Chronic antiepileptic monotherapy, bone metabolism, and body composition in non-institutionalized children

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LIST OF ABBREVIATIONS

25OHD	25-Hydoxyvitamin D
AED	Antiepileptic drug
BMD	Bone mineral density
CYP450	Cytochrome P450
DXA	Dual-energy X-ray absorptiometry
PTH	Parathyroid hormone
RANKL	Receptor activator of nuclear factor κB ligand
TRAP5b	Tartrate-resistant acid phosphatase 5b

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AIM The aim of this study was to determine the influence of chronic monotherapy with antiepileptic drugs (AEDs) on vitamin D levels, bone metabolism, and body composition.
METHOD Eighty-five children (38 males, 47 females; mean age 12y 5mo, SD 3y 4mo) were treated with valproate and 40 children (28 males, 12 females; mean age 11y 10mo, SD 3y) were treated with other AEDs (lamotrigine, sulthiame, or oxcarbazepine), comprising the non-valproate group. Forty-one healthy children (29 males 12 females; mean age 12y 1mo, SD 3y 5mo) served as a comparison group. Height, weight, body impedance analysis, 25-hydroxyvitamin D, calcium, phosphate, two bone resorption markers (receptor activator of nuclear factor κB ligand [RANKL] and tartrate-resistant acid phosphatase 5b [TRAP5b]), osteoprotegerin, and leptin were measured.
RESULTS No child was vitamin D deficient as defined by a 25-hydroxyvitamin D (25OHD) level of less than 25nmol/l (<10ng/ml). Leptin, body fat, weight standard deviation score (SDS), and body mass index (BMI) SDS were all significantly higher (each $p<0.001$) in valproate-treated children than in the non-valproate group, as were calcium ($p=0.027$) and RANKL ($p=0.007$) concentrations. Similarly, leptin was significantly higher in the valproate group than in control participants ($p<0.001$), as were body fat ($p=0.023$), weight SDS ($p=0.046$), BMI SDS ($p=0.047$), calcium ($p<0.001$), and RANKL ($p<0.001$), whereas TRAP5b concentrations were significantly lower in the valproate-treated group ($p=0.002$). Furthermore, calcium and RANKL levels were significantly higher in the non-valproate group than in comparison participants ($p<0.001$ and $p=0.016$ respectively).
INTERPRETATION Non-enzyme-inducing or minimal enzyme-inducing AED monotherapy does not cause vitamin D deficiency in otherwise healthy children with epilepsy. Valproate therapy is associated with increases in weight, body fat, and leptin concentration, as well as with a bone metabolic profile that resembles slightly increased parathyroid hormone action.

Chronic antiepileptic drug (AED) therapy has been associated with vitamin D deficiency, low bone mass, increased fracture risk, and altered bone turnover.[1] The underlying pathophysiological mechanisms are poorly understood but are probably multifactorial. Most older AEDs (e.g. phenobarbital, phenytoin, and carbamazepine) are strong cytochrome P450 (CYP450) enzyme inducers, thereby causing altered steroid and vitamin D metabolism, whereas valproic

acid (valproate) and the newer AEDs such as lamotrigine and oxcarbazepine are non-enzyme inducers or minimal enzyme inducers. Some, but not all, studies in adults treated with new AEDs have observed vitamin D deficiency (as defined by a 25-hydroxyvitamin D [25OHD] level <25nmol/l [<10ng/ml]) and low bone mineral density (BMD).[2–4] Studies on the effect of chronic AED therapy on bone metabolism in children have produced conflicting results. Valproate monotherapy was first reported to reduce BMD in children.[5] Since then, most studies have failed to demonstrate low bone mass,[2,6,7] but, as many studies using dual-energy X-ray absorptiometry (DXA) failed to apply the necessary size corrections, this issue remains unresolved. Similarly, a certain degree of vitamin D insufficiency (as defined by 25OHD between 25 and 80nmol/l [10–32ng/ml]), as well as alterations in bone turnover, have been observed in some, but not all, studies.[3,6–8] Of importance, and in contrast to adults,[9] there is insufficient evidence that chronic AED use is associated with an increased fracture rate in children.[1]

In adults and children, valproate therapy is associated with weight gain, high body fat, and hyperleptinaemia.[10] Weight gain may affect bone mass accrual and turnover, for example children who are tall and heavy for their age are known to have higher than normal concentrations of bone markers.[11] In addition, leptin independently affects bone mass and structure via its peripheral (but also its central) pathways, and in particular regulates the response of cortical bone to increasing loads resulting from increased body weight.[12–14] Thus, valproate and other AEDs could affect bone accrual and/or turnover indirectly through weight gain and the associated hyperleptinaemia.

