The Medical Journal of Australia

February 3, 1986
Vol. 144, No. 3

JOURNAL OF THE AUSTRALIAN MEDICAL ASSOCIATION

Registered by Australia Post. Publication No. NBG 0038.

Side-effects of corticosteroid agents*

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ABSTRACT Anti-inflammatory corticosteroid drugs are powerful therapeutic agents for a wide range of disorders. However, they do have recognized side-effects, most of which are related to the dose and the duration of therapy. Thus, short courses of even high doses of corticosteroid drugs have very few adverse effects. A detailed knowledge of the long-term side-effects of corticosteroid agents and their incidence will assist the physician in making informed judgements on the potential benefits of treatment with these drugs.

(Med J Aust 1986; 144: 139-142)

The development of corticosteroid agents represented a major advance in the treatment of numerous inflammatory diseases of varying causes; regrettably, their widespread use must be tempered by an appreciation of their side-effects, which occur commonly. As with any potent therapeutic agents, the prescribing of corticosteroid therapy should be guided by a careful consideration of its perceived benefits and potential risks. This article will review the unwanted effects of systemically administered anti-inflammatory corticosteroid agents.

In general, any of the complications of corticosteroid agents are related to the dose and the duration of therapy.[1] Thus, most of the well known problems will arise only during long-term treatment. On the other hand, remarkably few adverse effects are associated with short courses of corticosteroid drugs, even in relatively high doses.[1] In view of this clear distinction, short-term and long-term treatments will be considered separately.

Since prednisone, prednisolone and methylprednisolone are the most commonly used corticosteroid agents, most of the available clinical data on side-effects concern these drugs. Sound reasons exist for the administration of one of these agents in preference to the more potent corticosteroid drugs, such as dexamethasone and betamethasone. Prednisone, prednisolone and its methyl analogue have less mineralocorticoid activity than does cortisol, so their propensity to retain sodium and water will be less than that of cortisol. In addition, their biological half-lives are of intermediate duration (12–36 hours), allowing a once-a-day dosage regimen.[1] Furthermore, a patient's daily requirements can easily be obtained from the range of the available tablets and this facilitates the process of titrating dosage against disease to find the minimum dose that will control the disease. In contrast, although dexamethasone and betamethasone are virtually devoid of mineralocorticoid activity, they have much longer biological half-lives (36–54 hours) which are responsible for their profound suppression of the hypothalamic–pituitary–adrenal axis. Also, the available tablet strengths do not allow for the same fine titration of minimal daily dosage that is possible with prednisone and prednisolone.

*Fifth article in an occasional series on therapy with corticosteroid agents.

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Reprints will not be available from the authors. The series of articles on corticosteroid therapy will be published later in booklet form.

Short-term therapy

Doses of up to 100 mg of prednisone a day may be taken for three weeks or less without any great risk of the occurrence of adverse effects. Occasionally, patients may notice weight gain, mild fluid retention, insomnia or mood changes (euphoria, depression or, rarely, psychosis). Adverse psychiatric reactions are more likely to occur in patients with pre-existing psychological problems.[2] The metabolic actions of corticosteroid drugs may lead to hyperglycaemia, to ketoacidosis in diabetic individuals and to hypokalaemia. Superficial punctuate ulcerations of the gastric mucosa and associated haemorrhage may also occur.[1] However, these effects are reversed when the drugs are discontinued. A rare but serious complication of the intravenous administration of corticosteroid drugs in asthmatic patients is the development of anaphylactoid reactions; these may be difficult to differentiate from an exacerbation of asthma.[3]

Short courses of high-dose corticosteroid agents may produce transient abnormalities of the hypothalamic–pituitary–adrenal axis such as reduced basal plasma concentrations of cortisol, diminished adrenal gland responses to adrenocorticotrophin (ACTH) and blunted responses to insulin-induced hypoglycaemia.[4] Two days after the administration of prednisolone (25 mg twice a day for five days), the cortisol responses of 10 normal men to both the induction of hypoglycaemia and the administration of synthetic ACTH were reduced to about one-half their previous levels.[4] In a study of seven patients with chronic airflow obstruction, who were given prednisolone (20 mg twice a day for three weeks), basal plasma cortisol and plasma ACTH concentrations were suppressed at the completion of treatment but returned to normal values within four days.[5] Thus, it is evident that corticosteroid therapy can affect hypothalamic–pituitary–adrenal function within a few days of its commencement, even though the dysfunction usually disappears rapidly once treatment has been ceased.

