Seizure 1999; **8**: 339–342
Article No. seiz.1999.0301, available online at http://www.idealibrary.com on IDEAL

Bone density and antiepileptic drugs: a case-controlled study

L. J. STEPHEN*, A. R. MCLELLAN†, J. H. HARRISON†, D. SHAPIRO‡, M. H. DOMINICZAK‡, G. J. SILLS* & M. J. BRODIE*§

*Epilepsy Unit; †Bone Metabolism Unit, University Department of Medicine and Therapeutics; ‡Department of Pathological Biochemistry, Western Infirmary, Glasgow G11 6NT, Scotland, UK

Correspondence to: Professor M. J. Brodie, Epilepsy Unit, Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, Scotland, UK

This case-controlled study explored the relationship between bone mineral density (BMD) and long-term treatment with antiepileptic drugs (AEDs) in older adults with epilepsy. Seventy-eight patients (47 post-menopausal females, 31 males, aged 47–76 years) with epilepsy participated in the study. Each had only ever received treatment with either enzyme-inducing ($n = 52$) or non-inducing ($n = 26$) AEDs. Individuals were matched for age, sex, height and weight with a drug-naive control. All patients underwent bone densitometry at the lumbar spine and femoral neck and had blood sampling and urine collected for a range of bone markers. Male patients had lower BMD than controls at the lumbar spine ($P < 0.01$) and neck of the femur ($P < 0.005$). Female patients had significantly reduced bone density at the femoral neck ($P < 0.05$) only. AED usage was independently associated with an overall reduction in bone density at femoral sites and contributed to just over 5% of the variance at the femoral neck. Duration of treatment and type of AED were not independent factors for reduction in BMD. This case-controlled study supports the hypothesis that long-term AED therapy is an independent risk factor for reduced BMD in epileptic patients. Adults receiving treatment for epilepsy are at higher risk of osteoporosis and should be offered bone densitometry.

Key words: osteoporosis; epilepsy; antiepileptic drugs; bone density.

INTRODUCTION

Osteoporosis is a common bone disease affecting up to 40% of women and 12% of men[1]. Fractures resulting from reduction in bone mineral density (BMD) are an important cause of morbidity and mortality; over one-third of adult women will sustain at least one osteoporotic fracture. The risk of hip fracture in white females is doubled by usage of antiepileptic drugs (AEDs)[2]. Treatment with older AEDs, such as phenytoin, carbamazepine and phenobarbital, has been associated with the production of rickets and osteomalacia[3–5] and could, theoretically, contributed to bone demineralization through secondary hyperparathyroidism. However, evidence supporting a deleterious effect of AEDs on BMD is sparse and conflicting[6–12]. The aim of this study was to explore the relationship between BMD and long-term treatment with enzyme- and non-enzyme inducing AEDs in epileptic patients.

§ *E-mail:* Martin.J.Brodie@clinmed.gla.ac.uk

MATERIALS AND METHODS

Post-menopausal females and males over 47 years with treated epilepsy were recruited from the Epilepsy Clinic at the Western Infirmary in Glasgow. Females were asked about age at menarche and menopause, use of hormone replacement therapy, number of pregnancies, history of amenorrhoea, hysterectomy and oophorectomy. Patients with prior or current use of glucocorticoids, or recipients of other treatments likely to affect BMD or with a history of any disorder likely to affect bone, including thyroid disease, were excluded from entry. Each patient was matched with a non-epileptic control on no drug therapy for age, sex, height and weight. Women were also matched as far as possible for gynaecological and obstetric history, including use of hormone replacement therapy. Patients completed a 'osteoporosis risk factor' questionnaire, giving details of duration of epilepsy, seizure type and frequency, family history of osteoporosis, fracture his-

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tory, past medical and drug history, and alcohol intake. Details of the protocol were approved by the local ethics committee and all patients gave written informed consent to their participation.

All underwent dual-energy X-ray absorptiometry (DEXA) bone densitometry at the lumbar spine and femur (coefficients of variation ~1%) using a Hologic QDR-1000^{TM} densitometer (Hologic Inc., Waltham, USA). Bone mineral density was measured and T (the difference in standard deviations between a given bone density value and peak bone density in the normal reference population) and Z-scores (age-adjusted T-score) calculated. Blood was withdrawn at the same hospital visit for serum calcium and phosphate, 25-hydroxyvitamin D, and osteocalcin, which were assayed using standard commercially available methodologies. A fasting urine sample was collected for deoxypyridinoline crosslinks (Pyrilinks-D, Metra Biosystems, Great Haseley, UK). Comparisons were made using one-way analysis of variance, regression analysis, and a paired t-test using MINITAB for Windows statistical package (Version 10.1).

