

PERSPECTIVE

Systemic corticosteroid therapy—side effects and their management

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Corticosteroids have been used in ophthalmology for almost 50 years. Hench, in 1949,¹ was the first to report on the beneficial effects of ACTH and cortisone. His work was with rheumatoid arthritis and since 1929 he had noticed that rheumatoid arthritis improved in pregnancy and jaundice. He conjectured that an adrenal hormone might be the common agent causing this improvement. In 1948 he managed to acquire the necessary hormones and found clinical improvement in the rheumatoid arthritis and a reduction of the erythrocyte sedimentation rate on treatment with the hormones and relapse when they were stopped. His article concluded that theoretically these agents may be of benefit in other conditions which can be relieved by pregnancy and jaundice. Very soon after this steroids were used, both systemically and topically, to treat inflammation of the eye.

Within ophthalmology there are many indications for the use of corticosteroids. The decision to institute steroid therapy always requires careful consideration of the relative risks and benefits in each patient. In uveitis, for example, the use of corticosteroids may often be in high doses for long periods of time.² Before starting systemic steroids the ophthalmologist must consider:

- the reasons for initiating steroid treatment
- the expected visual outcome
- how the patient will be assessed
- the impact on any associated systemic disease.

If a beneficial effect is not seen within the expected time scale the corticosteroids should be reduced and stopped.

This review considers some of the non-ocular problems and dilemmas encountered when systemic steroids are used, with practical suggestions to minimise their side effects. In particular, the new recommendations by the Department of Health on the indications for intervention following exposure to chickenpox or shingles will be discussed and recent publications on the management of corticosteroid osteoporosis will be reviewed.

Dermatological

- Thin, fragile skin is a feature of corticosteroid use and the photograph in the Minerva section of the *BMJ* from 19 October 1996³ vividly illustrates this; it shows a flap of chest skin avulsed as the cardiac monitor is removed from a patient who had been on long term steroids
- Mild hirsutism
- Bruising
- Facial erythema
- Increased sweating
- Impaired wound healing, patients should be advised to take particular care to avoid injury
- Striae
- Acne

Haematological

Polycythaemia is a feature of Cushing's syndrome but does not appear to be a feature of corticosteroid therapy.

The total white blood count is increased in patients on corticosteroids. The various classes of white blood cells are affected in the following ways:

- Polymorphonuclear leucocytes increased
- Lymphocytes decreased; T cells are reduced to a greater extent than B cells although immunoglobulin synthesis is also decreased⁴
- Monocytes decreased
- Eosinophils decreased

Corticosteroid use promotes blood coagulation and alters the patient's response to anticoagulants and hence frequent checks on the extent of anticoagulation are necessary especially if the steroid dose is varying.

Fluid and electrolyte balance

Corticosteroid use is associated with sodium and water retention; this can be reduced by recommending a low salt diet.

Potassium loss occurs and a hypokalaemic alkalosis may develop. A diet rich in potassium (most fruits, vegetables, especially broccoli and carrots, fish, and poultry) is usually sufficient to make good this loss but occasionally potassium supplements are required.

The blood pressure should be checked at each outpatient visit and antihypertensive treatment may be necessary. If a thiazide diuretic is chosen as the antihypertensive agent the serum potassium should be carefully monitored. Thiazides also have a beneficial effect on osteoporosis by reducing calcium loss in the urine.

Corticosteroids should be used with extreme caution in patients with limited cardiac reserve as cardiac failure can develop.

Endocrine and metabolic

The patient should be warned about the development of a cushingoid habitus (moon facies, buffalo hump, central obesity). The appearance of these features is extremely variable; some patients seem able to tolerate prednisolone 30 mg/day while others become cushingoid on less than one half of this. The reason for this change in appearance is not clearly understood but one hypothesis is that truncal and peripheral adipocytes vary in sensitivity to the glucocorticoid facilitated lipolytic effect—that is, the peripheral adipocytes are more sensitive to this effect than the central adipocytes.

Weight gain, which can be enormous in some patients, can be minimised by the early use of a calorie controlled diet.

