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Scott Mintzer

Thomas Jefferson University, scott.mintzer@jefferson.edu

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Mintzer, Scott, "Metabolic consequences of antiepileptic drugs" (2010). *Department of Neurology Faculty Papers*. Paper 30.

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Metabolic Consequences Of Antiepileptic Drugs

Scott Mintzer, MD

Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University

900 Walnut Street, Suite 200, Philadelphia, PA 19107

phone: 215-955-1222

fax: 215-955-0606

e-mail: scott.mintzer@jefferson.edu

Dr. Mintzer is supported by the National Institute of Health (K23NS058669)

Abstract

Purpose of review: Chemical properties of the widely-used older generation antiepileptic drugs (AEDs) suggest that they might be responsible for a number of medical co-morbidities.

Recent findings: AEDs which induce the cytochrome P450 system adversely affect bone, lipid, and gonadal steroid metabolism. Specifically, phenytoin (PHT) causes loss of bone mass in women, and both PHT and carbamazepine (CBZ) produce increases in serum lipids and C-reactive protein, as well as decreases in bioactive testosterone in men. Patients treated with inducing AEDs are at increased risk of fracture. Some contradictory data raise the question of whether bone mass is truly related to enzyme induction, and analogously, of whether reductions in testosterone truly account for male sexual dysfunction. Data showing elevations of surrogate cardiovascular and cerebrovascular risk endpoints with epilepsy patients, mostly inducing AED-treated, are consistent and concerning, however. Another older AED, valproate, is associated with the occurrence of polycystic ovary syndrome when used in young adulthood or adolescence.

Summary: Older generation AEDs are associated with a panoply of metabolic abnormalities. While more research is needed to see whether individual drugs are directly tied to specific clinical outcomes (e.g. risk of infarction), extant data are sufficiently concerning to suggest that these drugs may produce significant adverse health consequences. Newer generation AEDs may be preferable.

Keywords: antiepileptic drugs, lipids, bone, polycystic ovary syndrome, enzyme induction

Introduction

It is uncommon for a patient to ask of her antihypertensive, antiplatelet agent, or proton pump inhibitor, “What will this medication do to me over the long term?” Yet patients with epilepsy ask this question routinely regarding their antiepileptic therapy, and it seems they have good reason: among the many classes of drugs prescribed for chronic use, antiepileptic drugs (AEDs) appear to have a unique proclivity for affecting metabolism in unanticipated ways. Much of this stems from the property, shared by many AEDs, of altering the effects of enzymes of the cytochrome P450 (CYP450) system. Research over the last two decades has revealed that the CYP450 system plays a prominent role in many metabolic pathways, not just drug metabolism as had initially been believed (and as many physicians still believe). The involvement of the CYP450 system in the metabolism of hormones, vitamins, cholesterol, and other substances forms the scientific underpinning for the empiric observation that many AEDs — especially those which induce the CYP450 system — produce alterations in these pathways, accompanied by additional effects of potential clinical significance.

An understanding of these effects is critical to the optimal care of patients who are treated with these agents, which include not only those with seizures, but also those with essential tremor, migraine, neuralgic pain syndromes, and psychiatric conditions. All of these disorders require long-term — often lifelong — treatment, making the potential slow accretion of metabolic effects a genuine risk. This review is an attempt to provide a capsule summary of the current state of knowledge regarding the metabolic effects of AEDs, highlighting the most recent evidence for clinically-relevant effects and concluding with recommendations for patient care and future research.

Bone and Vitamin D metabolism

Observations regarding the effects of AEDs on bone mass first surfaced in

the medical literature four decades ago. The prevailing hypothesis underlying this concern, and the evidence for and against it, were nicely reviewed in a recent manuscript (1). Briefly, the notion is that CYP450-inducing AEDs upregulate the enzymes responsible for the metabolism of vitamin D, leading it to be processed into inactive metabolites. Compensation for this necessitates increased conversion of the major storage form, 5-hydroxyvitamin D (25-OHD), to the active forms. Upregulating this reaction requires increased levels of parathyroid hormone (PTH) as a necessary cofactor. A side consequence of this increase in PTH is an increase in bone turnover, and this “churn” through bone eventually leads to significant loss of bone mass.

A substantial body of evidence indicates that the inducing AEDs are associated with reduced levels of 25-OHD, with the largest amount of evidence impugning carbamazepine (CBZ) (2-9)(10, 11) (Table 1). Other studies suggest increases in bone turnover markers in patients treated with the inducers CBZ or phenytoin (PHT), whereas bone turnover appears normal in patients taking the non-inducing drug lamotrigine (LTG) (6, 10). A well-done community-based investigation demonstrated rather convincingly that PHT is associated with accelerated bone loss in elderly women (12), and there is also evidence from case-control studies of increased fracture risk in patients taking inducing AEDs (13, 14). Yet not all of the available evidence is consistent with this hypothesis. Studies of patients taking CBZ have yielded mixed results regarding its effects on bone density (4, 15, 16). In addition, the enzyme-inhibiting drug valproate (VPA) has been implicated as a potential cause of reduced bone density(15, 16) and fracture risk (13, 14).