Since these findings suggest that patients theoretically may be at risk if they encounter stress within a few days of the abrupt discontinuation of corticosteroid therapy, it may be preferable to withdraw an agent gradually over five to seven days. For some inflammatory disorders, it may be necessary to reduce the dosage of a corticosteroid drug over a longer period of time to prevent recrudescence of the disease. Whetever possible, once-a-day regimens should be prescribed, since they are more likely to result in rapid recovery of the hypothalamic–pituitary–adrenal axis when corticosteroid therapy is ceased.[6]

Awareness of the transient disturbances which may occur with short-term courses of corticosteroid agents will ensure that these potent drugs are used safely and effectively.

Long-term therapy

It is with prolonged treatment that the unwanted effects, well known both to medical practitioners and to the lay public, are likely to be encountered. In general, the lower the maintenance dose of a corticosteroid agent, the less the risk of side-effects.

In adults, it is likely that daily doses in excess of 10 mg of prednisone will eventually lead to some side-effects.[7] It is probable that even smaller daily doses (for example, 7.5 mg of prednisone), if taken in the long term, are associated with complications in the elderly.[8] Thus, it is not possible to stipulate a daily dose at which the risk of side-effects is non-existent.

Hypertension

Although the salt-retaining properties of prednisone and prednisolone are less than those of cortisol, these synthetic corticosteroid agents may still cause hypernatraemia, fluid retention and hypertension. In addition, other mechanisms, such as the enhancement of the vasoconstrictor effects of endogenous substances and increased concentrations of renin substrate[9] have been postulated as contributing to the hypertensive effects of glucocorticoid hormones. These effects are probably related to the dose since long-term low-dose therapy does not carry any appreciable risk. In a study of 129 patients with chronic airflow obstruction who were taking prednisone or prednisolone (mean daily dose ± SD, 6.7 ± 3.3 mg for 9.7 ± 5.5 years) and 66 patients with rheumatoid arthritis who were taking prednisone or prednisolone (8.4 ± 2.7 mg for 8.4 ± 2.7 years), there was a small, statistically significant increase in systolic blood pressure without a significant increase in diastolic blood pressure.[10] However, multiple regression analysis showed that an increased systolic blood pressure level correlated with age and blood pressure before therapy, which suggested that these factors were the main determinants of increases in systolic blood pressure. It was concluded that low doses of prednisone or prednisolone are not important causes of hypertension.

In the elderly, the incidence of elevated blood pressure may be higher. Fifteen of 100 patients (aged 69 years or more) who were taking prednisolone (12.5 mg a day or less) for an average of 4.8 years developed hypertension (defined as

a diastolic blood pressure of greater than 115 mmHg or a systolic blood pressure of greater than 180 mmHg), compared with three of 100 age-matched and sex-matched controls.[8] The precise mechanisms by which elderly patients develop hypertension, and other side-effects of corticosteroid therapy, such as osteoporosis, more readily than others have not been elucidated. One possible contributory factor may be the increased plasma concentration of unbound corticosteroid drug due to the lower serum albumin level in the elderly.[11]

Electrolyte disturbances

Since prednisone and prednisolone retain some mineralocorticoid activity, they increase the distal renal tubular reabsorption of sodium in exchange for potassium, hydrogen and ammonium ions which may lead to hypernatraemia and hypokalaemia in some individuals.[12] In large doses, corticosteroid drugs may cause hypokalaemic alkalosis. However, alkalosis may develop in some patients without any evidence of potassium depletion, suggesting that increases in serum bicarbonate levels may be a direct effect of corticosteroid therapy.[12]

