and betamethasone is 75% and 60% respectively, and this is quite constant across a wide concentration rate (17). Thus, CBG binding is not a major determinant of plasma and biological half-lives of synthetic GCs.

However, especially for hydrocortisone and prednisone, pharmacokinetics are non-linear due to protein binding. As a result, higher doses result in more rapid clearance rates. It has to be mentioned that prednisone itself is biologically inactive and its 11-keto group must be reduced by hepatic 11βHSD1 to form the active drug, prednisolone. Moreover, clearance rate depends on age and is more rapid in children than adults (18) and also depends upon individual variability. Finally, certain diseases may influence synthetic GCs' pharmacokinetics. Thus, clearance is reduced particularly in renal and hepatic diseases and hypothyroidism and increased in hyperthyroidism. The concomitant use of other drugs influences synthetic GCs' half-lives and, thus, their final effect in target tissues (18, 19). Classic bioassays measure synthetic GC potency by testing the ability to suppress eosinophils and inhibit inflammation and the ability to stimulate hepatic glycogen deposition. The biologic effective half-life of glucocorticoids divides them into short-, intermediate-, or long-acting, based on the duration of corticotropin suppression after a single dose of the compound. The main corticosteroids used in clinical practice together with their relative biologic potencies and their plasma and biological half-lives are listed in Table 1.

Table 1: Glucocorticoid Equivalencies (11, 20, 21)

Glucocorticoids	**Equivalent dose (mg)**	**Gluco-corticoid potency**	**HPA Suppression**	**Mineralo-corticoid potency**	**Plasma half-life (min)**	**Biologic half-life (h)**
Short-acting						
Cortisol	20.0	1.0	1.0	1.0	90	8-12
Cortisone	25.0	0.8		0.8	80-118	8-12
Intermediate-acting						
Prednisone	5.0	4.0	4.0	0.3	60	18-36
Prednisolone	5.0	5.0		0.3	115-200	18-36
Triamcinolone	4.0	5.0	4.0	0	30	18-36
Methylprednisolone	4.0	5.0	4.0	0	180	18-36
Long-acting						
Dexamethasone	0.75	30	17	0	200	36-54
Betamethasone	0.6	25-40		0	300	36-54
Mineralocorticoids						
Fludrocortisone	2.0	10	12.0	250	200	18-36
Desoxycorticosterone acetate		0		20	70	

SYSTEMIC GLUCOCORTICOID ADMINISTRATION

Therapeutic Indications

GCs are used in both endocrine and non-endocrine disorders (11, 22). First of all, they are administered as replacement therapy in patients with primary or secondary adrenal insufficiency, and as adrenal suppression therapy in congenital adrenal hyperplasia and glucocorticoid resistance (11). They are also used in patients with Grave's opthalmopathy and for some diagnostic purposes such as in establishing Cushing's syndrome (11). Moreover, due to their immunosuppressive and anti-inflammatory properties they are used in a broad range of non-endocrine disorders affecting many different systems (22, 23). Thus, they are given to treat skin disorders such as dermatitis and pemphigus, rheumatologic diseases such as systemic lupus erythematosus, polyarteritis and rheumatoid arthritis, and also polymyalgia rheumatica and myasthenia gravis. In hematology, they are used, along with chemotherapy, for the treatment of lymphomas and leukemias (24) and in hemolytic anemias and idiopathic thrombocytopenic purpura. In addition, they are administered in gastrointestinal diseases such as inflammatory bowel disease, in liver diseases (chronic active hepatitis) and in respiratory diseases (angioedema, anaphylaxis, asthma, sarcoidosis, tuberculosis, obstructive airway disease). Moreover, GCs are used in nephrotic syndrome and vasculitis and also in the suppression of the host-versus-graft and graft-versus-host reaction in cases of organ transplantation. In nervous disorders such as cerebral edema and raised intracranial pressure the use of GCs is also beneficial (25, 26).

Acute administration of pharmacologic doses of glucocorticoids is advocated in a small number of nonendocrine diseases, such as for patients suffering from acute traumatic spinal cord injury, although two recent meta-analyses support that the use of methylprednisolone should be limited (27, 28). Moreover, steroid administration should be considered as a post-operative additional therapy for cases with severe neurological deficits even after surgery (29). Glucocorticoids are also used for postoperative pain relief after severe bone operations (30). In addition, as it is known that premature birth is associated with an increased risk of neonatal mortality and morbidity, including respiratory distress syndrome (RDS), and because 7-10% of all pregnancies in North America are under such risk, in 1994 the National Institutes of Health (NIH) Consensus Developmental Conference on the Effects of Corticosteroids for Fetal Maturation on Perinatal Outcomes concluded that all fetuses between 24 and 34 week gestation at risk of preterm delivery should be considered as candidates for antenatal treatment with GCs. Recommended treatment consisted of 2 doses of 12mg betamethasone given IM 24 hours apart or 4 doses of 6mg dexamethasone given 12 hours apart. In 2001 the NIH Consensus Developmental Panel recommended that repeat courses should not be used routinely until insightful findings are available. However, the Australian Collaborative Trial (ACTORDS), that has been completed, reported that repeat course synthetic GCs improved short-term neonatal outcome compared to single course therapy (31).

Acute administration of pharmacologic doses of glucocorticoids is also necessary in some types of acute illness. For years it is known that any type of acute illness or trauma results in loss of the diurnal variation in cortisol secretion. In the early phase of critical illness cortisol levels frequently rise and levels of CBG and albumin are substantially depleted. In the chronic phase of critical illness, however, high ACTH and cortisol levels are generally sustained and CBG levels gradually increase. Both very high and very low cortisol levels have been associated with increased mortality from critical illness. High cortisol levels reflect severe stress, whereas low levels reflect an inability to sufficiently respond to stress (32). The term "critical illness-related cortisol insufficiency" (CIRCI) defines a state of both the inadequate production of GCs as well as a corticosteroid tissue resistance. It has been estimated that the overall incidence of adrenal insufficiency in critically ill patients is approximately 20%, with an incidence as high as 60% in patients with severe sepsis and septic shock. It is possible that CIRCI is an epiphenomenon and a marker of illness severity (33).

