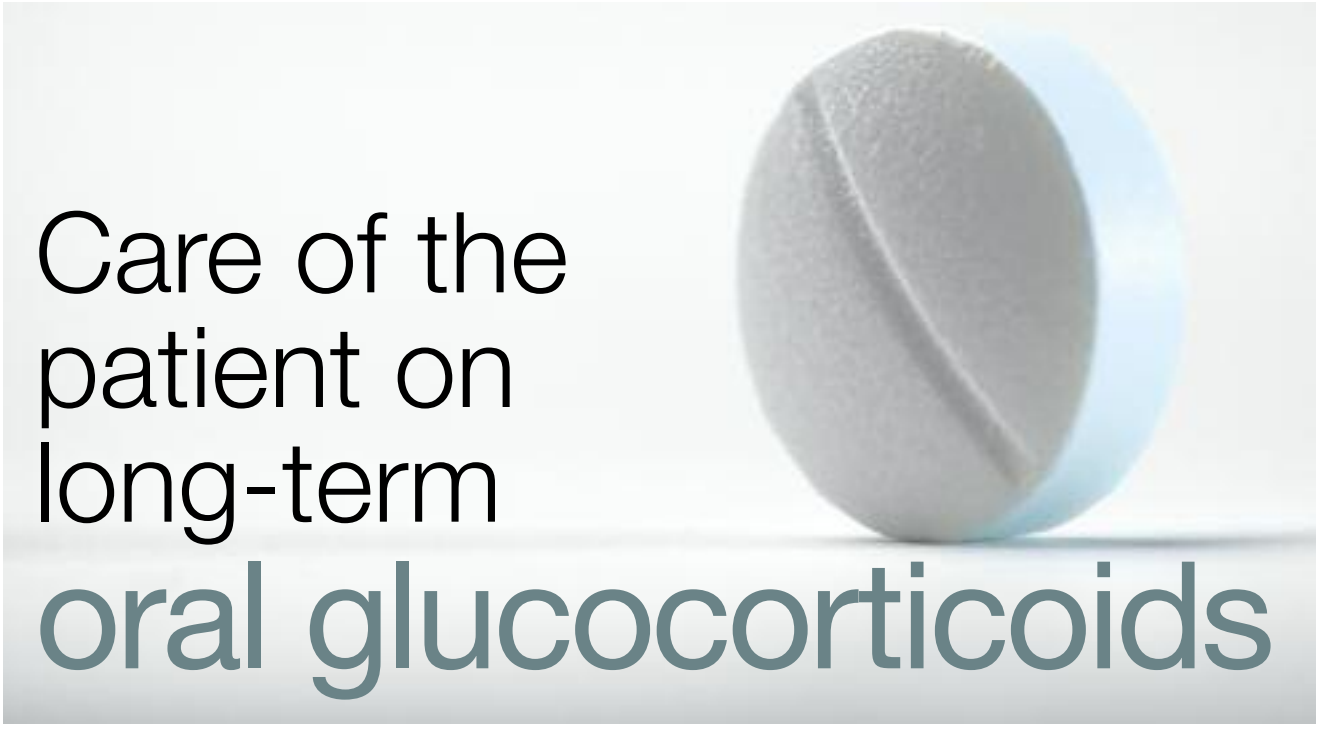

Care of the patient on long-term oral glucocorticoids

SHANNON McCARTHY MB BS(Hons), BMedSci, GradCertTertTeach

MARK KOTOWICZ MB BS, FRACP

Prolonged oral glucocorticoid therapy is particularly prevalent in older adults, and these patients are vulnerable to the varied complications of this treatment. Care must be taken to use the lowest possible dose and the shortest duration of therapy.

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Dr McCarthy is a medical registrar at Geelong Hospital, Geelong. Dr Kotowicz is Acting Director of the Department of Endocrinology and Diabetes at Barwon Health, Geelong, Vic.

Use of oral glucocorticoid therapy is widespread in our community for the treatment of inflammatory and autoimmune conditions, but is complicated by the significant side effects of these drugs. Although the most common indication for oral glucocorticoid therapy is respiratory disease, especially chronic obstructive pulmonary disease (COPD), rheumatological diseases are the leading indication for prolonged therapy (see the box on page 60).

Older adults and the elderly have the highest usage of oral glucocorticoids and are vulnerable to myriad complications. Most complications are directly related to the dose and duration of therapy.

This article provides a structured approach to the prevention and management of the common and serious complications of oral glucocorticoid therapy.