RESULTS

A total of 78 patients (median age 58 years, range 47–76) with epilepsy (26 idiopathic, 52 partial) were studied. Overall, 52 and 26 patients (median ages 58 and 57 years, respectively) had only ever been treated with enzyme-inducing and non-enzyme-inducing AEDs (Table 1). Duration of AED usage varied between 7–36 years (mean 23 years) for the enzyme-induced patients and 5–27 years (mean 10 years) for those taking non-enzyme-inducing drugs. Forty-eight patients (17 females (55%) and 18 males (69%) taking enzyme inducers, and 9 females (53%) and 4 males (44%) taking non-enzyme inducers) had a history of fractures, but in only 3 (6%) was this as a consequence of seizure activity. Thirteen (16%) patients had a family history of osteoporosis. A total of 45 (54%) patients had been or were smokers, but only 4 (5%) patients had a history of alcohol excess.

BMD data compared with controls are summarized in Table 2. Males with epilepsy had significantly lower values at the lumber spine ($P < 0.01$) and femoral neck ($P < 0.005$). Females with epilepsy had significantly lower BMD at the femoral neck ($P < 0.05$), but not at the lumbar spine.

There was no difference in BMD between patients taking enzyme-inducing and those taking non-enzyme-inducing AEDs. Both groups had lower BMD at the femoral neck and lumbar spine than controls. There were no differences between the epileptic patients and controls for serum calcium, phosphate and osteocalcin and urinary deoxypyridinoline crosslinks (data not shown). Mean serum vitamin D levels were significantly lower in enzyme-induced epileptic patients than in controls (41 vs. 61 nmol/L, $P < 0.0001$), but not in those taking non-enzyme-inducing AEDs (48 vs. 59 nmol/L).

Factors contributing to the variance in lumbar vertebral BMD were identified by best subsets regression. Of the five identified—age, weight, group (epilepsy coded as 1, controls coded as O), sex (females coded as 1, males as O) and smoking (smokers coded as 1, non-smokers as O), weight ($P < 0.0001$), age ($P = 0.003$) and sex ($P = 0.005$) were shown by multiple regression analysis to contribute significantly, accounting for 31.7% of the variance. The regression equation was:

$$\text{Lumbar vertebral BMD} = 0.941 - 0.00439 \text{ age} + 0.00414 \text{ weight} - 0.0760 \text{ sex}.$$

When BMD was expressed as a Z-score (which corrects for the influence of age), weight was the only factor that contributed significantly. Similar analyses were undertaken to assess factors contributing to the variance in BMD at femoral sites. Stepwise regression analysis of factors contributing to the variance in femoral neck bone mineral density are shown below:

Factor	R^2	P value
Weight	21.9%	< 0.0001
Weight + age	31.8%	< 0.0001 (age)
Weight + age + group	36.8%	< 0.0001 (group)
Weight + age + group + sex	40.6%	< 0.005 (sex)

Group (that is epilepsy or control) accounted for 5.5% of variance in BMD at the greater trochanter and 3.2% at Ward's triangle. This small but significant contribution was seen whether BMD was expressed absolutely or as a Z-score. The influence of AED treatment (enzyme-inducers vs. non-inducers) was assessed by multiple regression analysis. Enzyme-inducing treatment was coded as 1, while non-inducing medication was coded as O. No significant influence on femoral BMD was seen with the different subtypes.

DISCUSSION

Osteoporosis is a common condition with major public health and economic implications[13]. Although both preventable and treatable, the disorder is under-recognized[14]. A number of risk factors have been proposed, including AEDs[2]. In this study, middle-aged adult males with epilepsy had a reduction in BMD at the lumbar spine and femoral neck compared with matched controls. Post-menopausal females with epilepsy were also found to have reduced BMD at the

Table 1: Current antiepileptic drug usage in the study population.

Enzyme-inducers	Females	Males	Non-inducers	Females	Males
CBZ	10	0	VPA	11	4
PHT	3	3	LTG	2	1
PB	2	2	VGB	0	1
CBZ, PHT	8	4	VPA, LTG	2	0
PB, PHT	4	6	VPA, TPM	1	1
PB, CBZ	1	4	VPA, LTG, TPM	0	1
PB, PHT, CBZ	2	3	VGB, LTG, TPM	0	1
			VPA, GBP, LTG	1	0
Total	30	22		17	9

PB = phenobarbital, PHT = phenytoin, CBZ = carbamazepine, VPA = sodium valproate, LTG = lamotrigine, VGB = vigabatrin, TPM = topiramate, GBP = gabapentin.