Reduced carbohydrate tolerance accompanies corticosteroid use. Glucocorticoids increase gluconeogenesis and

blood glucose increases by 10–20%. Glucose tolerance and sensitivity to insulin is decreased but if pancreatic function is normal no diabetes should develop. However, hyperglycaemia and glycosuria should be checked for as one fifth of patients may develop “steroid diabetes”. The initial management is dietary modification with the addition of hypoglycaemic agents if necessary. This particular form of diabetes has a low sensitivity to insulin but does not tend to ketosis. When the steroids are stopped the diabetes normally disappears. The use of corticosteroids is not contraindicated in a known diabetic but patients should be aware that their blood glucose control is likely to deteriorate and that they will need increased treatment.

Suppression of the hypophyseal pituitary adrenal axis occurs with surprisingly little corticosteroid. A 1 week course has no significant effect but 2 weeks of supraphysiological doses (that is, greater than prednisolone 7.5 mg/day) within 1 year causes a degree of impairment which could become manifest in acute stress.⁵ Patients must be aware of the dangers of stopping steroid treatment suddenly and of the need to inform any medical practitioner of their past or present steroid usage. Patients with suppressed adrenals require the reintroduction of corticosteroids at the time of a surgical procedure, trauma, or intercurrent illness and those on long term steroids may need an increased dose.

Sex hormones, both testosterone and oestrogen, are reduced by the administration of corticosteroids.^{6,7} Oestrogen and testosterone play a part in the regulation of bone metabolism (hypogonadism in males and females is associated with osteoporosis) and are factors in the development of corticosteroid induced osteoporosis. Hormone replacement therapy has been shown to have a beneficial effect on osteoporosis in post-menopausal and amenorrhoeic women on corticosteroids⁸ (see below). The supplementation of testosterone in men on corticosteroids is not common practice but may provide an additional means of preventing osteoporosis in this group.

Menstrual irregularities and amenorrhoea can also occur.

Serum lipids, both triglycerides and cholesterol, may be increased during corticosteroid therapy.

Patients on corticosteroids have a negative nitrogen and calcium balance.

Pregnancy and lactation

The teratogenic effect of cleft lip and palate that has been seen in animal studies has not been confirmed in the children of corticosteroid treated women. There appears to be no teratogenic contraindication to using corticosteroids in pregnancy.

Intrauterine growth retardation has been reported.

Corticosteroid use in late pregnancy may cause adrenal suppression in the baby.

Mothers with pre-eclampsia and fluid retention require particularly close monitoring if placed on corticosteroids.

Corticosteroids are excreted in small amounts into the breast milk and the infant is therefore at risk of adrenal suppression.

Growth suppression

Corticosteroids inhibit linear growth. The mechanism is unknown but may involve a combination of reduced growth hormone production and a direct inhibitory effect on bone and connective tissue. There is some evidence that the administration of growth hormone can reverse these changes. Unlike the other side effects of steroids growth suppression is helped by alternate day treatment. Doses below prednisolone 10–15 mg on alternate days do not

slow growth velocity significantly.⁹ However, in our experience this mode of medication does not seem effective in the control of inflammatory eye disease.

Musculoskeletal

OSTEOPOROSIS

Within a few years of the introduction of steroids an increased tendency to osteoporosis and fracture were noticed. Many studies on the association of osteoporosis and steroid use have been performed on patients with rheumatoid arthritis where clearly additional factors for osteoporosis exist. The greatest rate of bone loss occurs in the first 6 months and is thought to continue at a lower rate for as long as steroids are used. Studies show a correlation between cumulative steroid dose and bone density; therefore, treating with the lowest possible steroid dose is important. There is no benefit in using alternate day therapy. Bone loss is greatest in trabecular (cancellous) bone, which is more metabolically active but also occurs in cortical bone. The mechanism of steroid induced bone loss is multifactorial¹⁰:

- Reduced osteoblast activity resulting in reduced bone formation
- Increased bone resorption due to increased osteoclast activity
- Reduced intestinal absorption of calcium and phosphate
- Reduced renal reabsorption of calcium
- Secondary hyperparathyroidism
- Reduced sex hormones.

The incidence of fracture in steroid treated individuals is between 10% and 20% and those at particular risk are:

- Under 15 years and over 50 years
- Post-menopausal or amenorrhoeic women
- Slim build
- Limited mobility.

