

THERAPEUTIC INTERVENTION

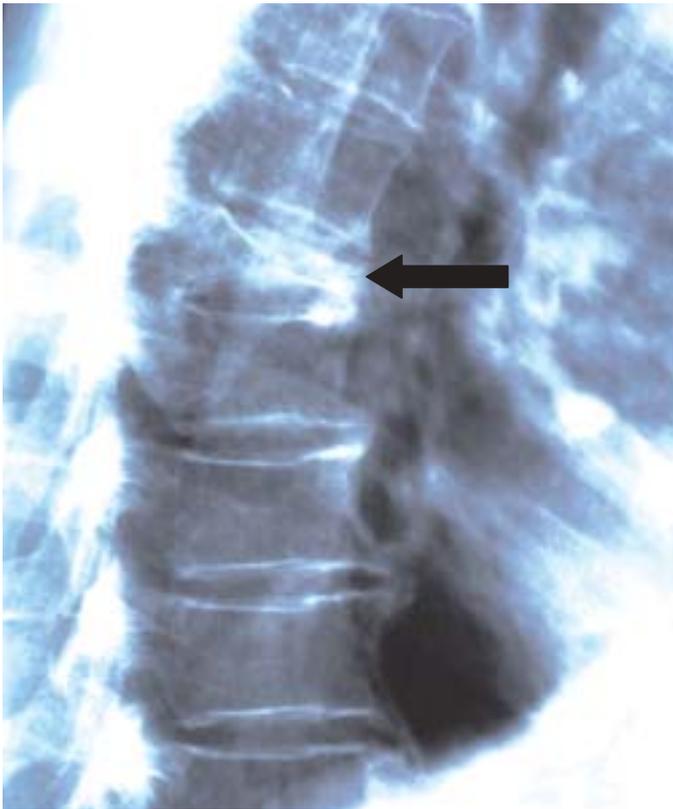
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Arrow shows collapse of an osteoporotic thoracic vertebra

INTRODUCTION

Glucocorticoids are widely used by a number of medical specialists, including neurologists. A recent study using the UK General Practice Research Database identified 1.6 million oral glucocorticoid prescriptions over a 10-year period in 683 practices from different geographic areas of the UK (van Staa *et al.* 2000). At any one time, the prevalence of oral glucocorticoid use was 0.9% of the total adult population, rising to 2.5% of those aged 70–79 years. However, the use of bone active medication in this population was extremely low (5% used hormone replacement therapy and only 1.8% used bisphosphonates). And yet, osteoporosis is a common and serious complication of treatment with glucocorticoids, being associated with an increased risk of vertebral and hip fractures.

Some important characteristics of glucocorticoid-induced bone loss have recently been identified:

- Even during the first few months of therapy the onset of bone loss is rapid and the fracture risk increased.
- There is an increased fracture risk even with low doses of oral prednisolone (<7.5 mg/day).
- There is rapid reduction in fracture risk when glucocorticoids are stopped.

These observations emphasise the importance of early intervention in those at highest risk, regardless of dose.

In December 2002 the Bone and Tooth Society of Great Britain, the National Osteoporosis Society and the Royal College of Physicians published evidence-based guidelines for the management of glucocorticoid-induced osteoporosis. In this brief paper I will summarise their recommendations – for neurologists.

Management of glucocorticoid-induced osteoporosis – for neurologists

WHICH INTERVENTIONS ARE EFFECTIVE IN GLUCOCORTICOID-INDUCED OSTEOPOROSIS?

A number of bone active interventions have been investigated in glucocorticoid-induced osteoporosis, although many of the studies were small and suboptimal in design. The best evidence is for the three bisphosphonates: etidronate, alendronate and risedronate, all of which have been shown to reduce or prevent bone loss in randomised controlled trials. Although fracture reduction was not a primary outcome in any of these trials, safety and post hoc analyses have shown a reduction in vertebral fracture in treated patients. All three bisphosphonates have regulatory approval for prevention and treatment of glucocorticoid-induced osteoporosis.

- Etidronate is given cyclically and intermittently with calcium: 400 mg daily is taken for 2 weeks followed by calcium supplements (500 mg/day) for 74 days at the end of which the 3 month cycle is repeated.
- Risedronate and alendronate are given once daily (5 and 10 mg respectively). Although once-weekly formulations are approved for treatment of postmenopausal osteoporosis these have not yet been approved for glucocorticoid-induced osteoporosis. Calcium and vitamin D supplements should be co-prescribed with risedronate and alendronate (400–800 IU and 1g daily respectively).