Into this breach have stepped a number of recent studies, which unfortunately serve to muddy the waters even further. Pack and colleagues (11) followed women on AED monotherapy with PHT, CBZ, LTG or VPA for a year. They found significant loss of bone at the femoral neck in PHT-treated patients; they also found that reductions in 25-OHD were associated with increases in bone turnover markers, all of which is consistent with the aforementioned prevailing hypothesis. Yet CBZ-treated patients, in whom one would expect similar results, showed no such changes, nor did those on VPA or LTG. This

study suggests that the effects of individual enzyme-inducing AEDs on bone may differ.

Another noteworthy study in this arena was a large, community-based study of elderly men in whom bone density was measured twice, an average of 4.6 years apart (17). After adjustment for a large number of potential confounders, those taking inducing AEDs had a rate of bone loss no different from controls, whereas those taking non-inducing AEDs had an accelerated rate of bone loss; in fact, this was larger in patients who were being treated at both time points than in patients who were being treated only at one time point, consistent with a dose-response relationship. This surprising result flies in the face of all previous expectations, and while the study appears quite methodologically sound, this author has reservations about its conclusions. One possible source of error concerns the study population: of the patients taking non-inducing AEDs, the vast majority (over 80%) were being treated with gabapentin, a drug which is overwhelmingly prescribed for pain rather than epilepsy in current practice. One wonders if the disease states for which these patients were taking gabapentin might have influenced their bone health relative to controls. Even if one sets aside this caveat, the results should be considered applicable to gabapentin specifically rather than to all non-inducing AEDs.

Another case control study of fracture incidence was recently published, demonstrating that hip fractures were significantly associated with a history of AED use, and that all of this risk accrued with the use of inducing rather than non-inducing AEDs (18). This reconfirms the results of other case-control studies (13, 14).

Data on specific newer AEDs is largely lacking, aside from previously-mentioned studies which included LTG (10, 11) and one study suggesting that patients treated with oxcarbazepine (OXC) had lower 25-OHD levels and increased bone turnover (6). The latter was replicated in another recent publication, which found that 18 months of OXC treatment in children resulted in higher bone turnover and lower 25-OHD, but no significant change in bone density(19).

Finally, to round out the confusion, one study found that bone density was

reduced in patients treated with either inducing or non-inducing AEDs but was worse in the former(20). Duration of AED therapy, with any kind of AED, was also associated with greater bone loss. This study is limited by its cross-sectional design.

Lipids and other vascular risk markers

A number of serologic markers which are relevant to cardiovascular risk have been found to be affected by the CYP450-inducing AEDs. These include cholesterol and specific atherogenic lipid fractions (21-23), lipoprotein(a) (23), and homocysteine (24). These alterations suggest that enzyme-inducing AEDs might produce elevations in cardiovascular risk, a notion reinforced by the epidemiologic data, most of which demonstrates that patients with epilepsy suffer from greater vascular mortality and morbidity than the general population (25-27)(28, 29) (Table 2). In fact, carotid intima-media thickness, which has proven itself a robust surrogate marker for both cardiovascular and cerebrovascular disease, has been shown to be elevated among epilepsy patients, particularly in those taking inducing AEDs (30, 31), supporting the notion that atherosclerosis is increased in this population. Most of these studies are cross-sectional in nature, which limits their ability to inform causative inferences.

One recent investigation directly examined the effects of switching from inducing to non-inducing AEDs on vascular risk markers (32). In this study, 34 patients on CBZ or PHT in monotherapy were crossed over to monotherapy with either LTG or levetiracetam (LEV). Serologic studies, including lipid profiles, lipoprotein(a) {Lp(a)}, homocysteine (HCY) and C-reactive protein (CRP) were performed before the switch and then once again 6 weeks after discontinuation of the old drug. Sixteen normal subjects who were not treated with an AED underwent the same serologic studies on two occasions to serve as a control group. After drug switch, the epilepsy patients showed a mean decline of 25 mg/dL in total cholesterol, mostly in its atherogenic fractions, as well as a decline of nearly a third in CRP. In addition, patients withdrawn from CBZ experienced a

sharp reduction in Lp(a), while those withdrawn from PHT had subsequent reductions in HCY. Whether patients were switched to LTG or LEV had no bearing on the outcome measures, suggesting that CYP450 de-induction was responsible for the observed changes, and that the vascular risk markers in question were likely increased by CBZ and PHT to begin with.