Osteoporosis

Patients who receive prolonged therapy with greater than physiological doses of corticosteroid agents tend to develop some degree of osteoporosis. Glucocorticoid agents decrease bone formation owing to a direct inhibition of osteoblastic activity and they increase bone resorption, which leads to loss of bone — preferentially that of trabecular bone in the spine and ribs.[10] Bone resorption occurs as a consequence of secondary hyperparathyroidism, which is caused by corticosteroid-induced hypercalciuria and inhibition of enteral calcium absorption.[13] Not all patients develop osteoporosis, but postmenopausal women and elderly or immobilized patients are at high risk of this complication. Since current pharmacological approaches at best halt, rather than reverse, corticosteroid-induced osteoporosis, one should aim to detect this problem before serious complications such as compression fractures of the vertebral column have occurred. While the reliable detection of early changes requires sophisticated techniques such as photon absorptiometry, plain x-ray films of the spine may also provide useful information. Once patients at risk have been identified, prophylaxis with vitamin D and calcium supplements, or vitamin D and hydrochlorothiazide therapy if hypercalciuria is present, should be considered.[13] Since no proof yet exists that such a programme of prophylaxis is effective, therapy should be embarked upon in preference to witnessing the relentless progression of osteoporosis in susceptible individuals. Alternate-day treatment, which reduces the incidence of some of the side-effects of corticosteroid drugs, would appear to have no advantage over daily use in terms of the development of osteopenia.[14]

Cutaneous effects

Easy bruising, purpura and ecchymoses, which are quite common in older patients on long-term corticosteroid treatment, typically involve the face and neck, the extensor surfaces of the arms and the hands and the areas below the knees. Although the mechanism is not clearly understood, it is thought to be related to the diminished phagocytosis of extravasated blood and changes in connective tissue.[12] Hirsutism has been reported in approximately 10% of patients and depends on the duration of treatment.[15] Acneiform lesions that affect the face and upper trunk may occur in a minority of patients on long-term therapy.[12]

Growth impairment

In children, long-term use of corticosteroid agents inhibits linear bone growth and epiphyseal closure, reducing skeletal growth. To facilitate the early detection of growth retardation it is essential that regular measurements of height and weight are plotted on percentile charts. Fortunately, accelerated growth back to the child's height percentile usually follows the cessation of corticosteroid therapy as the administration of corticosteroid drugs also inhibits epiphyseal closure. However, this growth catch-up may not occur after long-term use of high-dose corticosteroid therapy, leaving the child permanently stunted. If single doses of prednisone or prednisolone, which have a relatively short biological half-life, are taken in the morning, this regimen is least likely to affect the maximal secretion of growth hormone in the early hours of the morning.[16]

Glucose intolerance

Glucocorticoid agents impair carbohydrate metabolism by increasing hepatic gluconeogenesis and by decreasing the utilization of glucose by various tissues.[17] Fasting blood glucose concentrations are within normal ranges in most patients who are taking corticosteroid drugs but usually some reduction in the ability to respond to a glucose load is present, with a pattern in a glucose tolerance test that is indicative of insulin resistance. This impairment of glucose tolerance is greatest when corticosteroid treatment begins and the response improves considerably during long-term therapy.[17] The development of overt diabetes is unusual except in individuals with pre-existing abnormal results of a glucose tolerance test. Corticosteroid-induced diabetes is usually mild and can be managed along conventional lines by dietary measures, the administration of oral hypoglycaemic agents and the judicious use of insulin, if necessary. It is frequently reversible on cessation of corticosteroid therapy, although the reversal of the diabetic state may take several months.[18]

Aseptic necrosis of the femoral head

The use of corticosteroid agents is one of many factors which may predispose patients to the development of aseptic necrosis of the femoral head. Among the numerous theories that are advanced as a basis for this unusual complication of corticosteroid therapy, the currently favoured explanation is that fat microemboli occlude subchrondral end-arterioles and lead to bone-cell death.[19] The typical radiological appearance is that of a lucent area between the collapsed bone and the overlying cartilage. During a 10-year period, six patients (who represented approximately 1% of all patients in one study who were receiving corticosteroid drugs for pulmonary diseases) developed aseptic necrosis of the femoral head.[19] A typical patient had been receiving greater than physiological doses of corticosteroid drugs for more than three months, and more often for years. Recipients of renal transplants have an increased incidence of aseptic necrosis of bone, presumably as a long-term sequela of corticosteroid treatment. In a recent Australian survey, six of 52 renal transplant recipients who survived for more than 10 years developed aseptic necrosis of bone which involved other joints in addition to the hip.[20] A review of the literature suggests that high doses of corticosteroid agents in the first month after transplantation were associated with an increased prevalence of aseptic necrosis.[20] Patients with other disorders such as hyperuricaemia, alcoholism, hyperlipidaemia or polycythaemia, who also take corticosteroid drugs, may be at greater risk of developing aseptic necrosis than those without these disorders.[19]