The conflicting results of previous paediatric studies may be a result of low participant numbers, occult vitamin D deficiency, or differing selection criteria, for example inclusion of institutionalized or non-ambulatory children with other conditions that may affect bone health.[6–8] In addition, little attention has been paid to the differential effects of various AEDs, body weight, fat percentage, and leptin concentration on bone and vitamin D metabolism.

The aims of this study were (1) to determine the influence of chronic AED monotherapy on vitamin D levels, bone resorption (receptor activator of nuclear factor κB ligand [RANKL], tartrate-resistant acid phosphatase 5b [TRAP5b]), and bone formation (osteoprotegerin) in non-institutionalized children with epilepsy; and (2) to examine the impact of valproate-associated changes in body composition and hyperleptinaemia on bone metabolism.

METHOD

Participants and study design

This cross-sectional cohort study was conducted at the Department of Paediatrics, Medical University Innsbruck, Austria, from March to September in 2005 and 2007. Non-institutionalized children with epilepsy over 6years of age on chronic monotherapy treated (for >6mo) with valproate, oxcarbazepine, sulthiame, or lamotrigine (Table I) were recruited to the study during outpatient visits. Epilepsy was defined according to the Guidelines of the International League Against Epilepsy.[15] Morphological or neurodegenerative cerebral abnormalities were ruled out by computed tomography and/or magnetic resonance imaging. Healthy children seen as outpatients for routine or preoperative investigations, or for minor conditions requiring blood sampling, were recruited as comparison participants. All children were ambulatory, normally physically active, and were on no additional medication. Children known to have any disease that could affect bone metabolism, including immobility, cerebral palsy, chronic or inflammatory disease, endocrine disease, genetic syndromes, major congenital malformations, cancer, or any other neurological disorders except epilepsy, were excluded from the study. Informed consent was obtained from all study participants and/or their parents. The study protocol was approved by the local ethics committee.

Anthropometry and blood sampling

Height and weight were measured using a wall-mounted stadiometer and a calibrated weight scale respectively, with participants wearing underwear only. Body mass index (BMI) was calculated by using the formula BMI=weight (kg)/height (m^2). Age- and sex-specific standard deviation scores (SDS=[x−mean]/SD) for height, weight, and BMI were calculated according to German reference data.[16] Children with a BMI above the 85th centile were considered to be overweight.[17] Body impedance analysis was performed according to the standard tetrapolar procedure[18] using a Human-Im body impedance analyser (DS Medigroup, Milan, Italy). Fat mass was derived using the paediatric software for the analyser. Fasting blood samples were obtained from all children between 8am and 10am to avoid bias through diurnal variation. Each sample of whole blood (1ml) was centrifuged to obtain serum, which was immediately frozen at −80°C within 1 hour after sampling, and stored in aliquots until the assays were run.

Biochemical analysis

Serum 25OHD was measured using a competitive enzyme immunoassay from Immunodiagnostic Systems Ltd (IDS OCTEIA; Boldon, UK). Two bone resorption markers (RANKL and TRAP5b) and two osteoprotective markers (osteoprotegerin and leptin) were used in this study. RANKL and osteoprotegerin were measured by a sandwich enzyme immunoassay (Biomedica, Vienna, Austria), and TRAP5b was measured using the Bone TRAP Assay

Table I: Baseline clinical characteristics and body composition (mean [SD]) of the study population