According to the current recommendations, CIRCI should be suspected in hypotensive patients who respond poorly to fluids and vasopressor agents, particularly in the setting of sepsis. To diagnose CIRCI, the clinician may use a delta serum cortisol <9 μg/dl after cosyntropin (250μg) administration or a random plasma cortisol <10μg/dl. The authors suggest that clinicians should not use plasma-free cortisol or salivary cortisol level over plasma total cortisol. For patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy, the authors suggest IV hydrocortisone < 400 mg/day for ≥ 3 days at full dose. They, however, do not suggest using corticosteroids in adult patients with sepsis without any evidence of shock. The dose regimen in patients with early moderate to severe ARDS is methylprednisolone 1mg/kg/day for at least 14 days. Finally, glucocorticoids are not suggested for cases of major trauma (34). In a second part of the guidelines, the authors formulated statements for or against the use of synthetic corticosteroids for other common pathologic conditions, including community-acquired pneumonia, influenza, meningitis, and non-septic systemic inflammatory response syndrome (SIRS) that may be associated with shock, namely burns, cardiac arrest and cardiopulmonary bypass surgery (35).

Benefits of GCs replacement has been demonstrated in a number of other patient populations including low cardiac output syndrome after cardiac surgery (36), acute exacerbation of chronic obstructive pulmonary disease (37), and cirrhosis (38).

Adverse Effects (AEs)

Although synthetic GCs remain an important component of therapy for many conditions, in recent years there are arguments against their use based mainly on the concern of toxicity. Nowadays, GCs toxicity is one of the commonest causes of iatrogenic illness associated with chronic inflammatory disorders. Despite the fact that the adverse effects of GCs have been known for decades, the actual risk-benefit ratio is incomplete and/or inconsistent. This happens because it is in general difficult to separate the effects of GCs from the outcome of the underlying disease, other comorbidities, or the use of other medications. Moreover, toxicity reports usually concern patients using high doses of GCs, different types of GCs with different relative drug potencies, for a heterogeneous group of related diseases, and for different periods of time (39, 40).

Only recently there has been intense effort by scientists and clinicians to explore and quantify the incidence and severity of the AEs of GC therapy. Generally, it is known that GCs' toxicity is related to both the average and cumulative dose during their use (41). The question that arises is whether or not patterns relating the frequency of AEs to GC dosage and/or length of GC treatment exist (39).

Historically, GCs at a prednisone equivalent of 5-10mg/day are considered low dose. However, a review of "the 4 extensively reviewed trials on low dose GCs in rheumatoid arthritis" led to the conclusion that definitive association of low dose GCs with many AEs such as osteoporosis, myopathy, cardiovascular disease, glaucoma, increased incidence of any kind of infection, and behavior disturbances remains elusive, and that the fear of GCs toxicity is probably overestimated based on extrapolation from observations with higher dose treatment. However, according to the same analysis, the use of 5-10mg/day of prednisolone (or equivalent) for over 2 years is associated with an increase of mean body weight in the range of 4-8% (40).

The prevalence of GC associated AEs was identified in a large survey of 2167 long term (≥60 days) users of GCs with mean prednisone equivalent dose of 16±14mg/day. The AE with the greatest prevalence was weight gain, experienced by 70% of the individuals, followed by skin bruising/thinning, and sleep disturbances. Cataracts (15%) and fractures (12%) were among the most serious AEs. All AEs demonstrated a strong dose-dependent association with cumulative GC use. Acne, skin bruising, weight gain and cataracts were significantly associated with longer duration (>90 days) of low-dose GCs (≤7.5mg/day of prednisolone), while fractures and sleep disturbances were more strongly associated with small increments in daily dosage (within the 0-7.5mg/d range). In conclusion, this survey adds further evidence that more GC associated AEs are dependent on both the average dose and the duration of therapy and that even low dose GC therapy could lead to serious AEs (42).

As in more severe cases of chronic inflammatory diseases long-term (≥ 1month) dosage of GCs is medium to low (≤30mg/d prednisolone or equivalent), a systematic review of 28 studies (2382 patients) concerning patients with rheumatoid arthritis (RA), polymyalgia rheumatica, and inflammatory bowel disease was the first to present a pooled analysis of the commonest reported AEs associated with this pattern of administration. The AE rate depends both on the quality of the study and primarily- on the disease in the study population. The overall mean rate of AEs was 150 per 100 patient-years, varying from 43/100patient years in rheumatoid arthritis and 80/100patient years in polymyalgia rheumatica to 555/100 patient years in inflammatory bowel disease. Psychological and behavioral disturbances (e.g. minor mood disturbances) were most frequently reported, followed by gastrointestinal events (e.g. dyspepsia, dysphagia) (43).

A recent retrospective population-based cohort study and self-controlled case series aimed to assess the risk of sepsis, venous thromboembolism, and fracture in 327,452 adults aged 18 to 64 years who received at least one prescription for less than 30 days over a three-year period (44). The authors found increased rates of sepsis (incidence rate ratio 5.30, 95% confidence interval 3.80 to 7.41), venous thromboembolism (3.33, 2.78 to 3.99), and fracture (1.87, 1.69 to 2.07), which decreased within the next 90 days. The increased risk for these adverse effects was observed at prednisolone doses lower than 20mg per day (44).

An important observational study aimed to identify patterns of self-reported health problems relating to dose and duration of GCs in 1066 unselected patients with RA (39). The study identified 2 distinct dose-related patterns of AEs. A continuous, approximately linear rising with increasing dose was found for cushingoid phenotype, ecchymosis, leg edema, mycosis, parchment-like skin, shortness of breath, and sleep disturbance. The most clearly attributable adverse drug reaction to GCs, Cushing syndrome, becomes evident after at least one month of treatment and was observed in 2.7, 4.3, 15.8, 24.6% of patients with no GCs in the past 12 months, and <5, 5-7,5 and >7,5mg/d of prednisolone or equivalent for >6 months, respectively. The second pattern identified describes an elevation in the frequency of health problems beyond a certain threshold value and is defined as a "threshold pattern". The threshold for the increase in glaucoma, depression, and an increase in blood pressure was observed at dosages of greater than 7.5mg/d. Dosages of 5mg/d or more were associated with epistaxis and weight gain. A very low threshold was observed for eye cataract (<5mg/d). All the associations found are in agreement with biological mechanisms and clinical observations (39). However, more extensive research on the risk-benefit ratio of long-term GCs is needed and could help to create new targets for drug development.

An overview of the most common and most serious AEs associated with GC therapy is discussed below.