Peptic ulceration

Support for the theory that corticosteroid drugs lead to the development of peptic ulceration has waxed and waned over the years. The widely accepted clinical notion that there was an association was dispelled in 1976 by Conn and Blitzer, when they reviewed 42 randomized controlled trials and found that there was no significant relationship between corticosteroid therapy and peptic ulceration unless the drug was taken for more than 30 days or in large doses.[21] The burning question has been rekindled recently by Messer et al., who reviewed 71 controlled trials in which patients were randomized to receive corticosteroid therapy or non-steroidal therapy for at least four days.[22] The incidence of peptic ulcers was 1.8% in the corticosteroid-treated group compared with 0.8% in control patients.[22] Thus, current evidence suggests a small but significant association between corticosteroid therapy and peptic ulceration. However, in view of this low incidence it is illogical to institute prophylactic therapy — with antacids or with histamine H_2-receptor antagonists — in all patients who are receiving corticosteroid drugs. If a patient is sufficiently unlucky as to develop an ulcer during corticosteroid treatment, he or she should be managed with conventional therapy. In the absence of convincing evidence that "steroid ulcers" are resistant to therapy, there are no compelling reasons to discontinue corticosteroid treatment unless life-threatening complications of the ulcer have supervened.

Symptoms of gastrointestinal intolerance such as dyspepsia and nausea may occur, in which case antacid therapy is useful. It is important to choose agents such as aluminium hydroxide, magnesium trisilicate and magnesium hydroxide which do not appear to affect the absorption of prednisolone.[23]

Pancreatitis

Acute pancreatitis is a rare but serious compli-

cation of corticosteroid therapy, the onset of which is not related to the dose, duration or type of corticosteroid drug that is used. In a review of 112 patients with drug-induced pancreatitis, corticosteroid agents were the most common offenders, being implicated in 51 cases.[24]

Myopathy

Corticosteroid myopathy presents as weakness and wasting in the proximal limb and girdle musculature. Although the dosage of corticosteroid agent has frequently been high and sustained over many months, there does not appear to be good correlation between the total dose, the duration of treatment, the patient's age or sex and the severity of the myopathy. Since the incidence is higher with the fluorinated corticosteroid drugs such as triamcinolone,[25] such agents should not be used in the long term. Patients usually recover within a few weeks of the cessation of the corticosteroid therapy.

Ocular effects

Although an increase in intraocular pressure is more common with the topical administration of corticosteroid preparations, it can also occur with systemic corticosteroid agents but only after months or years of treatment.[26] The risk, which appears to be genetically determined, is greatest in individuals with myopia or diabetes. The proposed mechanism involves increased production of aqueous humour and swelling of the collagen in the trabecular meshwork in the drainage angle of the anterior chamber, leading to an increased resistance to aqueous outflow.[26] Increases in intraocular pressure are usually reversible if corticosteroid therapy is ceased.

Posterior subcapsular cataracts have been documented in patients who are receiving long-term corticosteroid therapy. The usual minimum time required for the onset of cataracts is one year of treatment with at least 10 mg of prednisone a day.[26] There is some evidence to suggest that this complication is more common in children and in patients with rheumatoid arthritis. In view of these ocular complications, it is prudent for all patients who are being treated with long-term corticosteroid therapy to undergo regular ophthalmological examinations.

