CORTICOSTEROID-INDUCED OSTEOPOROSIS

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Corticosteroid therapy is one of the major risk factors for the development of osteoporosis and associated fractures. This article will review current prevention and management strategies and the role of bone densitometry in the identification and monitoring of "at risk" patients.

Osteoporosis is a progressive, systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.

The precise mechanism whereby corticosteroid therapy leads to osteoporosis is not yet established but there is evidence for a dual effect on the skeleton with a reduction in osteoblastic bone formation and an increase in osteoclastic resorption. The decrease in bone formation results in a decrease in the mean wall thickness of packets of trabecular bone. In corticosteroid-induced osteoporosis (CIOP) there is thinning of the trabeculae with a small reduction in trabecular number, whereas in idiopathic osteoporosis, trabeculae are of normal width but are fewer, indicative of trabecular perforation⁽¹⁾. The mechanism of bone resorption is less clear but is also associated with decreased intestinal calcium absorption and increased urinary calcium excretion. Corticosteroids also have an effect on the suppression of sex steroids which contribute to increased bone turnover and loss in both sexes.

Approximately two thirds of patients on longterm corticosteroids will develop significant osteoporosis but it is not possible easily to identify those at risk and, while it is generally true that bone loss is related to the dose and duration of treatment, this is by no means universal. The most rapid loss of bone occurs in the first year of treatment⁽²⁾ and there is some evidence that bone loss at the spine is greater than that at the hip or distal radius⁽³⁾ (Figure 1). Bone loss, however, continues at a rate of 2-3 times normal on long term therapy in older patients. It is generally accepted that the use of corticosteroids increases the risk of fracture between two and fourfold⁽⁴⁾. The distribution of fractures in patients receiving corticosteroid therapy is similar to post-menopausal osteoporosis.

Figure 1 Bone loss after starting corticosteroids

The previous assumption that patients treated with corticosteroids suffered fractures at higher bone density values than in post-menopausal osteoporosis has been questioned by a recent regional study⁽⁵⁾.

SCOPE OF THE PROBLEM

A community-based study has suggested that 0.5% of the U.K. population and 1.7% of women aged 55 or over are taking oral corticosteroids⁽⁶⁾ (Figure 2). A hospital study has

Figure 2 Age and sex distribution of patients taking continuous oral corticosteroids

confirmed that 2% of medical outpatients were receiving longterm corticosteroids (greater than 5 mg a day) with the highest frequency in patients with obstructive airway disease and inflammatory arthritis⁽⁷⁾ (Figure 3). In general practice, 40 prescriptions for inhaled corticosteroids are written for every one prescription of oral therapy. There is some evidence that inhaled corticosteroids are associated with decreases in bone density but the overall effect is difficult to determine due to the compounding effects of previous oral corticosteroid therapy.

Figure 3 Diagnoses of patients taking longterm continuous corticosteroids

Despite the widespread use of corticosteroid therapy and awareness of associated osteoporosis, only a small proportion of patients (8-14%) are co-prescribed any therapy to prevent bone loss⁽⁸⁾. This suboptimal care could have important medicolegal implications in the future and there is now an obligation to inform patients of the risks and benefits of corticosteroid therapy, including osteoporosis. Helpful patient information leaflets available from the National Osteoporosis Society (see Resources).

DIAGNOSIS

A diagnosis of osteoporosis can be confirmed by measuring bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) at the hip and lumbar spine sites. DXA also provides an assessment of fracture risk and, in those patients who have radiological evidence of osteopenia or have sustained a fracture, the measurement is an essential means of confirming or refuting the diagnosis of osteoporosis. The WHO definition of osteoporosis is a BMD value of >2.5 SD below the mean for young adults of the same sex and race (T score -2.5). Repeat BMD measurements are also a valuable means of assessing the rate of bone loss or confirming a response to therapy.

