SAFE USES OF CORTISOL

This book is the ultimate reference on cortisol by Dr. William McK. Jefferies. It can be purchased directly from the publisher.

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DESCRIPTION

The Third Edition of this popular book brings up to date the material that so many readers found helpful in the previous editions. The text has been revised and reorganized with current chapters focusing on the history of cortisol use, sources of confusion regarding cortisol therapy, the significance of normal adrenocortical function, generally accepted uses of physiological dosage, viral infections, miscellaneous clinical conditions, and future directions for research and therapy. The author provides explanation and confirmation of the rationale for the effectiveness and safety of the uses of physiological dosages of cortisol in the treatment, not only of patients with rheumatoid arthritis and other autoimmune disorders, but also of patients with chronic allergies, chronic fatigue syndrome, gonadal dysfunction, infertility, shingles, acne, hirsutism, respiratory infections, and other less

Chapter 4

GENERALLY ACCEPTED USES OF PHYSIOLOGIC DOSAGES INCLUDING THE DIAGNOSIS AND TREATMENT OF MILD ADRENOCORTICAL DEFICIENCY

ADRENAL INSUFFICIENCY

The most logical use of physiologic dosages of cortisol is in the treatment of patients with known adrenal insufficiency. Severe examples of this disorder are manifested by hyperpigmentation of the skin, weakness, fatigue, anorexia, and susceptibility to collapse and shock with exposure to stress. This clinical picture was first described by Sir Thomas Addison in 1855 and subsequently has been called Addison's disease. For many years tuberculosis of the adrenals was its most frequent cause, but with the decreased incidence of tuberculosis resulting from improved prevention and treatment, "idiopathic" adrenal insufficiency or adrenal insufficiency resulting from an autoimmune phenomenon[1] have become more common diagnoses.

These are relatively rare disorders, however, and when cortisone and adrenocorticotropic hormone (ACTH) became available for human use in 1948, these hormones first attracted worldwide attention by their dramatic beneficial effects on patients with rheumatoid arthritis. The dosages employed were large, however, and when continued they produced undesirable and sometimes catastrophic side effects, so this treatment developed a reputation for being too dangerous for general use in patients with rheumatoid arthritis and other autoimmune disorders. This reputation has apparently caused a tendency to minimize the size of replacement dosages of steroids for patients with adrenocortical deficiency that are recommended in endocrine textbooks and sometimes even a preference for synthetic steroids over the natural hormone, cortisol.

Our rationale for the treatment of patients with adrenocortical deficiency has been based on the impression that nature usually has good reasons for choosing the specific chemical substances secreted as hormones, and the studies illustrated in Figures 1 and 2 (pages 15 and 16) provide information indicating that a total dosage of 35 to 40 mg of cortisol daily

administered in divided doses at maximum intervals of 8 hours should supply adequate glucocorticoid replacement for an unstressed adrenalectomized patient. Because patients with spontaneous adrenocortical deficiency usually seek medical care before a complete lack of cortisol develops, replacement dosages for such patients usually total less than 35 mg daily, taken as 7.5, 5, or 2.5 mg four times daily before meals and at bedtime (ac and hs). Supplementary sodium-retaining effect in the form of 9 alpha-fluorohydrocortisone (9 alpha-FF [Florinef®]), 0.1 mg daily or three times weekly, is rarely needed except in totally adrenalectomized patients.

Meanwhile, experience with the use of small, safe, physiologic dosages of cortisone or cortisol in patients with ovarian dysfunction and infertility revealed that patients with associated allergies, chronic fatigue or autoimmune disorders also reported improvement in these conditions while taking the steroid, without experiencing any undesirable side effects. These results were published in a leading medical journal,[2] but the reputation of glucocorticoids had become so bad that they received little attention. Subsequently, improved methods of diagnosis have enabled the identification of mild degrees of adrenocortical deficiency, thus providing an explanation for at least some of these beneficial effects.