CARDIOVASCULAR RISK

Many of the conditions requiring treatment with glucocorticoids are themselves risk factors for increased rates of cardiovascular events. However, glucocorticoid therapy compounds the risk of myocardial infarction, stroke, peripheral arterial disease and congestive cardiac failure.[1] Glucocorticoids increase insulin resistance and stimulate a hyperinsulinaemic state. They also increase rates of synthesis of very low density lipoproteins.

Patients on chronic treatment require assessment of cardiovascular risk factors at regular intervals. Although evidence is lacking that interventions to modify cardiovascular risk in glucocorticoid-treated patients do reduce risk, it would seem prudent to address these risk factors.

OSTEOPOROSIS

Glucocorticoid therapy is the most common cause of secondary osteoporosis (glucocorticoid-induced osteoporosis), but most patients on long-term glucocorticoid therapy are neither screened for osteoporosis, nor treated.[2] Both current and prior glucocorticoid use increase the risk of osteoporotic fracture beyond the attributable risk of bone mineral density differences alone. Even in patients with normal bone density, use of glucocorticoids

CONDITIONS THAT MAY REQUIRE LONG–TERM GLUCOCORTICOID THERAPY

Rheumatological
- Rheumatoid arthritis
- Large- and small-vessel vasculitis
- Systemic lupus erythematosus
- Polymyalgia rheumatica
- Arthritis associated with inflammatory bowel disease
- Polymyositis and dermatomyositis
- Ankylosing spondylitis

Respiratory
- COPD
- Asthma
- Interstitial lung disease

Renal
- Nephrotic syndrome
- Glomerulonephritis

Haematological
- Immune thrombocytopenia
- Acquired haemolytic anaemia

Neurological
- Duchenne muscular dystrophy
- Myasthenia gravis
- Chronic demyelinating peripheral neuropathy

Oncological
- Cerebral tumours
- Chemotherapy

Post-transplantation

increases the risk of vertebral fracture. However, discontinuation of glucocorticoid therapy results in a rapid reduction in fracture risk.[3]

Glucocorticoids inhibit bone formation, decrease gastrointestinal absorption of calcium, increase renal calcium excretion and may stimulate bone resorption. In addition, they suppress the pituitary gonadal axis and pituitary adrenal axis, reducing sex steroid concentrations, particularly in postmenopausal women.

Treatment with calcium and vitamin D can prevent bone loss.[4] Unless contraindicated, prophylactic bisphosphonate therapy should be considered in patients receiving prednisolone 7.5 mg or more per day (or equivalent) for more than three months. Antiresorptive therapy is indicated if patients on long-term glucocorticoid therapy suffer a fragility fracture.

Recent data suggest that use of the bone formation-stimulating agent, teriparatide, may be superior to bisphosphonate therapy in glucocorticoid-induced osteoporosis.[5,6] Assessment of additional osteoporotic risk factors, and nonpharmacological measures such as exercise and smoking cessation, are also beneficial. Elderly patients should receive a comprehensive falls prevention strategy, as 20% of patients with a fractured neck of femur will die within one year and 20% will require permanent residential care.[7]

Glucocorticoids are also the leading cause of avascular necrosis (AVN) of the femoral head, although the overall incidence of this complication is low.[8] Patients on more than 20 mg/day of prednisolone (or equivalent) or those with Cushing's syndrome are at the highest risk. AVN of the femoral head may be asymptomatic, or may manifest as groin pain, either on walking or at rest, and occasionally at night. A high index of suspicion is needed to diagnose this disorder in the early treatable stages, when x-rays are usually normal. MRI is the most sensitive test.

AVN of the femoral head may represent another indication for bisphosphonate therapy, with data indicating that these agents can preserve bone microarchitecture, permitting repopulation of the bony structure with bone cells.[9] Compared with historical controls, patients with AVN who were treated for three years with oral alendronate had better clinical function, lower rates of progression and lower rates of total hip replacement after a mean follow up of four years.[10]

GLUCOSE METABOLISM

Glucocorticoids lead to deranged glucose metabolism by stimulating hepatic gluconeogenesis and inhibition of adipose tissue glucose uptake. Although development of diabetes with glucocorticoid therapy in a patient with previously normal glucose metabolism is uncommon, patients with diabetes are very sensitive to the effects of glucocorticoids. The longer the duration of the patient's diabetes, the more exaggerated the hyperglycaemia when they take glucocorticoids.[11]

There are no trials and little evidence regarding the treatment of glucocorticoid-induced hyperglycaemia. Because glucocorticoids particularly affect postprandial glucose levels, rather than fasting levels, commencing acarbose, repaglinide or sulfonylureas is reasonable for patients with mild hyperglycaemia. For those with moderate to severe hyperglycaemia, insulin is required. Prandial insulin (short duration; rapid-onset or very rapid-onset) may be sufficient to maintain glycaemic control without additional basal insulin.

