*Karolina M. Nowak, Lucyna Papierska

Prevention and monitoring of the side effects of chronic corticosteroid therapy

Zapobieganie i monitorowanie działań niepożądanych przewlekłej steroidoterapii

Department of Endocrinology, Centre of Postgraduate Medical Education, Bielański Hospital, Warszawa
Head of Department: prof. Wojciech Zgliczyński, MD, PhD

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Address/adres:
*Karolina M. Nowak
Department of Endocrinology
Centre of Postgraduate Medical Education
Bielański Hospital
ul. Cegłowska 80, 01-809 Warszawa
tel. +48 (22) 569-05-29
klinendo@cmkp.edu.pl

Summary

Glucocorticoids are used in the treatment of autoimmune, hematological, allergic and other inflammatory diseases. Over the years many synthetic compounds were created in order to exert the strongest anti-inflammatory effect with the least side effects. While short-term treatment with glucocorticoids benefits usually outweigh the adverse events, with time, however, complications of therapy may become a burden for the patient as serious as the underlying disease. Typically the higher the dose and time of treatment, the more numerous and more serious side effects are. In most cases we are not able to give up treatment with corticosteroids and for that reason it is not possible to avoid the side effects. However, with proper prevention methods we can minimize them.

In the paper we present the literature review concerning monitoring the treatment and prevention of the most common side effects of glucocorticoids. We also propose the scheme of the management with patient during chronic glucocorticoid treatment.

Streszczenie

Glikokortykosteroidy (GKS) wykorzystywane są w leczeniu chorób autoimmunologicznych, hematologicznych, alergicznych i innych o podłożu zapalnym. Przez lata tworzono kolejne syntetyczne związki, mając na uwadze, aby wywierały jak najsilniejszy efekt przeciwzapalny i jak najmniejsze działania niepożądane. Podczas krótkotrwałego leczenia glikokortykoidami korzyści przewyższają zazwyczaj efekty uboczne, z czasem jednak powikłania terapii mogą stać się dla pacjenta obciążeniem równie poważnym jak choroba podstawowa. Zwykle im wyższa dawka i dłuższy czas terapii, tym liczniejsze i groźniejsze działania niepożądane. Należy pamiętać o tym, że w większości przypadków zaniechanie kortykoterapii nie jest możliwe – nie unikniemy więc działań ubocznych GKS, ale przez odpowiednio prowadzoną profilaktykę możemy je zminimalizować.

W poniższej pracy dokonaliśmy przeglądu badań dotyczących monitorowania leczenia glikokortykosteroidami oraz zapobiegania najczęściej przez nie wywoływanym działaniom niepożądanym. Zaproponowaliśmy też schemat postępowania z pacjentem poddanym przewlekłej kortykoterapii.

INTRODUCTION

For the first time glucocorticoids (GCS) were used in medicine over 60 years ago in the treatment of rheumatoid arthritis and Addison's disease which was then called a "cortisone miracle". Due to their anti-inflammatory and immunomodulative action GCS are widely used in the treatment of many diseases. Despite unquestionable beneficial effects of this group of compounds, these medications are characterized by a large number of adverse events. The disorders caused by GCS, dependent on dose, the duration of treatment and route of administration, range from iatrogenic Cushing's syndrome through hypothalamic-pituitary-adrenal axis suppression to neurological and psychiatrical diseases. Even inhaled glucocorticoids (ICS), intraarticularly injected or topically used are not free from systemic side effects. Due to the fact that GCS are one of the most used group of medicines, the important task facing modern medicine is to prevent the numerous adverse effects that they cause. The problem of serious side effects caused by glucocorticoids is the subject of studies for many years, however apart from the prevention of osteoporosis and gastrointestinal bleeding (with simultaneous use of nonsteroidal

anti-inflamatory drugs), there are no Evidence Based Medicine recommendations concerning prevention of adverse events during treatment.