Medications that increase the risk of osteoporosis include thyroxine and heparin.

Steroid bone loss appears to be reversible, as when Cushing's syndrome is cured the bone mass returns to normal. There are no longitudinal studies specifically addressing the question of whether steroid induced bone loss reverses when steroids are stopped, but evidence exists that significant increases in bone mineral density occur with specific therapy for steroid induced osteoporosis.¹¹

Patients who are about to begin or are receiving long term steroid treatment should have their bone mineral density (BMD) measured using dual energy x ray absorptiometry (DEXA). This is usually performed on the lumbar spine and femoral neck. The result is expressed as a standard deviation from controls of the same race and sex. Thus, a score of -1 SD indicates the patient has a low BMD and a score of -2.5 SD indicates osteoporosis. A DEXA scan should be performed at the beginning of steroid treatment and annually thereafter.

The following measures should be considered for a patient who is about to embark on steroid therapy or who is already on treatment:

- Undertake weight bearing exercise (such as brisk walking)
- Stop smoking
- Avoid excess alcohol intake
- Hormone replacement therapy may be considered for post-menopausal and amenorrhoeic women. Side effects,¹² in particular the recent reports of an increased risk of breast carcinoma, need discussing with the patient.
- Corticosteroid induced bone loss is in part due to reduced calcium absorption from the gut and increased urinary loss. Recent studies have shown that calcium

and vitamin D supplements are beneficial in preventing bone loss.¹³ The 1996 recommendations for the prevention of corticosteroid induced osteoporosis from the American College of Rheumatologists¹⁴ suggest an intake of 1500 mg/day of calcium through diet or supplements with vitamin D supplements. Calcitriol, activated vitamin D, with calcium supplements has also been shown to reduce bone loss but hypercalcaemia and hypercalciuria occurred in 25%; close monitoring is therefore necessary if this treatment is considered.¹⁵

The role of bisphosphonates as prophylactic agents in the prevention of steroid induced osteoporosis is not yet established. The long term consequences of these drugs is unknown; concern arises because they are deposited in bone but their use as a treatment for osteoporosis is considered safe up to 7 years.

No other action is necessary if the BMD is normal; this should be rechecked annually. If the BMD falls below -1 SD the patient should be referred to a specialist in the management of osteoporosis for consideration of anti-resorptive agents such as bisphosphonates or calcitonin, thiazides which decrease the urinary excretion of calcium, fluoride, or anabolic steroids.

Patients should be warned if they are at increased risk of fractures and the presence of back pain should be investigated with a lateral spine x ray to exclude a vertebral fracture.

MYOPATHY

During corticosteroid use there is a reduction in muscle protein synthesis and protein catabolism; therefore, muscle weakness and loss of bulk can occur. In its extreme form a steroid myopathy may develop, affecting the proximal muscles. This can be severe enough to affect mobility and is easily demonstrated by asking patients to stand from sitting without using their hands. Should a myopathy develop the steroid dose should be minimised and the use of steroid sparing agents considered. Recovery is slow and may be incomplete but can be helped by a programme to increase muscle strength. Muscle weakness can also occur as a result of hypokalaemia; electrolytes should therefore be checked in this situation.

OSTEONECROSIS

Osteonecrosis (previously known as avascular necrosis) is a serious complication of corticosteroid use and occurs in 5–25%; it rarely presents in the first 6 months. The risk increases with both dose and duration of treatment but it is not possible to predict who will be affected. Steroid use is the commonest cause of osteonecrosis in the UK.¹⁶ The femoral head is most frequently involved but other large joints may be affected.¹⁷ Joint pain and stiffness are the earliest symptoms and these complaints should alert the ophthalmologist to consider investigations for osteonecrosis. Pathology shows segmental necrosis of subchondral bone associated with marrow fibrosis and reactive bone formation. Though the pathogenesis remains obscure, a number of theories have been proposed:

- increased fat in the marrow cavity causes increased intraosseous pressure and this causes compression of the blood vessels with subsequent ischaemia
- increased lipids (induced by corticosteroids) cause fat emboli which occlude the blood vessels
- fatigue fractures occur, which because of corticosteroid use, cannot mend.