Table 2: Mean (SEM) bone density values in patients and controls.

			Lumbar spine (± SEM)			Femoral neck (± SEM)		
Group	Subgroup	*n*	Bone density	*T*-score	*Z*-score	Bone density	*T*-score	*Z*-score
All	Control	78	0.94 (0.02)	−1.15 (0.17)	−0.10 (0.15)	0.77 (0.02)	−1.54 (0.14)	−0.01 (0.12)
	Epilepsy	78	0.90 (0.02)	−1.46 (0.16)	−0.38 (0.15)	0.71 (0.01)[c]	−2.07 (0.13)[c]	−0.53 (0.12)[c]
Male	Control	31	1.06 (0.03)	−0.25 (0.25)	−0.28 (0.26)	0.86 (0.02)	−1.09 (0.17)	−0.32 (0.16)
	Epilepsy	31	0.96 (0.03)[b]	−1.18 (0.23)[b]	−0.65 (0.23)[b]	0.77 (0.02)[b]	−1.91 (0.19)[b]	−0.48 (0.19)[b]
Female	Control	47	0.85 (0.02)	−1.75 (0.19)	−0.35 (0.16)	0.71 (0.02)	−1.83 (0.20)	−0.23 (0.16)
	Epilepsy	47	0.86 (0.02)	−1.64 (0.21)	−0.20 (0.20)	0.67 (0.02)[a]	−2.18 (0.17)[a]	−0.55 (0.16)
Inducers	Control	52	0.94 (0.03)	−1.15 (0.22)	−0.06 (0.19)	0.76 (0.02)	−1.62 (0.16)	−0.04 (0.14)
	Epilepsy	52	0.91 (0.02)	−1.40 (0.18)	−0.28 (0.18)	0.71 (0.02)[b]	−2.09 (0.16)[b]	−0.49 (0.15)[a]
Non-inducers	Control	26	0.93 (0.03)	−1.16 (0.29)	−0.19 (0.24)	0.78 (0.03)	−1.39 (0.28)	−0.03 (0.24)
	Epilepsy	26	0.88 (0.04)	−1.58 (0.31)	−0.59 (0.27)	0.70 (0.03)[b]	−2.03 (0.23)[a]	−0.60 (0.21)[a]

Statistical significance determined by paired *t*-test: [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$.

femoral neck, but not at the lumbar spine. It is of interest that more than 50% of this patient population had a history of fracture largely unrelated to seizure activity.

Bone mineral density or bone mineral content (BMC) has been reported to be reduced at the appendicular skeleton in children and adults treated with AEDs in some studies[6,7,12], but not in all[9]. Bone mineral density and BMC were reduced at the axial skeleton in children but only after prolonged treatment[11]. An adverse influence on bone density was seen in one paediatric study with sodium valproate but not carbamazepine[12]. Evidence of a deleterious influence of AEDs on axial BMD in adults is derived from a small study of 38 patients[10]. Only phenytoin was associated with reduced BMD in women (but not in men), and no effect of carbamazepine was noted in either sex.

Bone demineralization has long been a recognized consequence of hepatic enzyme induction of vitamin D metabolism by AEDs[3–5]. The lack of variation in this study between the groups in terms of serum calcium, phosphate and osteocalcin and urinary deoxypyridinoline crosslinks suggests that our patients with treated epilepsy did not have increased bone turnover to account for the differences in BMD despite the significantly lower circulating vitamin D levels in the enzyme-induced cohort.

Although AEDs in this study were found to be an independent risk factor for osteoporosis accounting for just over 5% of the variation in BMD at the femoral neck, duration of disease and drug subtype were not. It is reasonable to assume that the lower BMD found in the treated epileptic patients is a consequence of the AED therapy rather than the seizure disorder *per se*. Further work is required to be undertaken in younger patients with epilepsy. Individual drugs should also be examined for their association or otherwise with the production of osteoporosis.

Antiepileptic drug choice is continually expanding with eight new drugs having been licensed in the 1990s and more to come[15]. Adults with epilepsy should be encouraged to attend for bone density screening. A range of pharmacological options are available for patients with reduced BMD including hormone replacement therapy (for post-menopausal and hysterectomized females), biphosphonates, vitamin D and derivatives, calcium and calcitonin. Patients with osteoporosis identified in this study have been commenced on treatment.

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