	Valproate group (*n*=85)	Non-valproate group (*n*=40)	Comparison participants (*n*=41)	p^a	p^b	p^c	p^d
Age, y:mo	12:5 (3:4)	11:10 (3:0)	12:1 (3:5)	0.567	NA	NA	NA
Male/female	38/47	28/12	29/12				
Height SDS	−0.3 (1.0)	−0.6 (1.0)	−0.3 (1.2)	0.285	NA	NA	NA
Weight SDS	0.3 (1.3)	−0.7 (1.2)	−0.3 (1.4)	<0.001	<0.001	0.046	0.312
BMI SDS	0.4 (1.3)	−0.6 (1.0)	−0.1 (1.2)	<0.001	<0.001	0.047	0.269
Body fat, %	22.6 (9.3)	12.7 (6.6)	15.9 (10.9)	<0.001	<0.001	0.023	0.311
Fat mass, kg	12.6 (9.2)	5.5 (4.3)	9.4 (10.4)	0.001	<0.001	0.198	0.146

[a]*p* values are given for overall comparison (ANOVA). [b]*p* values are given for the comparison of the valproate group and the non-valproate group. [c]*p* values are given for the comparison of the valproate group and comparison participants. [d]*p* values are given for the comparison of the non-valproate group and comparison participants. BMI, body mass index; NA, not applicable (as ANOVA not significant); SDS, standard deviation score.

(Medac, Hamburg, Germany). TRAP5b SDS were calculated using our previously published age- and sex-specific paediatric reference curves.[11] Serum leptin was determined using an enzyme-linked immunosorbent assay kit (ELISA; R&D Systems, Wiesbaden, Germany).

Statistics

Data are presented as mean (SD) values. Children were grouped into a valproate group, a non-enzyme-inducing or minimal enzyme-inducing AED group (non-valproate group), and a comparison group. Normal distribution of the data was tested using the Kolmogorov–Smirnov test. Logarithmic transformation was applied for leptin, fat mass, and RANKL as needed to achieve normal distribution. Two-way analysis of variance (ANOVA) was performed with these groups and sex as categorical variables, using post-hoc pairwise comparison (Scheffé's test) in case of significance. Pearson's correlation analysis (with 95% confidence intervals) was used to estimate correlations between anthropometric variables, body fat, concentrations of leptin, 25OHD, TRAP5b, RANKL, and osteoprotegerin and treatment duration. Additional univariate comparisons, using independent-sample *t*-tests, were carried out on overweight and lean children undergoing valproate therapy to assess weight-dependent effects on bone and fat metabolism. All statistical significance tests were two-tailed, with an alpha level of <0.05 indicating statistical significance. Statistical analysis was completed using the Statistical Package for Social Sciences for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 166 children fulfilling the inclusion criteria were eligible. All agreed to participate in the study and no child had to be excluded from data analysis. Eighty-five children aged less than 6 years with idiopathic epilepsy (38 males, 47 females; mean age 12y 5mo, SD 3y 4mo) received treatment with valproate (mean daily dose 869 [SD 380] mg/d). Forty children (28 males, 12 females; mean age 11y 10mo, SD 3y) received treatment with other AEDs (non-valproate group), of whom 12 were on sulthiame (150mg/d), 17 on oxcarbazepine (mean daily dose 840mg/d [SD 390]), and 11 on lamotrigine (284mg/d [SD 209]). Forty-one healthy children (29 males, 12 females; mean age 12y 1mo, SD 3y 5mo) served as comparison participants (Table I).

Comparison between the valproate group, the non-valproate group, and the comparison group (ANOVA)

None of the children had vitamin D deficiency as defined by a 25OHD level less than 25nmol/l (<10ng/ml). Forty participants receiving medication (32%) and six comparison participants (15%) showed vitamin D insufficiency (as defined by levels between 25 and 80nmol/l [10–32ng/ml]; Table II). Leptin, body fat, weight SDS, and BMI SDS were significantly higher (each $p<0.001$) in valproate-treated participants than in the non-valproate group, as were calcium ($p=0.027$) and RANKL ($p=0.007$) concentrations (Tables I and II). Similarly, leptin was significantly higher in the valproate group than in comparison participants ($p<0.001$), as were body fat ($p=0.023$), weight SDS ($p=0.046$), BMI SDS ($p=0.047$), calcium ($p<0.001$), and RANKL ($p<0.001$), whereas TRAP5b concentrations were significantly lower in the valproate-treated group ($p=0.002$). Furthermore, calcium and RANKL levels were significantly higher in the non-valproate group than in comparison participants ($p<0.001$ and $p=0.016$ respectively; Tables I and II).