THE CHEMICAL STRUCTURE, PHARMACOKINETICS AND METABOLISM OF GCS

Obtaining glucocorticosteroids with stronger anti--inflammatory activity can be achieved by modification of cortisol structure. These changes include the formation of a double bond between the 1st and 2nd position, which increases anti-inflammatory effect with reduction of binding with mineralocorticoid receptor (prednisolone). Other modifications include the introduction of fluoro group in 9th position (Dexamethasone, Triamcinolone, Fludrocortisone), methyl group in 6th position (Methylprednisolone) and 16th (Dexamethasone), which effected in further intensification of anti-inflammatory activity, reduction of mineralocorticoid effect and simultaneously prolongation of action. Exception in the mentioned group is fludrocortisone, which to a great extent is characterized by the mineralocorticoid effect and it is not used for anti-inflammatory activity. Modification in chemical structure and activity of glucocorticoids, comparing to cortisol, are presented in table 1 and figure 1.

The presence of hydroxyl group in 11th position is responsible for glucocorticoid and anti-inflammatory activity while substances with ketone group in the mentioned position (cortisone, prednisone) are biologically inactive and first have to be hydroxylated by 11β-hydroxysteroid dehydrogenase type 1. This enzyme is present in almost every tissue susceptible to glucocorticoids. The 11β-hydroxysteroid dehydrogenase type 2 is responsible for the reverse reaction of inactivation (oxidation). The medicines having in its structure a fluoro or methyl group are insensitive to the action of this enzyme. Cortisol, to a small extent, is also

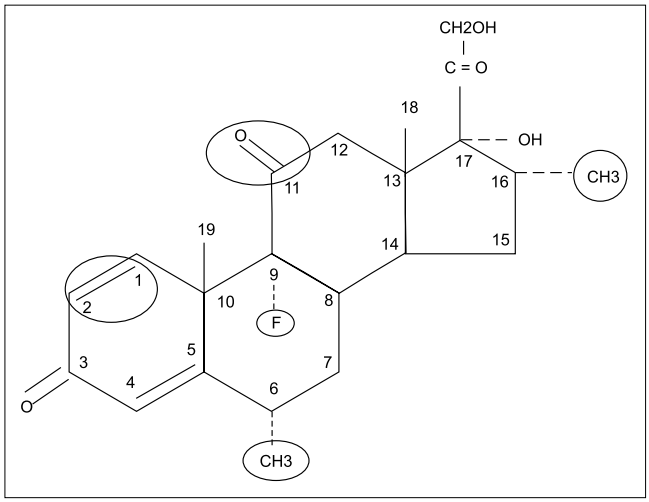

Fig. 1. Modification in chemical structure of cortisol (explanation in table 1).

metabolized by 6β-hydroxylase (to biologically inactive 6β-hydrocortisone). This reaction is catalyzed by cytochrome P450 3A4. Therefore, interactions can occur between glucocorticosteroids (including ICS and intranasally admitted) and drugs inducing or inhibiting CYP3A4. The strong inhibitors of CYP 3A4 may slow the metabolism of GCS and in consequence cause its' increased concentration and toxicity. The strong inducers of CYP 3A4 may cause the reverse reaction. The most important drugs that can influence the metabolism of glucocorticosteroids are listed in table 2.

Regardless of the effect on cytochrome P450, glucocorticoids may increase the potency of other drugs for instance warfarin by not well known multiple mechanism, diuretics by enhancing their kaluretic action or NSAIDs by increasing the risk of peptic ulcer (4).

Endogenous glucocorticoids in blood are bound mainly (in 75%) to CBG protein (Corticosteroid Bind-

Table 1. The structure and examples of equivalent doses and duration of action of glucocorticosteroids (1).