Raised intracranial pressure

A small proportion of patients, usually children or young women, develop papilloedema and signs of raised intracranial pressure when their corticosteroid dosage is being reduced. This syndrome has been designated either as "benign intracranial hypertension" or as "pseudotumour cerebri". The usual treatment is to increase the corticosteroid dose temporarily to relieve the symptoms and then to attempt a more gradual withdrawal.[27]

Infections

Corticosteroid drugs impair cell-mediated immunity by decreasing the number of circulating lymphocytes and monocytes, by blocking the sensitization of lymphocytes to antigen and by inhibiting the responsiveness of monocytes to the chemotactic factors that are elaborated by lymphocytes.[28] Antibody formation and turnover are not affected significantly by corticosteroid drugs. In spite of the recognized effects of corticosteroid agents and experimental studies that have demonstrated an increased risk of infection with numerous agents in corticosteroid-treated animals, it has been more difficult to document the degree of increased susceptibility in clinical studies.[28] Nevertheless, it is generally agreed that patients who are taking long-term corticosteroid drugs are predisposed to bacterial (mycobacteria, staphylococcus, listeria), viral (herpes, cytomegalovirus), fungal (candida, cryptococcus) and parasitic (toxoplasma, pneumocystis) infections.[28] In the case of tuberculosis, preventive measures should be taken. In patients with positive results of Mantoux skin tests to intermediate strength tuberculin (5 TU), but normal chest radiograph films, modest doses of corticosteroid agents (10–15 mg of prednisolone a day) do not appear to carry an increased risk of tuberculosis.[29] Therefore, such individuals do not benefit from prophylactic therapy with isoniazid. However, if patients have radiological features that are consistent with inactive pulmonary tuberculosis, they warrant treatment with two drugs such as isoniazid and ethambutol or rifampicin.[30] The physician should be alert to the possibility of both common and unusual infections in patients who are receiving corticosteroid agents, particularly if these are combined with other immunosuppressant drugs.

Adrenal suppression

In treating inflammatory diseases with corticosteroid agents, it is common to begin with high doses to obtain some measure of control. Therefore, the dose is reduced, according to indices of disease activity, until a satisfactory maintenance dose is reached. Ultimately it may be possible to cease the administration of corticosteroid therapy altogether, in which case certain guidelines should be observed. It is generally accepted that derangement of adrenal function occurs after a few days of high-dose corticosteroid therapy. In contrast to the rapid recovery after treatment that is limited to two to three weeks, long-term daily therapy with corticosteroid drugs may suppress hypothalamic–pituitary–adrenal function for up to nine months after the cessation of treatment.[31] Therefore, it is important to keep the daily maintenance dose as low as possible or to use alternate-day therapy,[32] because both of these strategies — particularly the latter — minimize the chances of blunting the stress response of the hypothalamic–pituitary–adrenal axis.

Since the recovery of the adrenal cortex lags behind that of the pituitary, one can usually assume that full integrity has been restored when the adrenal gland can mount an adequate secretory response of cortisol to synthetic ACTH.[31] Therefore, the following approach for the withdrawal of corticosteroid therapy is suggested.[31] First, wean the patient to "physiological" doses of a corticosteroid agent (such as 20 mg of hydrocortisone or 5 mg of prednisone) to be taken for one to two months; then halve the dose for the next one to two months; and then determine the morning plasma cortisol concentration, omitting the morning dose of corticosteroid agent on the day of plasma sampling. A morning cortisol concentration of greater than 0.28 µmol/L (10 µg/100mL) indicates that basal hypothalamic–pituitary–adrenal function has recovered. Adrenal reserve is then assessed by a tetracosactrin (ACTH) stimulation test. If the morning plasma cortisol level is less than 0.28 µmol/L (10 µg/100 mL), then corticosteroid treatment should be continued for another one to two months before another morning plasma sample is collected.

In most circumstances, a justifiable alternative to these diagnostic tests of adrenal function is to administer supplemental corticosteroid therapy during physiological stress (such as accidents, surgical procedures, febrile illnesses, repeated vomiting or dehydration) for a year after the medication is discontinued. Depending upon the clinical urgency, therapy can be given parenterally or by mouth in a daily dose that is equivalent to 200–400 mg of hydrocortisone.[31]

A syndrome called "steroid pseudorheumatism", which is distinct from simple adrenal insufficiency, has been recognized in patients who take their corticosteroid therapy erratically or whose dosage is reduced abruptly. It is characterized by fever, anorexia, malaise, myalgia and arthralgia.[1] These symptoms resolve after increasing the dose of corticosteroid agent; a more gradual reduction of corticosteroid drugs prevents their recurrence.

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(Received May 9; accepted July 11, 1985)

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