DRUG INTERACTIONS

Cytochrome P450 2C19-related

Prednisolone induces cytochrome P450 2C19, which is involved in the metabolism of several important groups of drugs – including many proton pump inhibitors, antiepileptics and antidepressants. Prednisolone may, therefore, cause reduced efficacy of:

- lansoprazole, omeprazole, pantoprazole, rabeprazole
- diazepam, phenobarbitone, amitriptyline, citalopram
- cyclophosphamide
- indomethacin
- progesterone
- propranolol.

Cytochrome P450 3A-related

Prednisolone and other glucocorticoids are metabolised by cytochrome P450 enzymes of the CYP3A family (CYP3A4, CYP3A5, CYP3A7 and CYP3A43). Inhibition of these enzymes by diltiazem, protease inhibitors and itraconazole can exacerbate dose-related side effects of these glucocorticoids. Conversely, inducers of these CYP enzymes, such as rifampicin, can precipitate an adrenal crisis.

GASTROINTESTINAL RISKS

Although glucocorticoids are traditionally believed to be a risk factor for gastrointestinal ulceration, there is some emerging evidence that glucocorticoids may be gastroprotective. However, patients taking glucocorticoids who have gastrointestinal haemorrhages have higher mortality. The risk of gastrointestinal bleeding with the concomitant use of NSAIDs and glucocorticoids is up to 20 times that of age- and sex-matched controls.[12] The risk of gastrointestinal ulceration and bleeding with glucocorticoids alone is lower than with NSAIDs alone, and prophylaxis with a proton pump inhibitor is not recommended unless the patient is also taking regular aspirin.

Patients taking glucocorticoids long-term also have higher rates of non-alcoholic fatty liver disease.[13]

RENAL COMPLICATIONS

Glucocorticoid therapy causes hypertension and fluid retention. This is particularly pertinent in patients with pre-existing hypertension and/or cardiovascular risk factors, and in patients with cardiac failure. Kaliuresis also occurs, but clinically significant hypokalaemia is rare.

IMMUNITY

Immunosuppression occurs at pharmacological doses of glucocorticoids. Various complex mechanisms contribute to immunosuppression, such as the decreased production of cytokines, impaired phagocyte adherence, eosinophil sequestration in tissues and decreased circulating T-cells.

Reactivation of latent tuberculosis and herpes zoster can occur, but routine screening for latent tuberculosis prior to glucocorticoid therapy is not advised. Influenza virus vaccine and pneumococcal vaccine remain immunogenic in patients taking glucocorticoids; these are both subunit vaccines. Patients taking doses greater than 20 mg/day prednisolone (or equivalent) should not receive live attenuated vaccines – that is, measles, mumps and rubella vaccine, varicella zoster vaccine, yellow fever vaccine and the oral polio vaccine (only used nowadays in regions with high incidences of polio).[14]

As with other patients who are heavily immunosuppressed (such as those with HIV infection and those undergoing chemotherapy), patients on long-term oral glucocorticoid treatment are at increased risk of malignancy, particularly nonmelanoma skin cancer.[15,16]

USE IN PREGNANCY

Women of childbearing age taking glucocorticoids for prolonged periods should receive counselling regarding the issues of contraception and pregnancy. High-dose oral prednisolone (more than 1 to 2 mg/kg/day) in the first trimester is associated with increased rates of cleft lip and palate in the fetus. Other adverse effects in the infant, while rare, include masculinisation of female infants, intrauterine growth restriction, neonatal cataracts and adrenal suppression.

Women planning to conceive should have an oral glucose tolerance test prior to pregnancy and this should be repeated after conception. They should also take calcium supplementation (to prevent osteopenia) and have regular blood pressure monitoring.

The use of dexamethasone is not recommended during pregnancy because, unlike hydrocortisone, prednisone, prednisolone and methylprednisolone, this drug crosses the placenta.[17]

Glucocorticoid requirements in women with adrenal suppression may or may not increase during pregnancy, and dosing should be tailored to the individual.[18] If the hypothalamic–pituitary–adrenal (HPA) axis is suppressed, labouring women require 150 mg/day intravenous hydrocortisone in divided doses.[19]

INTERCURRENT ILLNESS AND PERIOPERATIVE MANAGEMENT

Treatment with supraphysiological doses of glucocorticoids may lead to suppression of the HPA axis. Evening dosing, use of dexamethasone and doses equivalent to more than 5 mg/day prednisolone convey the highest risk of iatrogenic adrenal insufficiency, but suppression can occur even with low doses or short courses, and patients should be cautioned. A Medic Alert bracelet may be helpful.