Name	Modification in chemical structure comparing to cortisol	Examples of equivalent doses of glucocorticosteroids	Anti-inflammatory activity	Mineralocorticoid activity	Duration of action (T 1/2 in hours)
Cortisol	–	20 mg	1	1	8-12 h
Hydrocortisone	No modification	25 mg	0.8	0.8	8-12 h
Prednisone	Double bond between 1st and 2nd position, ketone group in 11th position	5 mg	4	0.8	12-36 h
Prednisolone	Double bond between 1st and 2nd position	5 mg	4	0.8	12-36 h
Methylprednisolone	Double bond between 1st and 2nd position, methyl group in 6th position	4 mg	5	0.5	12-36 h
Triamcinolone	Double bond between 1st and 2nd position, fluor group in 9th position	4 mg	5	0	12-36 h
Dexamethasone	Double bond between 1st and 2nd position, fluor group in 9th position methyl group in 16th position	0.75 mg	30	0	36-72 h
Fludrocortisone	Fluor group in 9th position	–	10	125	12-36 h

Table 2. Drugs influencing the metabolism of glucocorticosteroids (including ICS) (2, 3).

Strong inhibitors of CYP3A4	Weak inhibitors of CYP3A4	Strong inducers of CYP3A4
Antiviral drugs (e.g. Atazanavir, Cobicistat, Darunavir)	Amiodaron, Dronedaron	Nevirapine, Efavirenz, Etravirine
Boceprevir, Telaprevir	Aprepitant, Fosaprepitant	Phenytoin, Fosphenytoin, Carbamazepine, Oxcarbazepine, Primidone
Itraconazole, Ketoconazole, Pasaconazole, Voriconazole	Fluconazole, Clotrimazole, Miconazole	Griseofulvin
Clarithromycin, Telithromycin	Erythromycin, Ciprofloxacin, Norfloxacina, Metronidazole, Tetracycline	Rifampin, Rifabutin, Rifapentine
Imatinib	Crizotinib, Lapatinib	Vemurafenib
Conivaptan	Cyklosporine	Barbiturates
Cimetidine*	Grapefruit juice	Nafcillin
Diltiazem*, Nicardipine	Verapamil	Aminoglutethimide, Mitotane
Fluoxetine	Sertraline, Haloperidol, Desipramine	Modafinil
Isoniazid	Abiraterone, Bicalutamide	Enzalutamide

*These drugs are moderate inhibitors of CYP3A4 (2).

ing Globulin), in 15% are transported by albumins (in this form it is biologically inactive fraction) while 10% is a free fraction. CBG (transcortin) concentration increases under influence of medicaments such as mitotane, high estrogen levels (pregnancy, hormone replacement therapy, oral contraception) or in pathological conditions (diabetes, hyperthyroidism) (5). Increased CBG concentration may give falsely high values of serum total cortisol concentration. In such cases free cortisol in the blood or saliva should be measured.

Synthetic GCS (except prednisolone) are bound in 2/3 with albumins while the remaining 1/3 is present in serum in a free state (6). Protein binding also affects biological half-life, which for cortisol and cortisone is much shorter than that of the synthetic glucocorticoids. The results presented by Kozowera et al. shows that predisolone clearance in patients with side effects during corticotherapy was decreased comparing to those without adverse events (7). In the other study, elderly people had decreased corticoid clearance (8): for that reason it is necessary to lower GCS doses in this group of patients.

Comorbidities also affects the metabolism of GCS. The most important include:

Hyperthyroidism – the increased metabolism of prednisone and prednisolone, as well as the reduction of the biological effect, was reported (9). It may be necessary to use higher doses of GCS.

Inflammatory bowel disease – the investigation showed reduced protein binding with prednisolone in patients with active disease, probably caused by lower albumin concentration, which can accelerate the elimination of the drug from the body (10). Chronic kidney disease increases the half-life of GCS and thus it is necessary to reduce the dose. On the contrary, the patients on hemodialysis may need the increased dose of GCS.

Obesity – when determining the doses of glucocorticosteroids the ideal body weight should be taken into consideration instead the actual body weight.

Cirrhosis – together with deteriorating liver function, the concentration of 6β-hydroxylase may decrease, which leads to increased exposure to the biologically active form of corticosteroids (11). Hypoalbuminemia, increasing the free fraction of GCS is an additional factor causing that in this disease dose should be reduced.