Those patients receiving corticosteroids with a T score below -1.5 should be considered for preventative therapy (see algorithm). This T score value is consistent with the European regulatory guidelines and is similar to the mean baseline score (-1.44) of the 128 placebo-treated patients receiving corticosteroid therapy amongst whom 15% experienced a new vertebral fracture within 12 months⁽³⁾.

TREATMENT OPTIONS

The aims of the various treatment strategies are to limit bone loss and reduce fracture incidence. Whilst there are effective therapies for prevention and treatment, the results of drug studies are difficult to interpret due to the heterogeneity of the patient populations, the effect of underlying disease and the dose of corticosteroids used.

Therapy for preventing further bone loss could be started:

- At the onset of corticosteroid therapy (primary prevention)
- After low bone density has developed, without or with fractures (secondary prevention and treatment).

Whenever corticosteroid therapy is commenced patients should receive appropriate lifestyle advice about factors known to influence bone health such as diet, weight-bearing exercise, avoidance of smoking and limitation of alcohol consumption. These patients should eat a well-balanced diet containing at least 1 gram of calcium, and to achieve this, supplementation is required for many patients. The elderly housebound also require vitamin D supplementation to achieve an intake of 400-800 IU daily. This general lifestyle advice should be encouraged even though it is not based on formal clinical trial evidence.

Doses of corticosteroid therapy should be kept under regular review and kept to the minimum necessary for disease control. Although inhaled corticosteroids have less effect on bone than oral therapy, alternate day therapy does not have this advantage. There are some data to suggest that Deflazacort is a corticosteroid which has less effect on bone,

provided the assumption is correct that the inflammatory potency of 6 mg of Deflazacort is equivalent to 5 mg of Prednisolone⁽⁹⁾.

Currently the most effective agents for CIOP are the bisphosphonates. It is now established that cyclical Etidronate not only prevents spinal bone loss in patients starting on high dose corticosteroid therapy but may also ameliorate bone loss in patients with established CIOP⁽³⁾. It is the only bisphosphonate currently licensed for the both these indications. Clinical trials suggest that Alendronate has similar effects and further evidence regarding Risedronate is awaited.

Hormone replacement therapy (HRT) is the treatment of choice for post-menopausal osteoporosis but evidence of its effects in CIOP are limited. In men with CIOP and hypogonadism, testosterone replacement therapy limits further bone loss but evidence for a reduction in fracture incidence is awaited.

In younger patients there is some uncertainty about the safety of long term bisphosphonate therapy and, for these patients, Calcitriol may be a suitable alternative although serum calcium levels have to be monitored at regular intervals. There is currently little evidence to support the therapeutic use of vitamin D in either treatment or prevention but calcium and vitamin D supplements have a weak effect in secondary prevention.

MANAGEMENT OF INDIVIDUAL PATIENTS

Individual patients could be managed by adherence to the algorithm (Table 1) which is based on a consensus view from published literature⁽¹⁰⁾. The algorithm and explanatory notes apply to any adult about to commence or continue being prescribed an oral dose of 7.5 mg per day or more of Prednisolone for six months or more.

EXPLANATORY NOTES TO THE ALGORITHM

If there is a prevalent osteoporotic fracture, a diagnostic work-up is recommended and this should be performed before starting therapy. The tests that should be performed are to exclude myeloma, hyperparathyroidism, osteomalacia, malabsorption, thyrotoxicosis and hypogonadism.

DIAGNOSTIC WORK-UP

- Lateral spinal radiography to exclude prevalent fractures. These are strong risk factors in their own right for further fractures
- Full blood count, erythrocyte sedimentation rate
- Calcium, phosphate and alkaline phosphatase
- Protein electrophoresis
- Thyroid function tests
- Total testosterone (men)
- Oestradiol (amenorrhoeic pre-menopausal women).

Any abnormalities detected in the work-up should be treated as appropriate for the underlying condition.