To evaluate for adrenal insufficiency, the patient's endogenous serum cortisol level may be measured in the early morning, prior to the daily corticosteroid dose. If the cortisol level is below 83 nmol/L, the patient has adrenal

TIPS FOR GPS

Long-term oral glucocorticoid therapy is associated with significant side effects. Care must be taken to use the lowest possible dose and the shortest duration of therapy. Advice should be obtained regarding the use of steroid-sparing agents if complications occur. Particular points are listed below.

- Regular assessment of cardiovascular risk factors – blood pressure, cholesterol, glycaemic control and smoking – is required. If a patient is taking regular aspirin, proton pump inhibitor prophylaxis against gastric ulceration is recommended.
- All patients should receive calcium with or without vitamin D as bone protection. Bisphosphonate therapy should be considered in patients taking more than 7.5 mg/day prednisolone (or equivalent) for three months.
- Patients should undergo yearly fundoscopy to screen for glaucoma and cataracts.
- Patients are at increasing risk of nonmelanoma skin cancer and should follow the regular guidelines regarding sun protection.
- Neuropsychiatric side effects may occur.
- Patients are immunosuppressed and therefore; diseases such as tuberculosis and herpes zoster may reactivate. Patients taking more than 20 mg/day prednisolone (or equivalent) should not receive live vaccines.
- Patients should be educated regarding the dangers of sudden withdrawal of glucocorticoid therapy and about the management of intercurrent illness and preparation for travel.
- Expert advice in pregnant women.

suppression; if it is above 550 nmol/L, adrenal function is intact. For patients with intermediate values, a short adrenocorticotropic hormone (ACTH) test (the Synacthen test) may be performed to diagnose adrenal insufficiency.[20,21] If the patient fails to respond to exogenous ACTH (in the form of the synthetic ACTH tetracosactrin), there is adrenal dysfunction. If the patient responds to tetracosactrin but subsequently fails to respond to exogenous corticotropin-releasing hormone (CRH), there is central HPA axis dysfunction.

When the HPA axis is suppressed, patients experiencing minor illness or undergoing minor surgery should double their usual glucocorticoid dose until recovery. Severe illness or major surgery requires 75 to 200 mg/day of intravenous hydrocortisone in divided doses.[22,23]

OTHER ADVERSE EFFECTS

Prolonged therapy with oral glucocorticoids has a range of other adverse effects.

Dermatological effects

Prolonged oral therapy with glucocorticoids can be associated with skin thinning, purpura, acne, hypertrichosis and alopecia.

Ophthalmological effects

Patients taking glucocorticoids are four times more likely to develop cataracts, particularly bilateral posterior subcapsular cataracts.[24-27] This can contribute to visual deterioration and falls risk in the elderly. Patients also experience higher rates of glaucoma. Visual field testing using confrontation is not sensitive for detecting glaucoma, and regular fundoscopy by an experienced operator is recommended.

Myopathy

Corticosteroid myopathy rarely occurs at low doses.[28] It usually manifests as leg weakness greater than arm weakness, and patients may complain of difficulty rising from a chair. Examination reveals proximal muscle weakness without pain or tenderness.

This complication can occur at any time during treatment. There are no proven preventative agents.

Neuropsychiatric effects

Insomnia and euphoria are common in patients on prolonged oral glucocorticoid therapy, and depression, memory impairment, difficulty with concentration, akathisia and pseudotumour cerebri may occur. Glucocorticoid-induced psychosis is uncommon, and associated only with high doses.

Behavioural changes and dementia can also occur. The phenomenon of steroid dementia may take up to a year to resolve after cessation of treatment.[29]

DRUG INTERACTIONS

Glucocorticoids are metabolised in the liver and therefore may have effects on and be affected by other drugs that also have a hepatic metabolism, as discussed in the box on page 62.

As mentioned earlier, there is an increased risk of gastric ulceration with the concomitant use of glucocorticoids and NSAIDs.

CONCLUSION

Prolonged oral glucocorticoid therapy is associated with significant side effects and care should be taken that the lowest possible dose and the shortest duration of therapy are used. If complications occur, advice should be sought regarding the use of steroid-sparing agents instead.

Some tips for GPs who are caring for patients taking oral glucocorticoids for prolonged periods are provided in the box on this page. MT

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A list of references is available on request to the editorial office.

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SHANNON McCARTHY MB BS(Hons), BMedSci, GradCertTertTeach **MARK KOTOWICZ** MB BS, FRACP

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