GENERAL PRINCIPLES OF INITIATING THERAPY WITH GLUCOCORTICOIDS

Before initiation of therapy with GCS the indications should be carefully considered. The determination whether the patient can receive other treatment for the given disease and if it has already been implemented, whether the dose is optimal. Therapeutic targets, assumed duration of therapy, the dose (the smallest dose for the shortest time period) and the preparation of GCS need to be identified. The most important is to define the criteria of effectiveness and ineffectiveness of treatment, when the treatment should be absolutely stopped. The next step is to identify the comorbidities whose course may deteriorate during treatment and may affect the metabolism of GCS (along with chronically taken medications) what in consequence may intensify action of GCS and lead to occurrence of side effects. Even very small dose of GCS (< 5 mg of prednisone equivalent) may cause adverse events thus it is important to follow the given recommendation at every case of chronic treatment with GCS. The typical doses of glucocorticoids are presented in table 3.

Table 3. The classification od glucocorticosteroid doses.

The typical dose of glucocorticoids	The daily dose in prednisone equivalent
Small dose	≤ 7.5 mg
Moderate dose	> 7.5 mg and ≤ 30 mg
High dose	> 30 mg and ≤ 100 mg
Very high dose	> 100 mg
Pulse dose	≥ 250 mg

THE ADVERSE EVENTS OF CHRONIC CORTICOTHERAPY – PREVENTION AND MONITORING

Cushingoid appearence and weight gain

Considering the number of patients treated with GCS annually, the fact that the main cause of Cushing's syndrome is iatrogenic does not seem to be a surprise. The phenotype includes inter alia: weight gain, visceral obesity, plethora, dorsocervical fat pads ("buffalo

hump"), proximal myopathy, leg edema, ecchymoses, skin thinning and atrophy, red striae, hirsutism and acne (11). Not all of these symptoms must be present. The frequency of Cushingoid appearance is a "linear" dependent on dose and duration of treatment. It develops even while using less than 5 mg of prednisone/day and its occurrence is estimated from 4.3% after such doses to 24.6% when dosage increased over 7.5 mg prednisone/day during at least 6 months of glucocorticoid intake (12).

It was observed that the risk of weight gain increases abruptly beyond the threshold value of 5 mg/day of prednisone and is estimated at 22.4% for this dose (compared to 8.7% for < 5 mg/day) (13). The chance of this side effect does not increase even after further dose escalation. In the population based study patients treated with prednisone in dose lower than 7.5 mg/day for over 60 days, the weight gain was also observed (13). However, in contrast to the above cited study (12) the authors reported increasing percentage of patients with weight gain together with increasing cumulative dose of GCS. A limitation in the interpretation of this study includes lack of a control group and the assessment of the incidence of this side effect is based on data provided by the patients and not on objective anthropometric measurements. Although weight gain with redistribution of body fat is not a serious side effect is very often reported by patients as a burden (13). Increased appetite may be also a significant factor contributing to weight gain.

Unfortunately, there is no conclusive, based on EBM, data on prevention of these side effects. It is recommended to monitor weight, waist circumference and body fat distribution with measurements every 3-6 months. There is a beneficial effect of reducing diet, moderate exercise adaptable to the patient's capabilities and patient education (14). We recommend low calorie diet with a low glycemic index and high protein diet (to prevent muscle atrophy as a consequence of gluconeogenesis from protein). As shown in clinical practice, even in patients with Cushing's disease we can prevent these complications.

Glucose metabolism impairment

In patients with pre-existing diabetes, the worsening of glucose control can occur during treatment with GCS. Degree of impairment of glucose metabolism is proportional to the degree of glucose tolerance before treatment and depends on the dose of GCS (15). In a study on the large group of patients the risk of hyperglycemia increase along with the dose of administered glucocorticosteroids (OR 1.77 for a dose of 1-39 mg/d to OR 10.34 for a dose of > 120 mg/d of hydrocortisone equivalent) (15). There has been reported surprisingly rare occurrence of new onset diabetes during therapy with GCS. In four studies concerning low dose of GCS in rheumatoid arthritis there was no new cases of diabetes (16). Other authors estimate the incidence of this disease on 10-20% (17). In one research risk factors of glucocorticoid induced diabetes were identified and they are the same as for the development of type 2 diabetes: obesity, pre-diabetes, previous gestational diabetes and a positive family history (18). However in 2012 Australian researchers published the outcomes of their study comparing patients with steroid induced diabetes with patients with previously diagnosed type 2 diabetes (19). It was observed that patients with newly diagnosed steroid-induced diabetes had lower body mass index, less macrovascular complications and less frequent had a positive family history. Interestingly retinopathy did not develop in any of these patients, which may indicate on a less long-term exposure to hyperglycemia in this group.