Hence, the diagnosis and treatment of mild adrenocortical deficiency, a condition that is rarely mentioned in medical textbooks, has become important for all practicing physicians to recognize. It may be primary, resulting from inadequate production of cortisol by the adrenals and sometimes termed "low adrenal reserve," or it may be secondary to inadequate stimulation of the adrenals by adrenocorticotropic hormone (ACTH) from the pituitary or by corticotropin releasing factor (CRF) from the hypothalamus. Another possible cause of symptoms of cortisol deficiency is a defect in the cellular receptors for cortisol causing associated normal or elevated levels of plasma cortisol. A similar type of resistance to thyroid hormone that improved with administration of physiologic dosages of cortisol is described in Chapter 10. The recognition and treatment of these disorders is discussed in the chapters and sections devoted to them, but tests to determine the integrity of the hypothalamus-pituitary-adrenal (HPA) axis and general principles of treatment will be discussed at this time, since they apply to all disorders of adrenocortical function, whether primary or secondary, complete or partial. The causes for these disorders are largely unknown, but they are often related to stress and inherited predisposing factors.

The symptoms and signs of severe adrenocortical deficiency are well described in standard medical or endocrine textbooks, but mild adrenocortical deficiency has received little attention. When patients with rheumatoid arthritis or with other conditions that were later identified as autoimmune disorders were found to improve dramatically with administration of large dosages of ACTH or glucocorticoids, the possibility that they might have adrenal deficiency was considered, but because they did not have the characteristic features or laboratory findings of hypopituitarism or of Addison's disease, this possibility was eventually apparently forgotten even though at least some had abnormal levels of excretion of steroids in their urine. Recent reports have presented evidence that patients with rheumatoid arthritis and several other autoimmune disorders have abnormal responses of their HPA axes to stress, so the possibility that the development of these disorders might be related to defective HPA responses seems likely. This would explain the beneficial effects of small, physiologic dosages of cortisol that have been observed in some of these patients and support the advisability of testing the integrity of this axis and the use of therapeutic trials with safe, physiologic dosages of cortisol in patients with these disorders. Many patients with chronic allergies, another condition that improves with large dosages of ACTH or glucocorticoids, also have been found to have evidence of mild adrenocortical deficiency. These findings will be discussed in more detail in subsequent chapters, and they emphasize the importance of testing for the possibility of deficient adrenocortical function, either primary or secondary, in patients with these conditions.

Because chronic fatigue is frequently the earliest symptom of mild adrenal insufficiency, and with the availability of a simple method of determining adrenal responsiveness to ACTH, patients coming to our clinic complaining of chronic fatigue without other evident cause such as inadequate rest, anemia, hypothyroidism, or chronic illness of any type have been given ACTH tests in addition to having determinations of baseline levels of plasma cortisol and of plasma ACTH. Initially, commercial preparations of ACTH were used for the tests, but subsequently Cortrosyn® (Organon), an active ACTH fraction consisting of the first 24 of the 39 amino acids of natural ACTH, which has a relatively rapid effect enabling the test to be run in 30 minutes and is less apt to cause sensitivity reactions, has largely replaced ACTH for the tests.

It is preferable to have these tests run in the morning after the patient has had adequate sleep and has not taken for a sufficient interval of time

any glucocorticoid or other medication that might affect adrenal function or blood levels of cortisol, but helpful information can be obtained by running them at any time of day. A more sensitive low dose Cortrosyn test has been suggested for the diagnosis of mild adrenal deficiency,[3] but because therapeutic trials are usually justified, even in patients with apparently normal tests, sometimes it is preferable to delay further testing until a therapeutic trial has been made, especially if it might avoid otherwise unnecessary hospitalization.

It is important to be aware that test results that fall within the "normal range" do not rule out the possibility that a patient might have mild adrenal deficiency since the normal range was probably obtained from a group of people who did not have classical Addison's disease or hypopituitarism or any other known physical disorder and is rather broad. Hence, it might include persons with chronic allergies or other conditions that may be associated with mild adrenocortical deficiency. Furthermore, as previously mentioned, mild adrenal deficiency can occur secondary to inadequate stimulation by ACTH from the pituitary or by CRF from the hypothalamus. These patients may have low normal baseline blood cortisol levels that respond normally to Cortrosyn, but still improve with a physiologic dosage of cortisol. Hence results of Cortrosyn tests within the normal range do not exclude the possibility that patients might benefit from cortisol therapy, so a therapeutic trial might still be justified.