Further evidence for increased vascular risk in this population was provided by Tan et al(33), who obtained a series of serologic studies along with carotid intimal-medial thickness measurements in 195 patients with epilepsy and in controls. They found that epilepsy patients had higher levels of total cholesterol, CRP, and HCY, as well as increased carotid intimal-medial thickness, corroborating a likely increased risk of cardiac and cerebral ischemic disease. Multivariate analysis revealed that duration of AED therapy was significantly correlated with carotid thickness. This study is noteworthy because of its large size and its use of a strong and well-validated surrogate measure of vascular disease. An important weakness is that the results were not presented in a way that allows for the specific elucidation of the effects of enzyme inducers, as it appears that a group of patients taking inducers alone were compared with a polytherapy group, many of whom were likely on inducers as well.

Consistent with the two aforementioned studies, Tomoum et al(34) studied 22 children with epilepsy and found that total cholesterol, various lipid fractions, and apolipoprotein AI were elevated in CBZ-treated patients and reduced in VPA-treated patients relative to controls, reinforcing the notion that CYP450 activity is causative of these changes. Carotid intimal-medial thickness was measured as well, but the sample was small and this was not analyzed appropriately.

Reproductive hormones

Both enzyme inducers and VPA have been implicated in effects on reproductive hormones. Controversy has been present since the first demonstration that VPA is frequently associated with a constellation of symptoms resembling polycystic ovary syndrome (PCOS)(35). Verification of this cross-sectional study would be ideally done by prospectively examining

either the results of drug switch or the effects of randomized drug assignment. A study of the former type was published not long after the original report, documenting that patients with PCOS who were taking VPA had resolution of all symptoms following switch to LTG, conclusively demonstrating that the drug was causative of the symptoms in these patients(36). Now a study of the latter type has appeared, shedding further light on this association(37). A multinational team of investigators randomized a group of epilepsy patients, both newly-diagnosed and refractory, to treatment with either VPA or LTG for a mean of almost a year. Both clinical and endocrinologic evidence of PCOS were significantly more frequent in the patients receiving VPA, but only in women age 25 and younger. This may help to reconcile some of the conflicting evidence and opinion surrounding this issue, and also may provide some support for the use of VPA in women older than 25, at least when pregnancy is not planned(38).

Reproductive hormone function among men with epilepsy has also been a subject of active investigation, with one study demonstrating that men taking the enzyme-inducing drugs CBZ or PHT had significantly lower testosterone levels and lower sexual function scores than men with epilepsy who were taking LTG or who were untreated (39). In this cohort, testosterone levels and sexual function were significantly correlated, suggesting that CBZ and PHT induce testosterone metabolism, leading to clinically-relevant sexual impairment. While this story appears scientifically sound and sensible, conflicting evidence has recently been published (40). The latter investigators performed a similar study of both men with epilepsy and controls, but with the addition of validated measures of depression and anxiety. They confirmed the previous finding that men taking inducing AEDs had lower testosterone levels, but found that virtually all were still above the threshold needed for normal sexual function, and that testosterone levels did not correlate with sexual function scores. These scores were clearly lower in men with epilepsy, but were correlated with depression and anxiety rather than the hormonal measures. The reasons for the discrepancies between this study and previous studies remains unclear, and more work will clearly need to be done to further elucidate these findings.

Conclusions

Recent studies have added to the considerable evidence that AEDs, particularly the older-generation agents, may have diffuse and profound effects upon a variety of metabolic pathways. The several discussed here do not include others which are complex enough to engender full-fledged discussions of their own (e.g. drug interactions, teratogenicity). A common thread runs through much of this data: it is clear that enzyme-inducing AEDs produce substantial alterations of a host of serologic parameters, but demonstration of the clinical end effects of those changes remain to be elucidated. Thus, patients with epilepsy are at increased risk for fractures, and PHT and CBZ lower vitamin D levels, but only the former drug has been clearly shown to affect bone density, and it is not clear that reduction in vitamin D is responsible. In a similar vein, patients with epilepsy have significantly higher rates of cardiovascular and cerebrovascular disease, and there is mounting evidence that PHT and CBZ are clearly responsible for elevations of several strong and well-validated vascular surrogate markers, but epidemiologic data to compare the rate of vascular events attributable to specific drugs is lacking.

Another common thread is that the effects of individual drugs may differ; thus, while CBZ and PHT appear to have similar effects on cholesterol, testosterone, and 25-OHD levels, their effects on Lp(a) and bone density are different. More research is clearly needed to explore the mechanisms underlying these effects.