Prevention of steroid-induced diabetes and blood glucose monitoring: before initiating the treatment with GCS every patient must undergo blood examination such as concentration of fasting glucose and, if the incorrect values were found, oral glucose tolerance test should be performed. If diabetes or pre-diabetes are detected, it is advisable to implement appropriate management consistent with current guidelines. In patients already treated with GCS EULAR in daily practice recommends regular blood test for fasting glucose and "standard care" (14, 20). However, these recommendations are only based on opinion of experts (level of evidence IV). There are no EBM studies indicating benefits from such management. In current guidelines steroid-induced diabetes is an indication for insulin therapy (21).

Cardiovascular diseases

Systemic glucocorticoids cause an increased risk of cardiovascular diseases, while the use of articular, topical or inhaled GCS does not induce such effect. GCS action on gluco- and mineralocorticoid receptors trigger a number of adverse effects that contribute to negative impact on the cardiovascular system (22). Note that diseases of the cardiovascular system are the leading cause of death in patients with Cushing's syndrome (including iatrogenic). Increased risk of coronary heart disease, heart failure, atherosclerosis, stroke, transient ischemic attack (TIA), hypertension and all-cause mortality was stated in patients receiving prednisone at a dose of > 7.5 mg/day. These effects may not occur in patients taking lower doses of GCS (12, 22). The risk of death may be increased up to 7-fold compared to patients not treated with glucocorticosteroids (18). This risk was higher during continuous therapy (compared with the intermittent) and in patients receiving GCS for over 6 months prior to the study (12). In another large investigation higher risk of coronary heart disease and heart failure was also reported but there was no influence on the risk of stroke and TIA (23). In several other studies a higher incidence of atrial fibrillation and flutter was observed in patients beginning the therapy or being chronically treated (OR = 1.9), while there was no such effect in patients taking the drug in the past (24). There were

also cases of sudden cardiac death in patients treated with pulses of methylprednisolone (25). It should be remembered that the underlying disease may contribute to more cardiovascular events. The characteristic action for GCS is intensification of reabsorption of sodium and water and excretion of potassium. Thus it is important to control potassium concentration and supplement it if needed.

According to the recommendations based on expert opinion (level of evidence IV) the risk of cardiovascular disease, should be carefully evaluated prior to and during therapy. Coronary heart disease, heart failure, hypertension, dyslipidemia must be treated in accordance with current standards of cardiologic societies (14). During every visit patient should be asked about symptoms that could indicate on cardiovascular disease. Special attention should be paid to the presence of peripheral edema and blood pressure should be measured.

Gastrointestinal diseases

During the treatment with GCS a few complications from the gastrointestinal tract can be expected such as: peptic ulcer, gastrointestinal bleeding and gastritis. The use of oral glucocorticosteroids alone is associated with a low risk of development of above listed events. However, in combination with non-steroidal anti-inflammatory drugs (NSAIDs) GCS cause a two-fold increase in risk of complications compared with the intake of NSAIDs alone and a four-fold increase compared with those untreated neither with NSAIDs nor with GCS (26). Despite reports about the possibility of acute pancreatitis caused by GCS (27) these data has not been definitively confirmed (28). Proton pump inhibitors in patients on chronic therapy with GCS are not recommended unless parallel treatment with NSAIDs is conducted (level of evidence I) (14). The evidence of infection with *H. pylori* is an indication for eradication.