Correlation analyses of treatment duration, body composition parameters, and bone metabolism in valproate-treated children are given in Table III. In addition, no

Table II: Biochemical results of bone metabolism, mean (SD)

	Valproate group (*n*=85)	Non-valproate group (*n*=40)	Comparison participants (*n*=41)	p^a	p^b	p^c	p^d
Leptin, ng/ml	25.7 (19.8)	7.3 (7.7)	5.3 (8.7)	<0.001	<0.001	<0.001	0.216
25OHD, nmol/l	108.1 (64.0)	131.5 (78.7)	124.8 (84.5)	0.401	NA	NA	NA
25OHD, ng/ml	43.2 (25.6)	52.6 (31.5)	49.9 (33.8)	0.401	NA	NA	NA
Calcium, mmol/l	2.47 (0.08)	2.43 (0.08)	2.34 (0.09)	<0.001	0.027	<0.001	<0.001
Phosphate, mmol/l	1.35 (0.20)	1.43 (0.21)	1.46 (0.22)	0.061	NA	NA	NA
RANKL, pmol/l	0.23 (0.13)	0.15 (0.08)	0.08 (0.01)	<0.001	0.007	<0.001	0.016
Osteoprotegerin, pmol/l	2.81 (0.71)	2.98 (0.84)	2.96 (0.56)	0.634	NA	NA	NA
TRAP5b, U/l	5.24 (2.87)	6.37 (2.43)	8.42 (3.98)	0.006	0.128	0.002	0.170
TRAP5b SDS	0.47 (1.93)	0.78 (1.90)	2.21 (2.28)	0.028	0.302	0.008	0.167

[a]*p* values are given for overall comparison (ANOVA). [b]*p* values are given for the comparison of the valproate group and the non-valproate group. [c]*p* values are given for the comparison of the valproate group and comparison participants. [d]*p* values are given for the comparison of the non-valproate group and comparison participants. NA, not applicable (as ANOVA not significant); SDS, standard deviation score; 25OHD, 25-hydroxyvitamin D; RANKL, receptor activator of nuclear factor κB ligand; TRAP5b, tartrate-resistant acid phosphatase 5b.

Table III: Correlation analyses of treatment duration, body composition, and bone metabolism in children treated with valproate

Correlated variables	Correlation coefficient	95% CI	*p*
Treatment duration			
BMI SDS	−0.186	−0.29 to 0.13	0.442
Leptin	−0.015	−0.23 to 0.20	0.897
25OHD	0.096	−0.12 to 0.30	0.443
TRAP5b SDS	−0.101	−0.31 to 0.11	0.437
RANKL	0.133	−0.08 to 0.34	0.565
Osteoprotegerin	0.090	−0.13 to 0.30	0.478
Body fat (%)			
BMI SDS	0.741	0.63 to 0.82	<0.001
Leptin	0.687	0.56 to 0.79	<0.001
TRAP5b SDS	−0.265	−0.45 to −0.06	0.045
TRAP5b SDS			
Phosphate	0.327	0.12 to 0.50	0.011
Phosphate			
Leptin	−0.300	−0.48 to 0.09	0.009

BMI, body mass index; 25OHD, 25OH vitamin D; RANKL, receptor activator of nuclear factor κB ligand; SDS, standard deviation score; TRAP5b, tartrate-resistant acid phosphatase 5b.

significant correlation was found between treatment duration and BMI SDS (r=0.027, 95% CI −0.29 to 0.34; p=0.867), TRAP5b SDS (r=0.214, 95% CI −0.10 to 0.49; p=0.256), or leptin (r=0.014, 95% CI −0.30 to 0.32; p=0.933), 25OHD (r=0.107, 95% CI −0.21 to 0.41; p=0.547), osteoprotegerin (r=−0.139, 95% CI −0.43 to 0.18; p=0.464), and RANKL (r=−0.017, 95% CI −0.33 to 0.30; p=0.961) concentrations in the non-valproate group.