ADRENAL INSUFFICIENCY (AI)

Iatrogenic, tertiary adrenal insufficiency induced by chronic administration of high doses of GCs is the most common cause of adrenal insufficiency (45). Physiologically, the hypothalamus secretes CRH which stimulates the release of ACTH from the anterior pituitary. ACTH leads to the release of cortisol from the zona fasciculata of the adrenal gland, which in turn exerts negative feedback on CRH and ACTH release. Administration of exogenous GCs even in small doses for only few days leads to a measurable suppression of the HPA axis by decreasing CRH synthesis and secretion and by blocking the trophic and ACTH-releasing actions of CRH on the anterior pituitary. This leads to suppressed synthesis of POMC, ACTH and other POMC derived peptides and later, to the atrophy of the corticotrophin cells of the anterior pituitary. As a result, in the absence of ACTH, the adrenal cortex loses the ability to produce cortisol. Nevertheless, the adrenal cortex retains the ability to secrete enough cortisol for some period of time and also mineralocorticoids, as this latter function depends mainly on the renin-angiotensin system rather than on ACTH.

The association between AI and treatment with oral GCs has been recognized for decades, although the magnitude of the risk has not been determined until recently. It has also been reported that the inhibition of the HPA axis function induced by exogenous GCs may persist for 6 to 12 months after treatment is withdrawn (46). Based on the literature the absolute risk of adrenal crisis after cessation of oral and inhaled GCs might be considered rare, but it is likely to be substantially underreported in clinical practice (10, 47).

The first study that quantified the increased risk of AI in people prescribed oral and inhaled GCs in the general population was published in 2006 (48). This case-control study, that used data from a cohort of 2.4 million people, found a strong dose-response relationship between oral GCs exposure and the risk of AI with an OR of 3.4 (95% CI, 1.6-2.5) per course of treatment per year. Furthermore, the study indicated, that administration of inhaled GCs within 90 days of diagnosis is associated with an increased risk of AI (OR 3.4, 95% CI 1.9-5.9) and this effect was dose related. However, after adjustment for oral GCs exposure, this association was reduced (OR 1.6, 95% CI 0.8-3.2) although the dose relation remains. The largest increase in risk occurred in association with a recent prescription for fluticasone proprionate (48). These findings were confirmed by more recent studies that aimed to investigate the prevalence of AI in patients treated either with inhaled (49) or with oral GCs (47, 50). Interestingly, in a recently published systematic review the authors found that the percentage of patients with glucocorticoid-induced AI had a median (IQR) of 37.4%, ranging from 13%-63% (51). Three years after glucocorticoid withdrawal, AI persisted in 15% of retested patients. AI occurred in patients receiving <5mg prednisolone equivalent dose/day, for less than 4 weeks, and with a cumulative dose <0.5g (51).

CARDIOVASCULAR DISEASE

A population-based study that compared the risk for CVD in 68,781 patients using GCs versus 82,202 nonusers identified that the relative risk for a cardiovascular event in patients receiving high-dose GCs (≥7,5mg/d prednisolone) was 2.56 (CI 2.18-2.99) after adjustment for known covariates (52). Similar associations were noted in another observational study that included 50,656 patients and an equal number of matched controls. According to this study, current use of GCs was associated with an increased risk of heart failure (OR 2.66, 95% CI 2.46-287) and a smaller risk of ischemic heart disease (OR 1.20, 95% CI 1.11-1.29) (53). However, the previous results are not confirmed by other studies (54, 55). Additionally, an association of GCs use and the risk for atrial fibrillation and flutter has been established by several studies (56-58).

GLUCOSE HOMEOSTASIS

The alterations in glucose homeostasis induced by GCs are multifactorial and could be explained by several potential mechanisms including the induction of enzymes involved in hepatic gluconeogenesis, the decrease in glucose uptake in peripheral tissues, the stimulation of lipolysis, the prevention of insulin production, and the induction of ceramide biosynthesis leading to insulin resistance (59). An interesting review of the existing literature published between 1950-2009 shows that GC-induced hyperglycemia is common among patients with and without diabetes mellitus. The OR for new onset diabetes mellitus ranges from 1.5 to 2.5 and the induction of the disease is strongly predicted by GC accumulative dose and duration of therapy (60).

INFECTIOUS EVENTS

GC therapy is associated with an increased risk of infectious complications, as GCs are known to have suppressive effects upon both innate and acquired immunity. This is confirmed by several studies. According to a large observational study of 16,788 patients with RA, prednisone use, even at doses of 5mg/kg, increased the risk of hospitalization for pneumonia. Furthermore, there was a dose related relationship between prednisone use and pneumonia risk in RA (61). Another study of 15,597 patients with RA found that GC use doubled the rate of serious bacterial infections compared with methotrexate with a dose response relationship for doses greater than 5mg/d (62). The latter results were confirmed by additional studies that have identified GCs as an independent risk factor for infections (63, 64). Moreover, a more recent study demonstrated that patients receiving 5mg prednisolone continuously for the last 3 months, 6 months or 3 years, had a 30%, 46% or 100% increased risk of serious infection, respectively (65). Also, caution about GC use in patients with active or dormant TB is well accepted as these individuals are susceptible to contract or to sustain activation of the disease (66). An epidemiological study of patients with TB showed that they were nearly 5 times more likely to have been using GCs at the time of their diagnosis (67).

OSTEOPOROSIS

The effects of GCs on bone homeostasis are both systemic and local. Systemic effects include a reduction in calcium absorption from the intestine and a reduction in calcium reabsorption in the kidney, both enhancing PTH secretion and thus bone loss. Furthermore, the attenuation of sex steroids and growth hormone by GCs enhances bone loss. The direct effects of GCs on bone cells include induction of osteoblast and osteocyte apoptosis through activation of pro-apoptotic molecules, impairment of Wnt signaling, and induction of RANKL, a potent stimulator of osteoclastogenesis produced by osteoblasts (68). As a result, GCs induced osteoporosis is the most common type of iatrogenic osteoporosis. This has been confirmed by several studies. One of them showed that therapy with high-dose oral GCs caused significant decrease in BMD even in the first 2 months of therapy (69). As a result, there is an increased risk of osteoporotic fractures (70) and it has been estimated that fractures may occur in up to 30-50% of patients on GC therapy (71) but fortunately there is a rapid decrease of the risk on cessation of therapy (70, 72). Similar findings were observed by a more recent study showing that low daily dose prednisone (≤7,5mg/d) with high cumulative doses increases the risk for fractures. Intermittent high-dose regimens with cumulative doses less than 1gr, however, did not show an increased risk. Risk declines rapidly, the decrease beginning 3 months after cessation of therapy (73). For additional details please see the Endotext chapter on Glucocorticoid-induced osteoporosis (74).