Because of the very low intestinal absorption of bisphosphonates (around 1% of an orally administered dose), and the potential for nitrogen-containing bisphosphonates to cause oesophagitis, alendronate and risedronate must

be taken in the fasting state with a large glass of water, with the patient sitting or standing upright and remaining so for 30 minutes afterwards. The patient must also remain fasting during this time. Alendronate and risedronate should be avoided in patients with a history of significant oesophageal disease and used with caution in those with upper gastrointestinal symptoms such as reflux. They are contraindicated in patients who are unable to sit or stand upright for 30 minutes after the dose, which may well apply in some neurological patients. Etidronate does not cause oesophagitis but may be associated with other gastrointestinal adverse effects such as nausea and diarrhoea, which are often attributable to the calcium supplements in the formulation. Bisphosphonates should not be used in patients with severe renal dysfunction.

In situations where oral bisphosphonates cannot be tolerated or are contraindicated calcitonin, calcitriol or intravenous pamidronate therapy may be considered. The grading of recommendations for the bisphosphonates and other agents is shown in Table 1. In the UK the annual cost of etidronate, alendronate and risedronate is currently £226, £327 and £285 respectively. There are no data on cost-effectiveness

WHO SHOULD BE TREATED? (TABLE 2)

See Table 2. Because fracture risk rises rapidly after starting glucocorticoid therapy, primary prevention (i.e. co-prescription of a bone active drug at the time of initiation of glucocorticoids) is essential in those with the highest fracture risk. Such individuals can be defined on the basis of their age and previous history of fragility fracture (i.e. a low-trauma fracture). Thus primary pre-

Table 1 Effect of interventions on the prevention and reduction of glucocorticoid-induced bone loss and vertebral fracture. Grade A recommendations are made on the basis of evidence from meta-analysis of randomised controlled trials or at least one randomised controlled trial.

INTERVENTION	EFFECT ON		
	SPINE BONE MINERAL DENSITY	PROXIMAL FEMUR BONE MINERAL DENSITY	VERTEBRAL FRACTURE
Alendronate	A	A	A [†]
Calcitonin	A*	A*	nae
Calcitriol	A*	A*	nae
Calcium + vitamin D	A*	A*	nae
Cyclic etidronate	A	A	A [†]
Pamidronate	A	A	nae
Risedronate	A	A	A [†]

From Royal College of Physicians London (2002).

nae, not adequately assessed; * data inconsistent; [†] not a primary outcome event.

Table 2 Indications for primary and secondary prevention in patients committed to oral glucocorticoids for three months or more (any dose)

Primary prevention	Men and women aged 65 years or older or Previous history of fragility fracture
Secondary prevention	BMD score of -1.5 or lower* or fragility fracture during glucocorticoid therapy

*As younger individuals have a lower fracture probability for any given BMD, age should be taken into consideration when making treatment decisions.

on high doses of prednisolone and those with other risk factors for osteoporosis (for example untreated hypogonadism, low body mass index).

WHAT GENERAL MEASURES SHOULD BE ADVISED IN PATIENTS TAKING GLUCOCORTICIDS?

General measures to reduce bone loss should be taken in all individuals prescribed oral glucocorticoids:

- Reduce the dose of glucocorticoids to a minimum.
- Consider alternative formulations or routes of glucocorticoid administration – for example oral budesonide in patients with ileal Crohn's disease, or inhaled or topical administration of glucocorticoids.
- Consider use of alternative immunosuppressive agents (e.g. azathioprine, methotrexate).
- Ensure good nutrition with adequate dietary calcium and vitamin D intake.
- Encourage appropriate physical activity.
- Avoid tobacco use and alcohol abuse.
- Provide a falls risk assessment and advice where appropriate.

WHAT INVESTIGATIONS SHOULD BE PERFORMED IN PATIENTS WITH GLUCOCORTICOID-INDUCED OSTEOPOROSIS?

Other secondary causes of osteoporosis should be excluded in individuals on glucocorticoid with a previous fragility fracture. A general evaluation should include measurement of serum calcium, phosphate and alkaline phosphatase, assessment of renal and liver function, full blood count and thyroid function tests. If serum calcium is raised, serum parathyroid hormone levels should be assessed. Serum and urine immunoelectrophoresis should be performed to exclude myeloma (with bone marrow biopsy if indicated) and serum testosterone levels measured in men. In patients with height loss, kyphosis, or back pain suggestive of vertebral fracture lateral X-rays of the thoracic and lumbar spine should be performed.

SHOULD BONE PROTECTIVE THERAPY BE MONITORED?