Subanalysis within the valproate group

Subanalysis of bone and fat metabolism based on BMI was performed only in valproate-treated children, as the number of children who were overweight (BMI>85th centile) was significantly higher (χ^2 test, p<0.001) in the valproate-treated group (32/81) than in the non-valproate (3/40) or the comparison group (6/41). In the valproate group, overweight children (n=32), compared with lean children (BMI<85th centile, n=49), had higher absolute body fat (19.8 [SD 9.9]kg vs 7.5 [SD 4.5]kg; p<0.001), percentage body fat (30.1% [SD 6.7%] vs 17.1% [SD 7.0%]; p<0.001), and leptin concentrations (39.3ng/ml [SD 18.1] vs 16.1ng/ml [SD 14.7]; p<0.001). However, differences in serum concentrations of 25OHD and bone metabolic markers between overweight and lean children on valproate did not reach statistical significance.

DISCUSSION

This study found no evidence of vitamin D deficiency in non-institutionalized children with epilepsy on valproate or newer AEDs, in contrast to the results of some earlier, smaller, studies. Valproate-induced gains in body weight and fat were associated with higher concentrations of leptin, RANKL, and calcium and lower phosphate levels than in children on newer AEDs and comparison participants. This observation leads us to speculate that valproate may have direct or indirect (through hyperleptinaemia) effects on parathyroid hormone (PTH) secretion or inactivating effects on the calcium – sensing receptor. In contrast to the mainly leptin/fat-induced effects seen in the valproate group, chronic non-enzyme-inducing or minimal enzyme-inducing AED monotherapy resulted in only subtle changes in bone metabolism. To date, this is the largest

study examining the effect of non-enzyme-inducing (valproate, lamotrigine, sulthiame) or minimal enzyme-inducing (oxcarbazepine) AEDs on bone metabolism, and the first accounting for the effect of body composition and leptin in a carefully selected cohort of non-institutionalized children with epilepsy.

Of particular interest are the normal vitamin D concentrations in our study. Vitamin D deficiency in participants with epilepsy was reported to be common in some, but not all, earlier studies.[3,7] Most of these studies, however, included participants on carbamazepine, which induces hepatic P450 microsomal enzymes, thereby decreasing vitamin D levels. In contrast to carbamazepine, none of the AEDs used in our study is a strong enzyme inducer. None of our study participants had vitamin D deficiency (as defined by 25OHD<25nmol/l). Nevertheless, 32% of participants with epilepsy and 15% of comparison participants showed vitamin D insufficiency (as defined by levels between 25 and 80nmol/l [10–32ng/ml]). In fact, the levels observed are higher than usually seen in healthy Austrians.[19] Thus, factors other than AED monotherapy may have contributed to the high rates of vitamin D deficiency/insufficiency or the altered bone turnover reported in earlier studies,[3–8] for example the inclusion of participants receiving AED polytherapy[2,8] or those with severe learning disability*, immobility, or cerebral palsy, or other groups at risk for vitamin D deficiency. The last group comprises institutionalized participants, participants with physical disability, low outdoor activity, malnutrition, or a different sociocultural lifestyle, and black participants. Additional confounding factors are mixed paediatric and adult populations as well as differences in season, diet, sun exposure, and geographic area in which the study was conducted.

Another aim of this study was to assess whether AED-induced alterations in body composition (e.g. caused by valproate) would be reflected by changes in bone metabolism. Valproate-treated children were heavier and had higher body fat and higher serum leptin, RANKL, and calcium concentrations than the non-valproate group and comparison participants.

What conceivable mechanisms could explain these findings in valproate-treated children? First, heavier children reportedly have higher PTH levels[20] as well as higher bone marker concentrations in general.[11] Increased PTH action would explain the higher calcium and lower phosphate levels, and the greater RANKL but normal osteoprotegerin levels, in valproate-treated children, as the same metabolic profile has been observed in participants with primary hyperparathyroidism.[21] Unfortunately, PTH was not measured in our study. However, normal PTH levels but higher calcium levels have also been found in valproate-treated adults.[4]