NEUROPSYCHIATRIC EVENTS

Despite a slight increase in their overall sense of well-being independent of improvement in disease activity, it has been established that synthetic GC treatment may induce behavioral, psychic, and cognitive disturbances (75). These disturbances can be detected by structural, functional, and spectroscopic imaging. Behavioral changes in feeding and sleeping are commonly observed. Among psychic AEs, hypomania and mania are the most common during acute GC therapy and depression during long-term treatment. Suicides have also been reported (76). These AEs are usually mild/moderate but are severe in 5-10% of cases. Cognitive changes affect mostly declarative and working memory. All these AEs are generally dose and time dependent (infrequent at prednisone equivalent doses <20mg/d) and usually reversible. There has to be greater concern for pediatric patients. Several medications such as lithium, phenytoin, lamotrigine, memantine and other anti-seizure, anti-psychotics, and anti-depressants could be useful for treating such disorders (77, 78).

PEDIATRIC EVENTS

Prolonged GC treatment of children with chronic illnesses impairs their longitudinal growth (79). GCs exert multiple growth suppressing effects, such as inhibition of GH secretion and IGF-1 expression, reduction of bone and collagen formation, bone mineralization, and vascularization. These effects are more pronounced with daily oral GCs than alternate day oral GC therapy (80). According to a study of 224 children with cystic fibrosis who have received alternate day treatment with prednisone, boys but not girls, had persistent growth impairment (mean final height 4cm less than children who were treated with placebo) after discontinuation of treatment (81).

Apart from growth retardation, children may also be more susceptible to other AEs associated with GCs such as osteoporosis, glaucoma and cataracts. Moreover, fracture risk seems to be higher in GC-treated children (82).

Intrauterine exposure to GCs is able to affect fetal HPA axis development causing reduction in fetal and, in some cases newborn and infant HPA axis activity under basal conditions and more consistently after pain-related stress. Although baseline HPA axis function seems to recover within the first 2 weeks postpartum, there is initial evidence that blunted HPA axis reactivity to pain-related stress persists throughout the first 4 months of life. These effects are dose dependent and vary with the time between GC exposure and HPA assessment. It seems that programming of the HPA axis involves interaction with other endocrine systems such as the Hypothalamus-Pituitary-Gonadal axis (HPG). Moreover, exposure to GCs during pregnancy has been linked to impaired fetal growth and modulated fetal immune functions, indicators of compromised cognitive, neurological and psychological functions, and increased blood pressure into adolescence. Furthermore, there is some evidence that reduced HPA axis activity early in life will switch to a hyperactive state later in life due to over-adjustment and because of that, affected infants may be vulnerable to stress related disorders associated with hypercortisolemia such as depression and cardiovascular disease. Finally, it seems that changes in HPA axis function following antenatal exposure to GCs are trans-generational and likely involve epigenetic mechanisms (17).

In addition, according to a recent meta-analysis, early postnatal GC treatment (≤7 days), particularly with dexamethasone, causes short term AEs including gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy and growth failure (83, 84). Long term follow-up studies report an increased risk of abnormal neurological examination and cerebral palsy (85).

PHEOCHROMOCYTOMA CRISIS

Severe isolated cases of pheochromocytoma crisis have been reported after administration of exogenous GCs (86, 87). Thus, GCs should be avoided or administered only if absolutely necessary in patients with known or suspected pheochromocytomas.

The most common AEs of GC therapy are summarized in Table 2.

Table 2: Common AEs of Glucocorticoid Therapy (88)
Onset early in therapy, essentially unavoidable
Emotional lability
Enhanced appetite, weight gain, or both
Insomnia
Enhanced in patients with underlying risk factors or concomitant use of other drugs
Glucocorticoid-related acne
Diabetes mellitus
Hypertension
Peptic ulcer disease
When supraphysiologic treatment is sustained
Cushingoid appearance
Hypothalamic-pituitary-adrenal suppression
Impaired wound healing
Myopathy
Osteonecrosis
Increased susceptibility to infections
Delayed and insidious, probably dependent on cumulative dose
Atherosclerosis
Cataracts
Fatty liver
Growth retardation
Osteoporosis
Skin atrophy
Rare and unpredictable
Glaucoma
Pancreatitis
Pseudotumor cerebri
Psychosis

COMPARTMENTAL GLUCOCORTICOID ADMINISTRATION

Topical Glucocorticoids

Glucocorticoids are the first line of treatment for various skin disorders such as atopic dermatitis, vitiligo, psoriasis, etc. (10, 89-94). They are quite effective when applied topically and nontoxic to the skin in the short term. The factors that determine local penetration are the structure of the compound employed, the vehicle, the basic additives, occlusion versus open use, normal skin versus diseased skin, and small areas versus large areas of application. Fluorinated steroids (e.g. dexamethasone, triamcinolone acetonide, betamethasone, and beclomethasone) penetrate the skin better than nonfluorinated steroids, such as hydrocortisone. However, fluorinated steroids also produce more local complications and may be associated with systemic absorption and side effects.

The most frequent AEs are local and include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Less frequently, hypertrichosis, pigmentation alterations, delayed wound healing, and exacerbation of skin infections occur. Furthermore, the rate of contact sensitization against GCs is greater than previously believed. Systemic reactions such as hyperglycemia, glaucoma and adrenal insufficiency are less frequent (95). Some cases of Cushing's syndrome following overuse of topical GCs have also been described (96). The frequency of systemic effects by topical corticosteroids is increased in newborns and small children compared to adolescents and adults, because GCs penetrate the skin of newborns and small children more easily and in larger proportional amounts. Infants, especially, have a greater risk for Cushing's syndrome or adrenal insufficiency and also hepatosteatosis. An infant's death due to generalized CMV infection following administration of topical GCs has been reported (97). Based on the Body Surface Area, a simple guideline for how much topical GC to prescribe for a child has been proposed. Roughly, infants require one fifth of adults' doses, children two fifths and adolescents two thirds of adults' doses (98). Finally, the use of skin lightning cosmetics used in most African countries includes corticosteroids and may have many serious and sometimes fatal complications, including adrenal insufficiency (99).