In order to prevent the progression to joint destruction early diagnosis is essential. Early in the disease the plain x ray and computed tomography scan may be normal and a bone scan shows only non-specific changes. The magnetic resonance T2 weighted image shows a double ring sign

representing a central low intensity area of fat necrosis surrounded by an increased signal of vascular proliferation; this is pathognomonic for osteonecrosis. Treatment initially involves restricted weight bearing, physiotherapy to maintain the range of movement, and non-steroidal anti-inflammatory drugs; this gives relief of symptoms and may stabilise the condition. Some feel that surgical core decompression early in the disease decreases the rate of progression to joint destruction, others disagree. Total joint replacement is the only long term definitive treatment. These patients are often young and so wear and loosening of the prosthesis can be problems. The management of osteonecrosis remains a considerable problem.

Behavioural changes

Existing psychiatric problems can be aggravated by corticosteroid treatment and so a full medical history is vital. Mood swings, euphoria, depression, and suicide attempts may all occur in previously stable personalities.¹⁸ Sleep disturbance is well recognised with insomnia and unpleasant dreams; thus, the steroid should be given as a single morning dose.¹⁹

Psychosis has been reported and usually develops within 2 weeks of starting treatment, particularly with doses of >40 mg/day prednisolone. Symptoms respond to tapering of the corticosteroids, usually within 3 weeks.

Reports in the *Lancet* draw attention to the unsatisfactory state of the law with respect to steroid induced psychosis as a defence for criminal activity. For example, a man with ulcerative colitis who required prednisolone 30–60 mg/day was accused of shop lifting. While clearly hypomanic, he was found guilty.^{20,21} It is important to advise patients that their judgment may be altered while on high dose corticosteroids and a period away from work initially may also be prudent.

Immune response

Steroids act in multiple ways to inhibit the immune system and so their use is associated with an increased susceptibility to infection. The clinical presentation may be atypical and the severity of the infection may be masked—for example, septicaemia; this allows the infection to become advanced before being recognised. A predisposition to bacterial, viral, fungal, and candidal infections can all occur.

TUBERCULOSIS

When corticosteroids were first widely used the fear was expressed that reactivation of quiescent tuberculosis might occur. In 1952 isoniazid became available; it had a high activity against tuberculosis and a low toxicity rate compared with previously available treatments and was advocated for use as a prophylaxis in high risk patients. In 1965 the American Thoracic Society suggested that anyone put on corticosteroids with a positive tuberculin test to five tuberculin units should receive isoniazid 300 mg/day. By 1970 it was recognised that hepatotoxicity and hypersensitivity reactions were occurring more frequently than expected and it became important to know the risk of reactivating tuberculosis. Smyllie and Connolly 1968²² retrospectively compared 550 patients treated at the Brompton Hospital with corticosteroids and 499 matched controls, all with pulmonary disease. They were followed for 1.5 to 7 years. The corticosteroid group developed one new case of tuberculosis and no reactivations and the control group also developed one new case and one reactivation. Mayfield in 1962²³ surveyed the experience in 50 British chest clinics. There were 11 668 new cases of tuberculosis in 1959–60, only 30 of these had had corticosteroids within 6 months of diagnosis and there

were 10 cases of reactivation in patients on corticosteroids. Schatz *et al* in 1976²⁴ looked at 132 asthmatics on corticosteroids and found no cases of reactivation of tuberculosis. Ten patients had calcification on their chest *x* ray and 28% had a positive reaction to five tuberculin units. It therefore seems that the risk of reactivating tuberculosis while on corticosteroids is very small. The current situation was summarised by Senderovitz and Viskum in 1994²⁵; they recommend that before long term corticosteroids are started a search for evidence of tuberculosis should be made, including a chest *x* ray and tuberculin test (both of these are likely to be done as part of the investigation of posterior uveitis). If active tuberculosis is found it can be treated in the usual manner while corticosteroids are started. If the evidence suggests inactive tuberculosis chemoprophylaxis is unnecessary but the patient should be followed closely. In the USA the advice is different and isoniazid is recommended for all Mantoux positive patients. It is worth remembering that if a patient on corticosteroids starts rifampicin the corticosteroid dose may need to be increased because of increased metabolism of the corticosteroids.