Inevitably, our findings challenge the link between body composition changes and bone adaptation to increasing loads, and the evidence clearly indicates that leptin represents one mechanistic link.[12–14] Leptin directly stimulates periosteal osteoblasts, via its peripheral pathway, to increase cortical bone formation. Via its central pathway, leptin stimulates β-adrenergic receptors and the growth hormone axis, and thereby increases remodelling of trabecular bone. Valproate-induced hyperleptinaemia should, therefore, lead to greater release of bone formation and resorption markers. However, apart from the observed PTH-like bone profile, serum bone markers were not clearly altered, and also could not differentiate modelling, remodelling, and growth, limiting further interpretation. Second, being overweight, which can be regarded as a state of subclinical inflammation,[22] is associated with increased proinflammatory cytokines. Therefore, we speculate that RANKL, as part of the tumour necrosis factor-α superfamily, may be increased in participants who are overweight. However, to date, no study has investigated this relation in overweight children. Notably, apart from RANKL's well-known role in promoting osteoclastogenesis and bone resorption,[23,24] recent work suggests that RANKL and osteoprotegerin are biomarkers of vascular biology and risk factors for cardiovascular disease.[23,24] It remains to be shown whether RANKL, when upregulated by proinflammatory cytokines in the overweight state, has a systemic effect on bone resorption, especially as hyperleptinaemia inhibits osteoclast generation in the presence of RANKL in vitro.[13] As the other bone resorption marker, TRAP5b, was lower in valproate-treated children than in comparison participants and was negatively correlated with body fat, hyperleptinaemia does not seem to induce excessive bone resorption. However, without longitudinal or bone histomorphometric data, these speculations remain unsupported. Finally, fat tissue aromatizes androgens into oestrogens and is associated with hyperinsulinaemia, and both oestrogen and insulin have anabolic effects on bone tissue.

Taken together, we interpret the PTH-like changes in bone metabolism in valproate-treated children as either a direct effect of valproate or as an indirect effect mediated by hyperleptinaemia. However, as some changes in bone turnover markers were also observed in the non-valproate group, we cannot exclude the possibility that AED monotherapy, or epilepsy itself, has minimal effects on bone, or that small differences in mobility or muscle force could account for these changes.

The strengths of this study are the strict selection criteria, in particular the exclusion of institutionalized or

*North American usage: mental retardation.

disabled participants, the exclusion of children with reduced physical activity or receiving enzyme-inducing AEDs, and the fact that the recruitment period was from spring to autumn, thus minimizing bias through the known seasonal effect on vitamin D during Austrian winter months.[25] The limitations of the current study include the lack of bone morphometric, bone structure, or PTH measurements and the unequal sample size. Also, the amount of sunlight exposure received by individuals is unknown, and the potential, unreported, intake of vitamin D supplements cannot be completely excluded. Furthermore, no data on growth velocity, pubertal stage, postural stability, and muscle force, the main driver of bone modelling, were available. However, groups were age matched and the distribution of different AED monotherapies is not unusual for a large outpatient clinic for children with epilepsy. In addition, there are few paediatric reference data for osteoprotegerin/RANKL, which compromises interpretation of the experimental results. Nevertheless, our results improve the understanding of how non-enzyme-inducing AED monotherapy affects bone health and metabolism.

CONCLUSION

Our study shows that, when strict selection criteria are met, non-enzyme-inducing (valproate, lamotrigine, sulthiame) or minimal enzyme-inducing (oxcarbazepine) AED monotherapy does not cause vitamin D deficiency in otherwise healthy children with epilepsy. From a bone-health perspective, valproate-induced gains in weight and body fat and associated hyperleptinaemia produce a bone profile that slightly resembles that associated with increased PTH action, but it remains unclear whether anabolism or catabolism predominates. Current evidence does not suggest that fractures[1] or even low bone mass[1,2,6,7] are features of AED therapy in children, but reliable size-corrected DXA data are sparse, and other studies using more accurate imaging techniques or histomorphometry are non-existent. Long-term prospective studies are needed to assess the relation between being overweight, leptin, RANKL, proinflammatory cytokines, bone metabolism, and cardiovascular risk into adulthood. Other than the mainly direct or leptin/fat-induced effects seen in the valproate group, chronic non-enzyme-inducing or minimal enzyme-inducing AED monotherapy may additionally induce only subtle changes in bone metabolism. When several AEDs have to be given in combination, these changes could become more clinically relevant.

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