Fit for a fracture

Clinical record

A 55-year-old woman with chronic epilepsy and psychiatric problems was admitted to hospital in 2004 with a fractured neck of femur after a trivial fall.

She had been diagnosed with epilepsy in childhood and treated with phenytoin and phenobarbitone. Management was complicated by multiple, prolonged psychiatric admissions. Anticonvulsant compliance had been verified with measurement of serum phenytoin levels on a number of occasions. As a result of psychiatric problems, the patient became less able to care for herself and, at the age of 46 years, was admitted to long-term psychiatric hostel accommodation. Four years later, she had a non-displaced fracture of the olecranon after a fall; serum 25-hydroxyvitamin D level and bone mineral density were not assessed at that time.

During the current admission, the fractured neck of femur was treated surgically. Biochemical testing indicated vitamin D deficiency (Box), which was treated with daily calcium carbonate (1200 mg) and ergocalciferol (vitamin D_2) (2000 IU), and substitution of phenytoin with sodium valproate. ◆

Blood test results for a 55-year-old woman with an osteoporotic fracture*

	On admission	Follow-up		RR
		3 months	9 months	
Ionised Ca (mmol/L)	**1.1**	–	1.22	1.14–1.29
Phosphate (mmol/L)	**0.7**	**1.6**	1.3	0.8–1.5
Parathyroid hormone (pmol/L)	**58.2**	**14.5**	**10.9**	1.5–8
25-hydroxyvitamin D (nmol/L)	**9**	**34**	70	> 50
Creatinine (μmol/L)	51	–	–	30–95
Alkaline phosphatase (U/L)	**229**	**112**	103	35–105
Haemoglobin (g/L)	143	–	–	115–155
Mean cell volume (fL)	97	–	–	81–98

RR = reference range. *Results outside the RR are highlighted in bold. ◆

This patient had recurrent fractures at a young age caused by a preventable complication from long-term use of anti-epileptic medication. Osteoporotic fractures, particularly hip fractures, result in significant individual morbidity and mortality and major financial cost to the community. It is well documented that enzyme-inducing anticonvulsants increase fracture risk by an average of two- to threefold, and that phenytoin causes osteomalacia. A 7-year longitudinal study of 87 people with epilepsy treated with phenytoin showed that they had a fracture rate six times higher than that of the healthy population.[1] Fractures were not related to seizures. This high rate of fracture has been confirmed in many subsequent studies.[2,3]

Phenytoin induces hepatic microsomal enzymes and increases the catabolic clearance of a number of vitamin D metabolites. Hypermetabolism results in vitamin D deficiency, which induces a compensatory increase in serum parathyroid hormone (PTH) and bone turnover. Patients may develop a severe mineralisation defect and consequent osteomalacia. Other enzyme-inducing anti-epileptic drugs, such as primidone and perhaps carbamazepine, have similar effects on vitamin D metabolism.

Anti-epileptic drugs have also been shown to cause bone loss in the absence of vitamin D deficiency.[4] This effect was greater in patients taking multiple drugs, those with longer duration of epilepsy, and those taking enzyme-inducing drugs.[5] This suggests that anti-epileptic drugs have a direct effect on bone turnover and could cause bone loss without inducing vitamin D deficiency.

Vitamin D replacement has been studied in patients taking phenytoin. In at least one study, cholecalciferol and ergocalciferol were not bioequivalent.[6] Another found that patients taking phenytoin required larger doses of calciferol to reach positive calcium balance than a control group.[7]

Other factors predisposing to vitamin D deficiency should also be considered. Institutionalisation leads to low sunlight exposure and reduced skin synthesis of vitamin D. This can produce vitamin D deficiency, even in Australia and without the addition of anti-epileptic drugs.[8] People living in institutions may require higher replacement doses of vitamin D than those in the community. For example, a dose of 2400 IU calciferol (well above the accepted dose required for nutritional health) was required to reach adequate serum 25-hydroxyvitamin D levels in three-quarters of institutionalised patients treated with anti-epileptic drugs.[9]

Many medical practitioners fail to consider the diagnosis of osteoporosis or to provide adequate prevention and treatment. In a recent American study of neurologists, only one in four screened for bone disease, and fewer than one in 10 routinely prescribed prophylactic calcium and calciferol for patients taking anticonvulsants.[10] There are no published consensus guidelines, but a recent editorial recommended osteoporosis screening in all adults taking anti-epileptic drugs long term.[11] We believe appropriate investigations should include annual screening of serum 25-hydroxyvitamin D level. This is particularly important for those who are institutionalised.

Patients taking anti-epileptic drugs long term should be advised about optimal dietary calcium intake, smoking cessation and avoidance of excess alcohol consumption, adequate sun exposure and weight-bearing exercise to prevent osteoporosis. Calcium and calciferol could be offered to those who achieve less than three to four serves of calcium daily or those who have a serum 25-hydroxyvitamin D level < 50 nmol/L.

A recent position statement in the Journal provided useful advice about vitamin D replacement in people with vitamin D deficiency.[12] Vitamin D replacement is particularly important for those taking phenytoin or phenobarbitone. If an osteoporotic fracture has occurred, bone mineral density should be assessed (this is currently not reimbursed by Medicare unless a fracture has occurred), and specific treatment with bisphosphonate drugs could be considered. However, bisphosphonates should be prescribed only after calcium and vitamin D deficiency has been corrected. These measures may help avoid the occurrence of hip fractures in relatively young patients taking anti-epileptic medication long term.

Lessons from practice

- Patients taking anticonvulsant medication have a two- to threefold increased risk of fracture.
- Lifestyle measures, with exercise, adequate sunlight exposure, smoking cessation and sufficient calcium intake, should be encouraged for all patients with epilepsy taking anticonvulsant medication.
- Serum 25-hydroxyvitamin D levels should be assessed annually in all those taking anticonvulsant medication long-term.
- Calcium and calciferol could be offered to those who achieve less than three to four serves of calcium daily and to those with a serum 25-hydroxyvitamin D level < 50 nmol/L.
- Larger calciferol doses than typically required may be needed to treat vitamin D deficiency induced by anticonvulsant medication.
- Bone mineral density should be measured in all patients taking anticonvulsant medication long-term who sustain a fracture. ◆

Hannah M Seymour,* Paul Glendenning†

* Advanced Trainee in Geriatric Medicine, † Chemical Pathologist and Endocrinologist, Royal Perth Hospital, GPO Box X2213, Perth, WA 6000
Hannah.Seymour@health.wa.gov.au

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