Opthalmic Glucocorticoids

In the past 10 years intravitreal GCs injections have been increasingly used for patients with a variety of posterior segment diseases, including diabetic macular edema, branch and central retinal vein occlusion, pseudophakic cystoid macular edema, and uveitic macular edema (100). Currently, novel agents including preservative-free and sustained-release intravitreal implants are being studied in clinical trials. Potential complications of intravitreal steroid treatment are divided into steroid-related and injection-related side effects. Steroid-related side effects include cataract formation and glaucoma (101). Injection related side effects include retinal detachment, vitreous hemorrhage, and bacterial and sterile endopthalmitis.

Inhaled Glucocorticoids

GC inhalation therapy is widely used in patients with asthma and chronic obstructive pulmonary disease. Their relative topical to systemic effect ratio or therapeutic index depends upon the pharmacokinetic differences for inhaled GCs. Factors that enhance the therapeutic index are: decreased oral absorption retention in the lung and rapid systemic clearance once the drug is absorbed into the systemic circulation. More recently, it has been posited that the therapeutic index is also enhanced by high plasma protein binding. Inhaled GCs have important pharmacokinetic differences (102).

In general, inhaled GCs have fewer and less severe AEs than oral and systemic GCs. However, systemic AEs may be observed and this risk is influenced by the dose, the period of treatment, the delivery system used, the site of delivery (i.e. gastrointestinal tract, lung), the concomitant use of other medications, and the altered steroid metabolism due to individual's differences in the patient's response to GCs.

As far as growth deceleration in children is concerned, the results are somewhat contradictory. Although inhaled GCs seem to cause a dose-dependent reduction in height velocity (103), these changes are not significantly associated with final adult height (104). However, a study of 1041 asthmatic children treated with budesonide, nedocromil, and placebo for 4.3 years, a decrease in growth velocity was observed in the budesonide group which was most evident in the first year of treatment (105). When 90% of these children were followed-up for an additional 4.8 years, a lower mean height was found in the budesonide group and this was more pronounced in girls than in boys (106).

Moreover, as GCs effect on bone metabolism is of great concern, some studies have shown that inhaled GC therapy is associated with increased fracture risk (107, 108) but this has not been confirmed by a meta-analysis (109). Nevertheless, several studies confirm a negative relation between total accumulative dose of inhaled GCs and bone mineral density (110). The loss in BMD is of concern, especially in early postmenopausal women and boys during puberty (111, 112). Again, these results have been argued (113).

It has been shown that adrenal insufficiency is also associated with inhaled GCs, although with lower prevalence (114). The newest inhaled GC, Ciclesonide, appears to have different pharmacokinetics enhancing its therapeutic index. It is administered as a pro-drug converted to the active metabolite des-Ciclesonide in the lung. Thus, it has low oral bioavailability and also rapid clearance and high protein binding, factors that reduce pharmacologically relevant systemic exposure (115). Furthermore, Ciclesonide appears to have less suppressive effects on HPA axis function (116, 117).

Nasal Glucocorticoids

Intranasal GCs are effectively used for the treatment of allergic rhinitis, rhinosinusitis, rhinoconjunctivitis, and nasal polyposis (118, 119). Topical steroid drops are used for the treatment of sinus ostia stenosis in the postoperative period (120). Interestingly, molecules designed specifically to achieve potent localized activity with minimum risk of systemic exposure such as mometasone furoate, fluticasone proprionate, and fluticasone furoate may be preferable. Studies in children have not found any adverse effects including HPA axis suppression or growth retardation (118). Yet, some studies suggest a relationship between intranasal steroids and increased intraocular pressure (119). Generally, frequent and chronic use should be avoided to prevent local and systemic complications (121).

Intraarticular Glucocorticoids

The main beneficial effect of intraarticular GC injection is pain relief. Most favorable results are seen in juvenile idiopathic arthritis patients. Local AEs are either rare or insignificant and include joint infection, intraarticular and periarticular calcifications, cutaneous atrophy, cutaneous depigmentation, avascular necrosis, rapid destruction of the femoral head, acute synovitis, Charcot's arthropathy, tendinopathy, Nicolau's syndrome, and joint dislocation (122). Moreover, some systemic AEs have also been reported. These include a transient HPA axis suppression, a transient increase in blood glucose in diabetic patients, and other metabolic, hematologic, vascular, allergic, visual and psychological AEs (123). The most used intraarticular glucocorticoids are triamcinolone hexacetonide, triamcinolone acetonide, and methylprednisolone acetate (124).

MONITORING OF PATIENTS ON GLUCOCORTICOID TREATMENT

As osteoporosis, with resultant fractures, constitutes one of the most serious morbid complications of GC use, worsening patients quality of life, recently, the American College of Rheumatology (ACR) updated the 2010 recommendations for patients receiving oral GC therapy (125). In this systematic review, the authors addressed the initial assessment in patients that began or continue glucocorticoid treatment for longer than 3 months, and discussed the advantages and disadvantages of lifestyle modification, as well as for calcium, vitamin D and pharmaceutical treatment, including bisphosphonates, raloxifene, teriparatide, and denosumab. According to the ACR guidelines, there are three categories of fracture risk. High risk criteria include patients aged over 40 years, previous osteoporotic fracture, hip or spine BMD T-score ≤ −2.5, or 10-year fracture probability of ≥20% (major osteoporotic fracture) or ≥3% (hip fracture) (125, 126). Moderate and low risk criteria are based only on FRAX-derived fracture probability (10–19% and >1 to ≤3% respectively for moderate risk, and <10% and ≤1% respectively for low risk) (125, 126). In patients aged less than 40 years, a previous osteoporotic fracture is considered as a high-risk criterion, whereas the criteria of moderate and low risk are based on the BMD. Patients at low fracture risk are recommended to receive only calcium and vitamin D, whereas adults at moderate-to-high fracture risk should be treated with calcium and vitamin D plus an oral bisphosphonate. However, adults in whom oral bisphosphonates are not appropriate, are recommended to continue calcium plus vitamin D but switch from an oral bisphosphonate to another anti-fracture medication (125). Finally, adults who complete a planned regimen with oral bisphosphonates and continue glucocorticoid treatment, are recommended to continue oral bisphosphonate treatment or switch to another anti-fracture medication (125). Recommendations were also suggested for children, women of childbearing potential, and people with organ transplants, as well as patients receiving very high doses of glucocorticoids (125). For additional details please see the Endotext chapter on Glucocorticoid-induced osteoporosis (74).