Osteoporosis

The negative impact of corticosteroids on bone metabolism has been relatively well investigated (29). The largest loss of bone mass (10-20%) occurs in the first year of therapy and then decreases to reach a stable level of about 2-5%/year (30). The risk of fracture is increased in every age group irrespective of the pre-existing fractures and gender. This phenomenon depends on dose and duration of the treatment. It has been demonstrated for even small doses of prednisone in the range of 2.5 to 7.5 mg/day (31). At a dose of 10 mg prednisone/day for more than 90 days the risk of hip fracture was 7-fold, and fracture of the spine 17-fold higher than in the control group (32). Thus prevention is extremely important in view of the fact that about 30-50% of this group of patients undergo asymptomatic fractures of the spine, ribs and femoral neck (31). The general principles for prevention include: administering the dose as low as possible for the period of time as short as possible, choosing locally acting GCS whenever possible, preventing falls, avoiding cigarettes and excessive amounts of alcohol, exercise adapted to the patients' capabilities that will allow not only to prevent bone loss but also muscle atrophy. There is no unified international recommendations on pharmacological prophylaxis, but most often cited recommendations of the American Society of Rheumatology and the Royal School of Physicians in the UK are broadly similar (31, 33, 34). Before initiating treatment with prednisone at a dose of more than 5 mg/day for over 3 months patients have to undergo densitometry (DXA of femoral neck and spine) and repeat measurements must be performed at the same location every 6 to 12 months. In addition, it is recommended to measure growth every 3 months (35). Prophylactically in all patients calcium (1000 U/day) and vitamin D (at least 800 J/d) supplementation is recommended to maintain the concentration of 25(OH)D levels between 30 and 80 ng/ml. In case of vitamin D deficiency it is needed to treat it with higher dose 2000-4000 j/day until the target concentration is reached (36). 25(OH) concentration needs monitoring every 3 months. Furthermore patients who require medium and high doses of glucocorticosteroids should receive active forms of vit. D 1 mg/day of alfacalcidol or calcitriol 0.5 mg/day (31). Treatment with bisphosphonates (alendronate, risedronate, ibandronate) is recommended in patients after 50 years old in the case of confirmed osteoporotic fracture (even in individuals under age 50) with T score < -1.5 and the risk of fracture above 5% calculated using FRAX calculator (35). Prophylactic therapy should be considered in all patients after 65 years treated with dose above 7.5 mg/day of prednisone for over 3 months even in case of absence of other risk factors of fracture (36). If during treatment with bisphosphonates for minimum 12 months at therapeutic doses another low-energy fracture occur it should be considered to apply the therapy with teriparatide (35). It has the advantage over bisphosphonates that it shows an anabolic effect, and GCS cause strong inhibition of bone formation. Therapy with another anabolic drug (Strontium ranelate, DHEA) also effectively stimulate bone formation and causes increase bone mass, but there are no studies showing the antifracture efficacy in patients treated with glucocorticoids (37).

Osteonecrosis

Glucocorticosteroids are one of the known etiologic factors of osteonecrosis particularly in the femoral head. Its prevalence varies between 21-37% and is also associated with the underlying disease (38). Patients chronically treated with high doses of GCS are more likely to develop osteonecrosis. The outcomes of most studies shows the risk of this side effect in patients treated with less than 20 mg of prednisone/day is very low (39). There are no recommendations concerning monitoring and preventing this adverse event except these about clinical trials (13).

Ophtalmological complications

During chronic therapy with corticosteroids cataract and glaucoma can be expected particularly. It has been shown that cataract can occur even in patients receiving < 5 mg prednisone/day for over 6 months while glaucoma in individual treated with more than 7.5 mg/day (12). The outcomes of other studies shows that the risk of developing cataract (subcapsular form) depends on the dose and duration of therapy (40). The use of systemic GCS, also in the form of eye drops, can increase intraocular pressure, cause glaucoma or worsen an existing illness, especially in individuals with a family history of diabetes or high myopia (12, 41). According to expert opinion (level of evidence IV) before treatment intraocular pressure measurement and ophthalmological consultation should be carried out, especially in patients with risk factors (glaucoma, diabetes, myopia) (14, 20). Patients should go for regular eye check-up (but it was not specified how often it should be performed).