VARICELLA

The incidence of chickenpox is increasing and the proportion of cases in the over 14 year age group has increased from 10% to 25% between 1970 and 1990.²⁶ In 1994 a near fatal case of chickenpox occurred in 27 year old woman on corticosteroids for idiopathic thrombocytopenia purpura.²⁷ Within 24 hours she required ventilation and developed pneumonia, disseminated intravascular coagulation, renal failure, hepatitis, and bilateral acute retinal necrosis. This case illustrates how severe and rapid varicella can be in patients on corticosteroids. To avoid such cases, before starting corticosteroids patients should be asked if they have had chickenpox—it has been shown that a positive history correlates well with immunity. If patients are unsure or have not had chickenpox their serology should be tested. At St Thomas's Hospital a study among healthcare workers found that 143/145 (99%) with a positive history of having had chickenpox were antibody positive and 50/58 (86%) with an uncertain history were antibody positive; therefore, most adults are not at risk of developing chickenpox.

Patients who have no antibodies to chickenpox should be instructed to avoid chickenpox and if they are in inadvertent contact they should report this to their doctor immediately. Since 1994 the steroid card given to patients has been amended and now gives clear instructions to the patient to contact their doctor in such circumstances.

The ophthalmologist should consult with the virology department who will confirm the antibody status if this is unknown. For patients who are seronegative zoster immunoglobulin will be considered. If zoster immunoglobulin is given within 10 days of exposure to chickenpox it will attenuate or prevent the infection. Not all seronegative patients on corticosteroids will require zoster immunoglobulin. Zoster immunoglobulin is expensive and in rather short supply. It comes from pooled plasma of blood donors with a recent history of chickenpox or herpes zoster or who, on screening, have a high antibody titre.

The Department of Health handbook *Immunisation against Infectious Diseases*,²⁸ defines those with immunosuppression as:

- children who, within the previous 3 months, have received prednisolone in a daily dose of 2 mg/kg/day for at least 1 week or 1 mg/kg/day for 1 month
- adults who have received prednisolone 40 mg/day for more than 1 week in the previous 3 months. Patients on

lower doses of corticosteroids will be immunosuppressed if they are given in combination with cytotoxic drugs.

Exposure to chickenpox is defined as:

- contact with a person with chickenpox or exposed herpes zoster
- during the period 48 hours before the rash until it crusts
- for more than 15 minutes in the same room or face to face.

An adult who fulfils these criteria requires four vials of zoster immunoglobulin by intramuscular injection. The protection lasts for 3 weeks and if exposed again the treatment needs to be repeated. The Department of Health handbook comments that severe chickenpox can still develop despite zoster immunoglobulin and varicella immunisation should be considered for patients at long term risk. There is a live attenuated vaccine not yet licensed in the UK but available on a named patient basis. It has been used in children taking steroids to prevent infection in hospital.

Another alternative to zoster immunoglobulin is the use of prophylactic aciclovir. The Committee on the Safety of Medicines does not recommend this as an alternative but it has been used in healthy children exposed to chickenpox who then developed only mild or subclinical infection.

Gastrointestinal disease

Gastrointestinal side effects include peptic ulcer disease, candidiasis, and pancreatitis.

The impression that corticosteroids were potentially ulcerogenic originated from early anecdotal reports of peptic ulcer disease (PUD) in steroid treated patients and also from the knowledge that "stress ulcers" occurred during periods of high endogenous corticosteroids. Following these reports some studies confirmed and some refuted an association between PUD and corticosteroids. In 1976 Conn and Blitzer²⁹ reported combined data from 50 randomised clinical trials where corticosteroids had been given for a variety of diseases and found neither the prevalence of PUD nor its complications to be significantly greater in patients treated with corticosteroids than in controls. In 1983 Messer *et al*³⁰ used a similar experimental design and examined the relation in 71 studies where treatment was assigned at random; corticosteroids had not been used before randomisation; there was no concomitant use of non-steroidal drugs or antacids; and where side effects were adequately discussed. They concluded that corticosteroids significantly increased the prevalence of PUD. In 1985 Conn and Poynard³¹ analysed 93 double blind controlled trials with 6500 patients and found PUD in 0.3% of placebo treated patients and in 0.4% of corticosteroid treated patients. When the same methods were applied to diabetes mellitus, hypertension, and psychosis they were all significantly increased in the corticosteroid group. The main criticism of this work is that the studies used had not been originally designed to assess side effects but to establish the benefit of corticosteroids in the treatment of various diseases.