CONCOMITANT USE OF GLUCOCORTICOIDS WITH OTHER DRUGS

Special attention is required in the concomitant use of glucocorticoids with other drugs because of potential interactions, and because some drugs may affect the metabolism of the steroids, which may lead to a decreased or increased glucocorticoid effect on their target tissues (20). Such interactions and effects are shown in Tables 3, 4 and 5.

Table 3: Interactions of Glucocorticoids with Other Drugs (20)

Drug	Side effect	Comments
Amphotericin B	Hypokalemia	Monitor potassium levels frequently
Digitalis glycosides	Digitalis toxicity Hypokalemia	Monitor potassium levels frequently
Growth hormone	Ineffective	-
Potassium-depleting diuretics	Hypokalemia	Monitor potassium levels frequently
Vaccines from live attenuated viruses	Severe generalized infections	-

Table 4: Effects of Glucocorticoids on Blood Levels of Other Drugs (20)

Drug	Drug blood levels	Comments
Aspirin	Decreased	Increased metabolism or clearance. Monitor salicylate level
Coumarin anticoagulants	Decreased	Frequent control of prothrombin levels
Cyclophosphamide	Increased	Inhibition of hepatic metabolism. Adjust the dosage
Cyclosporine	Increased	Inhibition of hepatic metabolism
Insulin	Decreased	Adjust the dosage of the drug
Isoniazid	Decreased	Increased metabolism and clearance
Oral hypoglycemic agents	Decreased	Adjust the dosage of the drug

Table 5: Effect of Drugs on Plasma Glucocorticoid Concentrations (20, 127, 128)

Drug	Drug blood levels	Comments
Antacids	Decreased	Possible physical absorption to antacid
Carbamazepine	Decreased	Increased cytochrome P450 activity
Cholestyramine	Decreased	Decreased gastrointestinal absorption of glucocorticoids

Colestipol	Decreased	Decreased gastrointestinal absorption of glucocorticoids
Cyclosporine	Increased	Inhibition of hepatic metabolism
Ephedrine	Decreased	Probably increased metabolism
Erythromycin	Increased	Impaired elimination
Itraconazole	Increased	Decreased cytochrome P-450 activity
Mitotane	Decreased, with elevated transcortin	Total plasma cortisol unreliable. Adjust glucocorticoid levels
Oral contraceptives	Increased	Impaired elimination, increased protein binding
Phenobarbital	Decreased	Increased cytochrome P-450 activity. Adjust glucocorticoid dosage
Phenytoin	Decreased	Increased cytochrome P-450 activity. Adjust glucocorticoid dosage
Rifampin	Decreased	Increased cytochrome P-450 activity (?) Adjust glucocorticoid dosage
Ritonavir	Increased	Decreased cytochrome P-450 activity
Troleandomycin	Increased	Partially resulting from impaired elimination

PREDICTING GLUCOCORTICOID-INDUCED HPA AXIS SUPPRESSION

Several predictors of glucocorticoid-induced HPA axis suppression have been discussed, the major of which are the following:

Kind of Steroid Used and GC Potency

As shown in Table 1 long acting preparations have a longer tissue life which induces a chronic state of tissue hypercortisolism, making HPA axis suppression more likely. Thus, hydrocortisone and cortisone acetate are the least potent and, therefore, least suppressive agents. Prednisone, prednisolone, methylprednisolone and triamcinolone are moderately suppressive, and dexamethasone suppresses ACTH the longest.

Systemic Versus Compartmental Therapy

Systemic GC therapy, particularly parenterally, is more likely to suppress the HPA axis. However, other routes of administration such as inhalation, topical, intra-ocular cause HPA axis suppression as well as other systemic AEs and this depends on the systemic bioavailability of the drug (19, 48, 49, 95, 114, 123).

Daily Therapy

There is evidence that patients are at lower risk for adrenal insufficiency if they can take glucocorticoids on alternate days from the outset or if they can convert to alternate-day therapy before the HPA axis is suppressed (21, 129).

Split Doses and Night Doses

Administering GCs in several different doses during the day imposes a greater risk for HPA axis suppression. In the same way, evening doses of glucocorticoids tend to suppress the normal early morning surge of ACTH secretion, resulting in greater adrenal suppression. Whenever possible, it is better to treat patients with a single morning dose. Once-a-day dosing is usually feasible for intermediate or long acting GCs e.g. prednisone, triamcinolone and dexamethasone. The short-acting hydrocortisone and cortisone acetate are usually given twice a day, at waking and around 5 PM. To mimic normal diurnal cortisol rhythms, the morning dose is two thirds, and the afternoon dose one third of the total daily dose (19, 130, 131).

Duration and Cumulative Dose of Glucocorticoid Treatment

Although traditionally the duration of glucocorticoid therapy and the cumulative dose of glucocorticoid received have been considered as predictive of the likelihood of HPA axis suppression, several studies suggest that they only roughly predict HPA axis suppression (132-134). Adrenal insufficiency is extremely rare in patients treated for 1 week or less (135, 136). Nevertheless, with a so called "short-term" 14 day course of systemic GCs, generally considered safe, in patients with acute exacerbation of chronic obstructive pulmonary disease, suppression of the HPA axis has been defined (47).

Cushingoid Features

Patients with Cushing's syndrome symptoms due to GC therapy are more likely to have a suppressed HPA axis and adrenal atrophy (19).

It has been suggested that the best predictor of HPA axis suppression is the patient's current glucocorticoid dosage. A strong correlation has been found between prednisone maintenance doses above 5 mg/d and a subnormal ACTH-stimulation test result (137). Finally, it can be assumed that patients who are more likely to develop HPA axis suppression are those who receive high doses (>20-30mg prednisolone or equivalent) of systemic GCs for long periods (>3weeks) and those who appear to have Cushingoid features. As the HPA axis function in patients treated with synthetic GCs cannot be reliably estimated from the above parameters several tests are commonly used in order to assess the axis' recovery.