Infections

Because of acquired immunodeficiency caused by GCS the risk of infection is increased. Symptoms of infection in these patients may be unusual: reduced secretion of proinflammatory cytokines can result in a lack of fever and normal concentrations of inflammatory markers in spite of severe infection. Special attention should be given to the possibility of opportunistic infections (such as *Pneumocystis jiroveci*) and the onset of latent tuberculosis (16). In a meta-analysis of 71 studies receiving doses above 10 mg/day of prednisone was associated with a twofold increase in the risk of infection (42). In patients treated with GCS the use of live virus vaccines (e.g. MMR and varicella) is contraindicated. The exceptions are patients taking low doses of the drug for 14 days or less, patients receiving substitution therapy and receiving corticosteroids locally (inhaled, topical etc.). If the discontinuation of corticosteroid treatment is possible vaccination should be postponed to a minimum 1 month after termination of therapy. After inoculation of influenza and *S. pneumonia* patients had lower antibody concentration compared to the control group not receiving GCS (43, 44). Nevertheless prophylactic vaccination against these diseases is recommended. In addition, the recommendations concerning the prevention of infection (level of evidence IV) state that the foci of infection (including tuberculosis) must be ruled out before initiating treatment with corticosteroids (14).

Neurological and psychiatric complications

The range of disorders observed in this group of patients is very broad: most common are benign and reversible states such as emotional lability, euphoria, hypomania, anxiety, memory problems, confusion or disorientation (45). Sleep disorders were reported in 33% of patients during treatment with < 5 mg of prednisone daily and in 44% taking > 7.5 mg/day while in the control group this percentage was lower – 20% (12). More serious complications can occur, such as depression or psychosis, which older people with a history of depression and alcoholism are particularly vulnerable to (46). When large doses of GCS are used psychotic states may develop within a few days (47). These psychiatric symptoms subside (at > 90%) after dose reduction or termination of treatment. However, they can sometimes require treatment with psychotropic drugs sedatives, antipsychotics, antidepressants or tranquilizers. There is no specific recommendation dedicated to the prevention of psychiatric complications, but the patient and his family should always be informed about the possibility of occurrence these side effects.

Hypothalamic-pituitary-adrenal (HPA) axis suppression and glucocorticoid withdrawal

Every method of administration of GCS may result in suppression of HPA axis and diminished ACTH secretion, which leads to the atrophy of the adrenal cortex and to the secondary adrenal insufficiency. In one large study authors described normal and abnormal adrenal response to CRH, ACTH administration and hypoglycemia both in patients treated for less than 4 weeks with dose between 5-30 mg prednisone/day as well as in patients receiving the therapy for more than 100 weeks and dose above 25 mg prednisone/day (48). This study shows that HPA axis suppression cannot be precisely predicted based on dose and time of treatment. Nevertheless, this phenomenon is least likely in a group of patients using GCS for less than 3 weeks or individuals treated with alternate-day therapy (4, 49). Usually, in this situations abrupt discontinuation is safe. On the contrary, the group most likely to have HPA axis suppression, consist of patients with iatrogenic Cushing's syndrome, individuals using more than 20 mg of prednisone/day for more than 3 weeks or receiving a single bedtime dose for more than few weeks. These patients should be treated as anyone who has secondary adrenal insufficiency and therefore the dose should be tapered slowly (without previous testing for HPA axis function). Everyone who is not assigned to one of the two mentioned groups has uncertain risk of HPA axis suppression. Such patients needs testing for HPA function if the abrupt discontinuation of treatment is planned.