Patients with secondary adrenocortical deficiency may need to have x-rays of the sella turcica and determinations of blood growth hormone (GH), thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) levels because of the possibility that they might have a tumor or other lesion in this area, but most patients with this disorder do not seem to have identifiable organic lesions. Other studies that might be helpful include a complete blood count with differential, blood sedimentation rate and tuberculin test because of the possibility of an infectious process, and x-rays of the adrenal areas and chest.

For a *Cortrosyn test,* blood is drawn for baseline plasma cortisol and ACTH levels, recording the time of day. As mentioned above, although it is preferable to perform the test in the morning when plasma cortisol levels are highest if the patient is on a normal sleep-wake schedule, adrenal responsiveness can be determined at any time of the day. The patient does not have to be fasting, although this is also preferable, but he or she should not have taken any glucocorticoid for at least 12 hours,

and preferably not for several weeks, because an abnormal Cortrosyn test due to low adrenal reserve may return to normal after a short course of cortisone acetate or cortisol or probably of any other glucocorticoid, and evidence of low reserve may not return until medication has not been taken for a month or longer. After the blood for baseline cortisol and ACTH is drawn, the patient receives an injection of 25 units of Cortrosyn into the deltoid muscle of the upper arm. Thirty minutes later a second blood specimen is drawn for plasma cortisol determination. The patient is then instructed to record any change in symptoms over the next 24 hours. A normal response is considered an increase in cortisol level to at least double the baseline value, but most normal persons will have an increase greater than twofold, and patients with secondary adrenocortical deficiency will often report a transient improvement in symptoms suggesting a mild deficiency in their production of ACTH. When plasma cortisols are determined by radioimmunoassay, as was done in our laboratory, baseline plasma cortisols are normally between 15 and 30 mcg/100 ml in the morning and between 5 and 15 mcg/100 ml in the afternoon.

This test is an example of the impossibility of having strict end points in designating normal ranges of hormone levels, especially for a dynamic hormone such as cortisol, whose levels may fluctuate from minute to minute depending upon the degree of stress in addition to diurnal variation. Hence, patients with adrenal insufficiency may have plasma cortisol levels within low normal range, especially in the afternoon and evening, and patients with hyperadrenalism may have plasma cortisol levels within upper normal range in the morning. It is therefore possible that milder degrees of low adrenal reserve may not be detected unless Cortrosyn tests are performed in the morning at a time when baseline cortisol levels are maximum. Furthermore, patients vary in their susceptibility to various degrees of stress, including the stress of having injections and blood tests, so these factors must be considered in interpreting the results of tests. Hence, a diagnosis of mild adrenocortical deficiency should depend primarily on the clinical picture and therapeutic trials are often justified even when the results of tests fall within the normal range.

It is also important to bear in mind that normal ranges for baseline levels of plasma cortisol have been determined by measurements on apparently normal subjects who had no clinical evidence of hyperadrenalism (Cushing's syndrome), hypoadrenalism (Addison's disease),

congenital adrenal hyperplasia (adrenogenital syndrome), or any other apparent illness. As is evident from subsequent discussion, adrenal dysfunction can be present in persons who do not fall into any of the above groups, hence so-called "normal" ranges are probably greater than those that would be obtained by excluding, for example, any subject with acne, hirsutism, or allergies, conditions that may have associated mild disorders of adrenocortical function. Adrenal insufficiency is also characterized by an elevated plasma ACTH level, but patients with low adrenal reserve and not under stress may have normal plasma ACTH, so the Cortrosyn test of adrenal response is a more sensitive method for diagnosing this disorder.