WEANING PATIENTS FROM GLUCOCORTICOID THERAPY

Besides their multiple therapeutic uses, GC withdrawal is indicated when their use is no longer recommended as the maximum therapeutic benefit has been obtained or when significant side effects appear and become uncontrollable, such as GC induced psychosis, diabetes mellitus, severe hypertension, and incapacitating osteoporosis. The goal of a successful GC withdrawal regimen can be described as the rapid transition from a state of tissue hypercortisolism to a state of total exogenous GC deprivation without resurgence of the underlying disease and without adrenal insufficiency or any other GC dependency. Although there are no consensus documents, several tapering regimens have been published so far. In clinical practice, the majority of physicians develop their own withdrawal regimens. The common point is that GC withdrawal should never be abrupt (19).

A systematic review published in 2002 found 9 randomized, controlled clinical trials, 7 of which investigated bronchial asthma and chronic obstructive pulmonary disease, which compared different GC tapering regimens. According to this review there was no significant difference between rapid or slow tapering, regarding the diseases' exacerbation and relapse rates, suggesting that prolonged withdrawal may not be necessary for a better outcome of the underlying disease. However, the same review highlighted the uncertainty about the safety and efficacy of GC withdrawal in many chronic diseases, emphasizing the need for further research in this area (131).

In general, patients taking any steroid dose for less than 2 weeks are not likely to develop HPA axis suppression and can stop therapy suddenly without tapering. The possible exception to this is the patient who receives frequent "short" steroid courses e.g. in asthma. Where there has been chronic therapy, the objective is to rapidly reduce the therapeutic dose to a physiological level (equivalent to 7.5mg/d prednisolone) e.g. by reducing 2.5mg every 3-4 days over a few weeks, and then proceed with slower withdrawal in order to permit the HPA axis to recover (19, 21).

As far as patients with underlying disease are concerned it is recommended that all available clinical, biochemical and laboratory data on the activity status of the disease be collected in order to easily identify signs of recurrence. In such a case prescribed doses should be increased (19).

After the initial reduction to physiological levels, doses should be reduced by 1mg/d of prednisolone or equivalent every 2-4 weeks depending upon patient's general condition, until the medication is discontinued. Alternatively, after the initial reduction to 5-7.5mg of prednisolone, the clinician can switch the patient to HC 20mg/d and reduce by 2.5mg/d every week until the dose of 10mg/d is achieved. After 2-3 months on the same dose, the HPA axis function should be assessed through a Corticotropin (ACTH-Synachten) test or through an Insulin Tolerance test (ITT). A pass response to these tests indicates adequate function of the axis and GCs can be safely withdrawn. If the axis has not fully recovered, treatment should be continued and the axis function should be reassessed (21).

Other tapering regimens have been published some of them dealing with switching the patient to an alternate dosage of GC before discontinuation (138).

Irrespectively of the tapering regimen used, if GC withdrawal syndrome, adrenal insufficiency's symptomatology, or exacerbation of the underlying disease appears, the dose being given at the time should be elevated or maintained for a longer period of time. Moreover, in the absence of evidence of HPA axis full recovery in patients who have been treated with GCs for prolonged periods, supplementation equivalent to 100-150mg of HC is recommended during situations of severe stress such as major surgery, fractures, severe systemic infections, major burns, etc.

Finally, it has become obvious, that all patients treated long-term with GCs should be treated in a similar fashion to patients with chronic ACTH deficiency, thus, they should be instructed to carry some type of identification (worn around the neck or wrist or carried as a card) (19, 21).

ACUTE ADRENAL CRISIS

Full HPA axis recovery after cessation of GC therapy may take as long as 1 year or more (11, 139). Abrupt cessation of glucocorticoid treatment or quick tapering can precipitate an acute adrenal insufficiency crisis. The main symptoms range from anorexia, fatigue, nausea, vomiting, dyspnea, fever, arthralgia, myalgia, and orthostatic hypotension to dizziness, fainting, and circulatory collapse. Hypoglycemia is occasionally observed in children and very thin adult individuals. The diagnosis is a medical emergency, and treatment should be immediate administration of fluids, electrolytes, glucose, and parenteral glucocorticoids.

GLUCOCORTICOID WITHDRAWAL SYNDROME (GWS)

Chronic administration of high doses of GCs and also other hormones such as estrogens, progestins, androgens and growth hormone induce varying degrees of tolerance, resulting in a progressively decreased response to the effect of the drug, followed by dependence and rarely "addiction". Traditionally, the term "Endocrine Withdrawal Syndromes" has been used to describe symptoms and signs of specific hormone deficiency after discontinuation of hormonal therapy or removal of an endocrine gland. However, discontinuation of hormonal therapy frequently results in a mixed picture of two different syndromes: a typical hormone deficiency syndrome and a generic withdrawal syndrome. Four aspects of GCs withdrawal after cessation of pharmacological high-dose therapy are important: 1) relapse of the underlying disease for which the drug was prescribed 2) HPA axis suppression which can persist for a long time 3) psychological dependence 4) a non-specific withdrawal syndrome despite normal HPA axis function and even while patients are receiving physiological replacement doses of GCs (140, 141).

Amatruda et al. first defined the steroid withdrawal syndrome as a symptom complex resembling true adrenal insufficiency, with nonspecific symptoms like weakness, nausea, and arthralgias, occurring in patients who have finished a dosage reduction of glucocorticoid therapy and who respond normally to HPA axis testing (142). Thus, after cessation of GC therapy patients may develop anorexia, nausea, emesis, weight loss, fatigue, myalgias, arthralgias, weakness, headache, abdominal pain, lethargy, postural hypotension, fever, skin desquamation, tachycardia, emotional lability, and even delirium, and psychotic states even if the response of the HPA axis to stimuli has returned to normal (140). Children and adolescents may experience signs and symptoms of GWS even when GCs are still being administered in supraphysiological doses (19). Biochemical evidence related to the GWS includes hypercalcemia and hyperphosphatemia (140).

The GWS has been considered a withdrawal reaction due to established physical dependence on supraphysiological GC levels (140). It has also been described as a state of relative GC resistance in these patients, effectively rendering them hypoadrenal (141). The mechanisms responsible for GWS have not been fully elucidated. Nevertheless, several mediators should be considered and include CRH, vasopressin, POMC, several cytokines such as IL-1β, IL-6, TNF-α, prostaglandins such as E2, I2, phospholipase A2 and also alterations of the noradrenergic and dopaminergic systems (19, 140).