Glucocorticoid withdrawal

In the literature many schemes of GCS withdrawal can be found, but there is no conclusive evidence on the superiority of any of them. If the patient was receiving GCS for less than 3 weeks (even in large doses) usually the therapy can be discontinued without tapering the dose. In other cases (especially if the HPA axis function is uncertain) it is crucial to gradual withdrawal. One of the proposed schemes assumes an initial reduction of the dose of 2.5 mg of prednisone every 3-4 days until a dose of 7.5 mg prednisone/day. Then the dose is reduced by 1 mg every 2-4 weeks. When

the dose of 5 mg prednisone/day is reached, drug can be used every other day or be replaced with hydrocortisone substitution dose of 20 mg/day (as in secondary adrenal insufficiency). Then the dose should be reduced from 20 mg/day to 10 mg/day every 2.5 mg/week. After 2 to 3 months, we examine morning blood concentration of cortisol 24 hours after the last dose of hydrocortisone (50). With the result < 5 μg/dl substitution dose must be continued and the test should be repeated after 2 to 3 months. Cortisol concentration between 10-15 μg/dl is considered safe to discontinue therapy with GCS, but patients should use hydrocortisone in stressful situations. When the concentration of cortisol reaches 5-10 μg/dl we should perform a test with 1-24 ACTH and further management is dependent on the results. Cortisol concentration above 18-20 μg/dl after the 1-24 ACTH test excludes secondary adrenal insufficiency and the therapy with GCS can be terminated. In other case the chronic dose of GCS should be continued and evaluation of HPA axis should be performed after 2-3 months. Please note that patients chronically treated with GCS often need extra doses of glucocorticoids during surgery, as they do not have a pituitary reserve that allows the ejection of ACTH (and in consequence cortisol) in a situation of stress. Small surgeries under local anesthesia usually do not require such cover; during the 'moderate' operations (e.g. cholecystectomy) one of the proposed schemes are recommended: administration of a morning dose than intravenous injection of 50 mg of hydrocortisone just before surgery followed by 25 mg every 8 hours for 24 hours – after that the previous scheme can be used. During large intervention (e.g. hemicolectomia) intravenous administration of 100 mg of hydrocortisone just before the procedure is proposed, then 50-100 mg every 6-8 hours for 24 hours, then the dose should be reduced half daily until the chronic dose is reached (4). In the situation of fever or infection extra dose of hydrocortisone is necessary. We can also double or triple the chronic dose of GSC.

CONCLUSIONS

In most diseases requiring treatment with corticosteroids this therapy cannot be replaced by any other. Due to the large number of side effects this therapy requires particular attention by the attending physician and cooperation with other (diabetologist, nutritionist, ophthalmologist, orthopedist, endocrinologist). Only recommendations for the prevention and treatment of osteoporosis and the use of proton pump inhibitors in patients taking NSAIDs are based on the EBM (level of evidence I). Other recommendation are not based on evidence as equally strong but on expert opinion (level of evidence IV) (14). However, in the best interests of patients they cannot be treated as less important. Before initiating of treatment all the possible complications and ways to prevent them should be carefully discussed with the patient. If a chronic therapy is planned the patient should be obtained in a card with information about the dosage and its changes in particular situations (infections, surgery). Next step is to investigate the presence of comorbidities (and if diagnosed begin their treatment) and to evaluate the presence of risk factors of side effects occurrence. Particular attention should be paid to hypertension, diabetes, peptic ulcer, osteoporosis, cataracts, glaucoma, the presence of infections (including latent TBC), treatment with NSAIDs, lipid disorders and the heart failure. GCS should be used at the lowest effective dose and the possibility of the drug discontinuation should be regularly checked. If dose above 7.5 mg prednisone/day for over 3 months will be used patients need an adequate supplementation of vitamin D and calcium. In the case of co-administration of NSAIDs proton pump inhibitor or misoprostol should be applied. During treatment it is necessary to monitor body weight, waist circumference, blood pressure, blood glucose, lipid profile, bone mineral density, regular eye check-up and vaccinations (14). It cannot be forgotten that every form of GCS can result in inhibition of the hypothalamic-pituitary-adrenal axis and cause secondary adrenal insufficiency, which, if left undiagnosed, can be life threatening. The proper diagnose, treating comorbidities, as well as monitoring the possible side effects, can protects the patient from multiple complications of corticosteroid therapy.

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