Experimentally, corticosteroids have been shown to increase gastric acid secretion, reduce gastric mucus, and to cause gastrin and parietal cell hyperplasia in animal studies. Corticosteroids have also been shown to delay healing and to enlarge experimental ulcers. Clinically corticosteroids do mask gastrointestinal symptoms, especially those of major crises such as perforation. Piper *et al*³² found that in 1415 patients hospitalised with PUD there was no increased incidence in those taking corticosteroids alone but there was an increased risk in those taking non-steroidal anti-inflammatory drugs and a marked increased

Table 1 Checklist for patients about to start systemic corticosteroids

Full history including psychiatric, smoking, alcohol, and drugs
Measure blood pressure
Measure blood sugar
Varicella—history of chickenpox, check antibodies if necessary, and advise against contact with chickenpox and shingles
Tuberculosis—history of tuberculosis, chest x ray, and tuberculin test
Osteoporosis—dual energy x ray absorptiometry scan, weight bearing exercise, ensure adequate intake of calcium and vitamin D, hormone replacement if appropriate
Peptic ulcer disease—history of peptic ulcer disease, prophylaxis if in high risk group

risk in those taking both. They postulated that corticosteroids potentiate the ulcerogenic capacity of other agents.

For practical purposes, when a patient is prescribed corticosteroid treatment those who have risk factors for PUD such as a past history of PUD; smoking; high alcohol intake; or receiving ulcerogenic drugs should be given a prophylactic agent such as ranitidine. Those who do not have risk factors for PUD require no prophylactic treatment. It is prudent to prescribe enteric coated prednisolone where possible. Any suggestion of PUD should be promptly investigated with gastroduodenoscopy.

Drug interactions

Reduced therapeutic effect of corticosteroids occurs with:

- rifampicin
- carbamazepine
- phenobarbitone
- phenytoin
- primidone
- aminoglutethimide.

Corticosteroids reduce the therapeutic effect of the following drugs:

- hypoglycaemic agents
- antihypertensives
- diuretics
- heparin.

Corticosteroids potentiate the hypokalaemic effect of:

- acetazolamide
- diuretics
- carbenoxolone.

Corticosteroids potentiate the ulcerogenic effect of non-steroidal anti-inflammatory drugs.

High dose methylprednisolone increases plasma cyclosporin levels.

Cyclosporin increases plasma levels of prednisolone.

Summary

The anti-inflammatory effects of corticosteroids cannot be separated from their metabolic effects as all cells use the same glucocorticoid receptor; therefore when corticosteroids are prescribed measures should be taken to minimise their side effects. Clearly, the chance of significant side effects increases with the dose and duration of treatment and so the minimum dose necessary to control the disease should be given.

Before embarking on a long term course of corticosteroids the factors summarised in Table 1 should be considered. A full discussion with the patient is necessary in order to explain the benefits and risks of corticosteroid treatment. A patient information leaflet is now provided by the manufacturers of all systemic corticosteroid preparations. As emphasised by the recent publication by the Committee on the Safety of Medicines,³³ advice to patients is the key to the safe use of long term systemic corticosteroids and it recommends discussing the following points with the patient:

- not to stop taking corticosteroids suddenly
- to see a doctor if they become unwell

- of the increased susceptibility to infections, especially chickenpox
- of the serious side effects that may occur
- to read and keep the patient information leaflet
- to always carry the steroid treatment card and to show it to any health professional involved in their treatment.

In addition the following suggestions may help to minimise some side effects:

- a single morning dose
- early dietary modification—low calorie, low sodium, and high potassium
- awareness of possible errors of judgment on high doses.

Once started on corticosteroids the patient should be regularly reviewed to assess the response to the treatment with adjustments to keep the dose at a minimum.

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