It should be emphasized that a "normal" baseline plasma cortisol and response to Cortrosyn does not rule out the possibility that a patient might improve with a physiologic dosage of cortisol, so for patients with disorders that suggest the possibility of mild adrenal deficiency, therapeutic trials with a small, subreplacement dosage of cortisol might still be helpful. Hence inability to obtain baseline cortisol and ACTH levels and Cortrosyn stimulation tests does not contraindicate therapeutic trials with physiologic dosages of cortisol in patients with disorders that might improve with such treatment, but the demonstration of deficiency provides a clear indication for treatment.

Cortisol, like adrenalin and insulin, is a very dynamic hormone whose production can vary from minute to minute, or even from second to second, depending upon the amount of stress being experienced. This stress may be physical, mental or emotional. In the unstressed state it is normally produced on a diurnal pattern depending upon a person's sleep-wake schedule, maximum production occurring about an hour after awakening in the morning, then slowly decreasing during the day, reaching a low point about an hour after retiring at night. Since the duration of effect on each dose of cortisol is a maximum of about 8 hours, an optimum replacement schedule would have a maximum interval of 8 hours, but for several reasons most patients prefer to take four doses daily, one before each meal and the fourth at bedtime.

Because spontaneous adrenal insufficiency results from progressive destruction of adrenal tissue, symptoms appear when the process reaches the point where remaining adrenal tissue is insufficient to maintain normal well-being. As mentioned earlier, this may require destruction of over 90 percent of the glandular tissue, but the remnant is capable of some function, so replacement dosages of cortisol in chronic adrenal

insufficiency are usually less than the 35–40 mg daily that are required for the totally adrenalectomized patient. Most patients can be maintained on between 20 and 30 mg daily in divided doses. Although some patients may feel well on less than 20 mg daily, it seems preferable to give at least this much cortisol, even to patients with low adrenal reserve, because it takes the strain off of the residual adrenal tissue and provides for more functional reserve in times of stress. Under some circumstances, it appears to provide an opportunity for residual tissue to regenerate. A few patients with low reserve have demonstrated evidence of recovery of reserve after months or even years of such treatment, but most seem to require some replacement for the remainder of their lives.

In patients with adrenal insufficiency secondary to tuberculosis, the administration of cortisol was initially employed with hesitation because of the well-known anti-inflammatory effect of large doses of glucocorticoids, causing a tendency for tubercles to break down and enable dissemination of the previously walled-off tubercle bacilli. Later, when it was found that the use of glucocorticoids in conjunction with antituberculous therapy actually enhances the effectiveness of the latter, the combined use of the two types of therapy became accepted practice. A patient with adrenal insufficiency secondary to tuberculous infection, therefore, should initially receive a suitable course of antituberculous therapy in addition to replacement cortisol in physiologic dosage.

A schedule of replacement glucocorticoid therapy in adrenal insufficiency employing two-thirds of the daily dosage before breakfast and one-third before supper has been widely recommended.[4] This is based upon the characteristic diurnal variation in plasma cortisol levels, with a peak shortly after waking in the morning and a low point shortly after retiring at night. Patients with adrenal insufficiency will do fairly well on this schedule, but when we have had them compare it with the same total dosage in four divided doses, they have invariably preferred the latter. This is not surprising in view of the evidence that the half-life of cortisol in the blood is only 100 minutes, and some metabolic effects of even large doses do not last longer than eight hours.[5] Furthermore, although plasma cortisol reaches its lowest level shortly after retiring in the evening, it begins to rise during sleep so that by the time the patient arises in the morning it is almost at its peak for the 24 hour period. Hence, instead of the twice daily dosage more closely imitating the natural diurnal pattern, it causes a peak level in the morning followed by a period of lower than normal levels in the afternoon, then a smaller

peak after supper followed by lower than normal levels during sleep and at the time of awakening in the morning. It is not surprising that a schedule employing four doses taken before meals and at bedtime produces more energy and less fatigue.