The role of monitoring the effects of bone protective agents in glucocorticoid-induced osteoporosis has not been established. Depending on the rate of bone-loss prior to treatment, significant treatment responses in individuals may be detectable within 1 or 2 years using dual energy X-ray absorptiometric measurements

although alternate day glucocorticoid administration may suppress growth less than a daily regimen in children, the few data available in adults do not support a bone sparing effect

vention is indicated in men and women over the age of 65 years, and in others who have a history of previous fragility or low trauma fracture This recommendation applies to all individuals who are likely to be exposed to oral glucocorticoids for 3 months or longer, regardless of the dose. It should be emphasised that these patients do not require bone density assessment before starting bone protective therapy.

For assessment of fracture risk in other individuals treated with glucocorticoids, measurement of bone mineral density (BMD) at the hip \pm spine, using dual energy X-ray absorptiometry (DXA), is recommended. A BMDT score of -1.5 or lower at the spine \pm hip (i.e. 1.5 or more standard deviations below normal peak bone mass) may indicate the need for intervention with a bone-sparing agent. In addition, treatment should be advised for individuals who develop a fragility fracture whilst taking glucocorticoids. However, the effect of age on fracture probability in an individual should be taken into account when making treatment decisions based on BMD. In particular, the absolute risk of fracture in premenopausal women and younger men is generally low. In addition, bisphosphonates cross the placenta and are contraindicated in pregnancy. A lower BMD threshold may therefore be appropriate for younger individuals treated with glucocorticoids unless other strong risk factors are present (e.g. hypogonadism, previous fracture, low body mass index).

WHAT SHOULD I DO IF THERE IS NO ACCESS TO BONE DENSITY MEASUREMENTS?

Unfortunately, there is no or restricted access to bone densitometry in many parts of the United Kingdom, and elsewhere. For those physicians who cannot obtain bone density measurements, a more proactive approach to primary prevention may be indicated. Examples include individuals



DXA of the lumbar spine

of BMD. However, in individuals taking high doses of glucocorticoids, large changes in BMD may be detectable earlier and measurement at 6 months may be appropriate.

Because non-compliance is the main reason for failure to respond to bone protective therapy, careful explanation to the patient of the reasons for taking the drug, the possible adverse effects, and the importance of adhering to dosing instructions are essential. Many experts now believe that routine monitoring of bone density is not cost-effective and that patient counselling is likely to be superior in this respect – this strategy also saves scarce bone densitometry resources.

HOW SHOULD I TREAT PATIENTS TAKING SHORT-TERM, HIGH DOSE GLUCOCORTICOID THERAPY OR INTERMITTENT COURSES OF GLUCOCORTICOIDS?

Most studies of bone loss and its treatment have been conducted in individuals taking glucocorticoids for at least 6 months. The effects of short term, high-dose therapy or intermittent courses of glucocorticoids over long periods of time are less well studied. Because rates of bone loss are greatest in the first few months of glucocorticoid administration, treatment for periods as short as 3 months may result in increased fracture risk and thus the need for prevention of bone loss and fractures should be carefully assessed in this situation. Evidence that bone loss is related to the cumulative dose of glucocorticoids provides a strong rationale for considering preventive measures in individuals receiving intermittent courses of oral prednisolone over longer periods

of time. Finally, although alternate day glucocorticoid administration may suppress growth less than a daily regimen in children, the few data available in adults do not support a bone sparing effect.

HOW LONG SHOULD BONE PROTECTIVE THERAPY BE CONTINUED FOR?

At present the optimal duration of bone protective therapy in patients taking glucocorticoids is unknown. As a general rule, it should be continued for the duration of glucocorticoid therapy regardless of dose and, when the glucocorticoids are stopped, bone density should be reassessed to determine whether further treatment is indicated. If bone density cannot be measured then it would seem reasonable to continue bone protective therapy in everyone over the age of 65, and in younger patients who have had a fragility fracture.

REFERENCES

- VanStaa T, Leufkens HGM, Abenham L, Zhang B & Cooper C (2000) Use of oral corticosteroids and risk of fractures. *Journal of Bone and Mineral Research*, **15**, 993–1000.
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CONCLUSIONS

- Glucocorticoid-induced osteoporosis is a common and neglected problem in clinical practice, including neurology.
- Bone loss and increased fracture risk occur early in the course of glucocorticoid treatment.
- Increased fracture risk is observed at all doses of oral glucocorticoids.
- Primary prevention should be instigated in all high risk individuals committed to oral glucocorticoid therapy for >3 months.
- Fracture risk should be assessed in other glucocorticoid-treated individuals and treatment given as appropriate.
- Bisphosphonates are the treatment of choice for prevention and treatment of glucocorticoid-induced osteoporosis.