The severity of GWS depends on the genetics and developmental history of the patient, on his environment, and on the phase and degree of dependence the patient has reached (140). The syndrome is self-limited with a median duration of 10 months. Its management should include a temporary increase in the dose of GCs followed by gradual, slow tapering to a maintenance dose (141).

BIOCHEMICAL DIAGNOSIS OF ADRENAL INSUFFICIENCY

Glucocorticoid treatment may not suppress the HPA axis at all, or it may cause central suppression and adrenal gland atrophy of varying degrees. Several endocrine tests have been used to define progression of glucocorticoid-induced adrenal insufficiency. The insulin tolerance test and the metyrapone test have been employed in the diagnosis of adrenal suppression and are quite sensitive, however, the risks involved with both tests do not justify their use when a rapid ACTH stimulation test can distinguish clinically significant adrenal suppression.

To evaluate the adequacy of hypothalamic-pituitary-adrenal axis recovery, the rapid Synachten (or high-dose ACTH stimulation test) is mostly used. An intravenous bolus of 250 ug of corticotropin 1-24 is administered and cortisol is measured after 30 or 60 minutes or both. A plasma cortisol concentration > 18 - 20 μg/ dL at these times indicates adequate recovery of the hypothalamic-pituitary-adrenal axis (139).

The low-dose Synachten test (1ug or 500 ng ACTH(1-24)/1.73 m2) is also being used for the assessment of the HPA axis after prolonged use of GC medication (143-145). It is unclear if the low-dose test is superior to the high-dose test for the detection of secondary adrenal insufficiency. Some studies have shown that the low-dose Synachten test is more sensitive in detecting partial secondary adrenal insufficiency (as can occur in chronic use of GCs), which is not detected by the standard high-dose test because the latter provides a supraphysiologic stimulus able to stimulate a partially damaged adrenal (146-149). A meta-analysis of 28 studies evaluated the utility of the high and low-dose ACTH test. At a specificity of 95% the sensitivity of the high-dose test for primary adrenal insufficiency was 97%, greater than that for secondary adrenal insufficiency (57%). The sensitivities for secondary adrenal insufficiency were similar between the high-dose (57%) and the low-dose Synachten test (61%) (150). In contrast, a review of the literature published between 1965 and 2007 suggests that the low-dose test is the best test currently available for establishing the diagnosis of secondary AI (151). Further studies are needed to establish if the low-dose Synachten test is preferable for the diagnosis of secondary AI.

The Corticotropin Releasing Hormone (CRH) test can also be used in patients taking GC treatment for prolonged periods, as it can assess both the ACTH and cortisol responses and can distinguish between secondary and tertiary adrenal insufficiency (133, 152).

The Dexamethasone Suppression Test has been shown to predict the later development of an impaired adrenal function after a 14-day course of prednisone in healthy volunteers and this information may allow a more targeted approach for the patients after cessation of steroid therapy (153).

FUTURE PERSPECTIVES ABOUT GLUCOCORTICOID THERAPY

Although hydrocortisone (HC) is the most commonly used regimen for replacement in patients with primary and secondary adrenal insufficiency, it is evident that this conventional therapy cannot provide the physiological rhythm of cortisol release. Moreover, with current replacement therapy, the majority of patients with adrenal insufficiency report impaired health-related quality of life, early morning fatigue, socioeconomic health problems and, finally, increased mortality (154). Circadian infusions of HC delivered by a programmable pump can mimic the normal rhythm of cortisol secretion and improve biochemical control and quality of life in patients with adrenal insufficiency and congenital adrenal hyperplasia. Because such infusions are not a practical solution, new formulations of oral HC, which mimic cortisol physiology have been evaluated. A dual-release hydrocortisone tablet with an immediate-release outer layer covering a sustained-release core, has been used in patients with Addison's disease showing improvements in cardiovascular risk factors, including body weight, hemoglobin A1C and blood pressure, as well as a significant improvement in fatigue (154-156). In the long-term, this once-daily formulation was well-tolerated with a small number of adverse effects (157). Another modified-release multi-particulate hydrocortisone capsule formulation has been developed recently (158). This formulation was well tolerated and very effective in controlling disease biomarkers of congenital adrenal hyperplasia, such as androstenedione and 17-hydroxyprogesterone, with a lower hydrocortisone dose equivalency (154).

Apart from their use for hormonal replacement, the clinical success of synthetic GCs as anti-inflammatory agents is largely attributed to their ability to reduce the expression of proinflammatory genes, via activation of the GR and the concomitant inhibition of the activity of proinflammatory transcription factors, including NF-κB and AP-1, through a mechanism called trans-repression. On the other hand, the appearance of their AEs mainly arise from their ability to activate, after induction of the GR, target genes involved in the metabolism of sugar, protein, fat, muscle and bone via a mechanism called trans-activation (159, 160). There is a plethora of recent work dealing with the characteristics of novel selective GR ligands with equal efficacy and improved side-effects profiles, in other words ligands that show an improved therapeutic index (159-162). These efforts have resulted in a number of different terminologies: Selective GR modulators, selective GR agonists, gene-selective compounds, dissociated compounds, etc. (161, 163), which have been developed and are still being developed mainly focusing on the trans-repression mechanism and stimulating the side-effect pathway to a lesser extent, at least in specific tissues. Nevertheless, the likelihood of finding a compound that actually separates all activated genes from all repressed genes is highly unlikely mainly because the transactivation vs trans-repression characteristics are highly cell-type and gene specific. Moreover, it is also unclear whether such a compound would be truly desirable, as upregulation of anti-inflammatory genes may also play a role in the treatment of many diseases (159-161). In addition, many non-steroidal dissociated GR modulators, some of which do not support trans-activation, have shown promising benefit to side-effect ratios (e.g. ZK216348, CpdA) (159).

Considering the complexity of pathways regulated by GR, it is clearly too naive to assume that an ideal exogenous GR modulator only eliciting the beneficial anti-inflammatory effects without any trace of side-effects will ever be found. Complementing genome-wide gene profiling studies and transcription factor/DNA binding patterns on various target tissues at once will become an adamant strategy for the future (159). However, recent reports of Selective GR modulators provide fertile ground for additional efforts and it is obvious that any progress in this area would be a major benefit for thousands of patients receiving GC therapy (161).

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