A four times daily schedule also seems to result in greater decrease in pigmentation in patients with this manifestation of adrenocortical deficiency. It is therefore possible that a schedule of only two doses daily in patients with more severe deficiency may not produce sufficient feedback to prevent excessive ACTH production, and this might contribute to the tendency for some patients on this program to develop pituitary adenomas (Nelson's syndrome).[6] Longer acting derivatives of cortisone or cortisol, such as prednisone or dexamethasone, on a once daily schedule, have therefore been suggested,[4] but because nature usually has a reason for using the hormones normally produced by the body, and because extensive experience with the normal hormones in physiologic dosages has confirmed their safety and effectiveness, it seems preferable to continue their use for treatment of patients with adrenocortical deficiency, either primary or secondary, complete or partial.

The taking of any medication every eight hours or four times daily might be considered too difficult for patients to follow, but this has not been a problem with patients with mild adrenal deficiency. Their subjective improvement has been sufficient to keep most patients taking their medication regularly. Taking cortisol three times daily, or even twice daily, will produce some improvement, but for optimum benefit the four times daily schedule has usually been more helpful and easier to follow. Patients working on night shifts or traveling to different time zones will need to adjust their schedules for taking their medication to their new mealtimes and bedtimes but when they do this promptly, they often report that this adjustment seems to diminish their tendency to develop travel fatigue or "jet lag."

Some patients report that cortisone acetate seems to less apt to cause acid indigestion than cortisol, so if it is available, it may be tried, but since cortisone must be converted or cortisol before producing therapeutic effects, it is becoming less frequently used. Also, although a lower dosage at supper time is logical and seems to diminish a tendency to insomnia that occurs in some patients, a lower dosage at bedtime is not always desirable because with normal diurnal variation the plasma cortisol level rises during sleep to reach a peak shortly after awakening in the morning.

An undesirable effect of taking any dosage of glucocorticoid at bedtime is that it tends to cause persistent renal function during sleep, resulting in the need to get up and void once or twice during the night. This is not a serious problem, and most patients prefer this inconvenience to the morning fatigue that may result from an inadequate dose of steroid at bedtime. If the patient has sufficient adrenal reserve, the bedtime dosage may be decreased or omitted entirely without difficulty. The occasional patient who complains of inability to sleep after the bedtime dosage of glucocorticoid may be found to be taking it without milk or food, and the insomnia appears to be related to a tendency to acid indigestion aggravated by the steroid. Such a complaint can usually be corrected by taking an antacid or milk or other light nourishment at the time of the bedtime dosage.

Also, insomnia after the bedtime dosage may be related to an excessive intake of coffee or other caffeine-containing beverages that patients with chronic fatigue frequently resort to in an effort to obtain more energy. Patients with untreated or inadequately treated adrenal insufficiency seem to be tolerant of larger amounts of caffeine; hence, when suitable replacement dosages of cortisol are administered and their tolerance return towards normal, they may develop symptoms of excessive caffeine intake. It is, therefore, wise to caution patients who are starting on physiologic dosages of glucocorticoid regarding this possibility.

Patients with chronic adrenocortical deficiency can usually be well maintained with cortisol, 5 or 7.5 mg orally before each meal and at bedtime. If a patient has a peptic ulcer or predisposition to this disorder, antacid should be taken with each dose. If this is done, the administration of physiologic dosages of cortisol may be continued with suitable ulcer therapy without preventing healing of the ulcer.[2,7] Printed instructions, such as those on page 21, are helpful for patients to keep in a prominent place at home, such as a bulletin board or refrigerator door, where they can be referred to easily.

Patients who have been totally adrenalectomized or who have more severe degrees of adrenocortical deficiency can usually be satisfactorily maintained on cortisol in a dosage of 10 mg at breakfast and lunch, 5 mg at supper, and 10 mg at bedtime. Supplementary sodium-retaining activity may be necessary, and 9-alpha-fluorohydrocortisone (9-alpha-FF, marketed as Florinef®), 0.05 to 0.1 mg daily or three times weekly, is sufficient in most cases. Patients with spontaneous chronic adrenal deficiency may not require supplementary sodium-retaining steroid unless