In addition, further research is needed to fill in these gaps regarding the effects of specific drugs on particular health outcomes (e.g. myocardial infarction, fracture); such studies will be large and challenging epidemiologically and will require independent (not corporate) funding. Equally important will be determination of the other side of the clinical equation: the relative efficacy of the various drugs for seizure prevention. This is all the more relevant given the availability of a whole generation of AEDs, almost all chemically distinct, that likely avoid adverse metabolic effects. Funding for such research should hopefully be readily available in light of the U.S. government's newfound interest in comparative treatment efficacy. Study of this kind is desperately needed in

the field of epilepsy, where we lack any data to answer one of our most basic practice questions: if a patient is seizure-free on a drug, what is the likelihood that she will remain seizure-free on a different drug?

The latter point is germane to the concluding opinion of this review. The author is already on record with his views regarding the practical import of the manifold metabolic effects elucidated herein (32, 41). At the very least, all patients taking an older-generation AED, whether for epilepsy or any other indication, should be aggressively screened for the appropriate clinical consequences; this would include cardiac risk serology for those taking inducers, signs and symptoms of PCOS for women taking VPA, and bone density testing (as well as vigilance against potential drug interactions) in both groups. If metabolic complications are found, they may be treated, but switching to another AED may well be better medical practice, as it might reduce costs, complications, and co-morbidities. In any case, the specter of these potential metabolic complications make it difficult to recommend the use of older AEDs as first-line therapy at the present time, pending better data regarding comparative efficacy.

Acknowledgements

Dr. Mintzer has received research funding from Johnson and Johnson, UCB Pharma, Eisai, Ovation, Medtronic and Neuropace. He has functioned as a consultant for Eisai and Sepracor and a speaker for UCB Pharma and Glaxo SmithKline. His research, described herein, was funded by the Epilepsy Foundation through the Edna Flaig Evans Trust.

Table 1. Studies comparing 25-hydroxyvitamin D levels in carbamazepine-treated patients and in subjects not taking an enzyme-inducing drug

| Study | CBZ pts | Control pts | % Δ from ctrl |
|----------------------------|---------|-------------|---------------|
| Pack 2008(11) | 23.4 | 25.2* | -7% |
| Kim 2007(4) | 23.0 | 33.8* | -32% |
| Mintzer 2006(6) | 20.4 | 27.5 | -26% |
| Pack 2005(10) | 21.0 | 30.0* | -33% |
| Verrotti 2002(8) | 26.2 | 27.0 | -3% |
| Verrotti 2000(9) | 38.7 | 39.0 | -1% |
| Lamberg-Allardt 1990(5) | 22.8 | 27.5 | -17% |
| Gough 1986(2) | 22.9 | 39.2 | -42% |
| Hoikka 1984(3) | 11.1 | 17.6 | -37% |
| Tjellesen 1983(7) | 22.9 | 26.2 | -13% |

Controls were untreated with any antiepileptic drugs except for the values marked with an asterisk*, which represent lamotrigine-treated control subjects. CBZ = carbamazepine. % Δ from ctrl = percentage difference in 25-hydroxyvitamin D levels in the CBZ-treated group relative to the control group. All values in ng/mL.

TABLE 2. Vascular mortality and morbidity in patients with epilepsy, general population studies

| Mortality Study | Study size (follow-up) | Standardized mortality ratio | 95% confidence interval |
|------------------------|----------------------------------|---|--|
| Ding et al(25) | 5,114 person-years | Myocardial infarction: 10.7* | 5.6 - 95.3 |
| Nilsson et al(26) | 53,250 person-years | Ischemic heart disease: 2.5* Cerebrovascular disease: 5.3* | 2.3 - 2.7 4.9 – 5.8 |
| Cockerell et al(27) | 7,528 person-years | Ischemic heart disease: 1.2 Cerebrovascular disease: 3.7* | 0.7 - 1.9 2.4 – 5.4 |
| Annegers et al(28) | “Approached 10,000 person-years” | Ischemic heart disease: 1.2 IHD, patients age 25 - 44: 5.7* IHD, patients age 45 - 64: 2.5* | 0.9 – 1.5 1.8 – 13.3 1.4 – 4.1 |
| Morbidity study | Total epilepsy population | Morbidity (prevalence) ratio | 95% confidence interval |
| Gaitatzis et al(29) | N=5843 | Ischemic heart disease: 1.34* Ischemic heart disease (age < 65): 1.63* Cerebrovascular disease: 6.96* Cerebrovasc. Disease (age <65): 14.19* | 1.19 – 1.5 1.34 – 1.98 6.38 – 7.6 12.04 – 16.73 |
| Annegers et al(28) | N=725 | Ischemic heart disease: 1.63* IHD, idiopathic epilepsy only: 1.49* | 1.2 – 2.15 1.00 – 2.15 |

Data marked with an asterisk* are statistically significant (i.e. the lower limit of the 95% confidence interval is ≥ 1). IHD: ischemic heart disease.

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