Table 1 The prevention and management of corticosteroid-induced osteoporosis

If they are not assessed as part of the prevention or treatment strategy, spine and hip DXA should be considered if required for monitoring the response to treatment.

Strong risk factors for osteoporosis include:

- premature menopause (<45 years)
- personal or family history of low trauma fractures
- history of amenorrhoea
- slender build (BMI <20 kg/m²)
- immobility

Monitoring and follow-up

For those patients on treatment in whom baseline BMD measurements have been undertaken, measurements of the lumbar spine and hip BMD after one year and then every 1-3 years, depending on the result, are recommended.

If annual bone loss is greater than 4% at the spine and/or 7% at the hip

- if not on treatment, osteoporosis therapy should be started
- if on treatment, an alternative therapy should be considered and/or referral to a specialist.

Adherence to this treatment plan would provide valuable audit projects in both primary and secondary care.

COST BENEFIT AND ANALYSIS

The described algorithm has not been subjected to formal costings and any attempt at such analysis would be based on theoretical models. However, lack of objective data should not be used as a reason not to offer effective therapy both to

prevent and to treat CIOP which is associated with significant morbidity and mortality.

The acute hospital cost of treating a hip fracture is estimated to be £4800, and when the social cost of admission to long-stay institutions is taken into consideration, then the average cost per case is £12,000. Estimates of other osteoporotic fractures are limited but may vary from £400-£500 upwards.

Patients with CIOP have a higher risk of fracture than other groups of patients with osteoporosis and so are likely to be a relatively cost-effective group to treat. Although cyclical Etidronate and Calcitriol have similar drug costs (Table 2), the need to monitor serum calcium levels will increase the actual costs of Calcitriol.

For patients receiving HRT there is no evidence that the more expensive transdermal preparations are more bone-

Cost for 90 days

£24.30	Cacit D3 (200 IU Vit. D)
£29.70	Calcichew D3 forte (400 IU Vit. D)
£40.20	Cyclical Etidronate
£82.57	Alendronate
£22.16	Sequential combined HRT therapy (average cost)
£29.72	Continuous combined HRT therapy (average cost)
£18.31	Unopposed oestrogen (average cost)
£46.28	Deflazacort (9mg/day)*
£38.81	Calcitriol
£2.09	*Prednisolone 7.5 mg/day for 90 days

Based on MIMS pricing

Table 2 Cost of therapy options

sparing that other cheaper forms and a case could be made for using the cheapest preparation with which the patient is compliant. In general, the more expensive the treatment, the more logical it is to target therapy to those at greatest risk of fracture.

SUMMARY

- Osteoporosis is a major complication of corticosteroid therapy and an important cause of morbidity
- The potential for preventing osteoporosis is great but current evidence suggests that only a minority of patients receive preventative therapy
- A treatment algorithm is presented for adults receiving Prednisolone 7.5 mg daily or more, for more than six months
- Bone densitometry provides a means of identifying those patients at increased risk of fracture, confirming a diagnosis of osteoporosis, and assessing the response to treatment
- Bisphosphonates are effective for both the prevention and treatment of corticosteroid-induced osteoporosis.

RESOURCES

- A strategy to prevent and tackle osteoporosis has recently been published by the Department of Health and the local response has been to update osteoporosis management guidelines which have been circulated to all local general practitioners. Further copies can be obtained from the Rheumatology Department, Royal Lancaster Infirmary.
- A quick reference primary care guide and laminated guideline card are available from the Department of Health, PO Box 410, Wetherby, West Yorkshire LS23 7LM.
- Further information is on the department's website at <http://www.open.gov.uk/doh/osteop.htm>
- Guidance on the prevention and management of corticosteroid-induced osteoporosis (endorsed by British Geriatric Society, British Society for Rheumatology, National Asthma Campaign, Primary Care Rheumatology Society, Royal College of Nursing) is available from the National Osteoporosis Society, P.O. Box 10, Radstock, Bath, BA3 3YB (01761 471771).

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