



## Plaques on the Wall: Inducing Anticonvulsant Use and Atherogenesis

### Effects of Long-Term Antiepileptic Drug Monotherapy on Vascular Risk Factors and Atherosclerosis.

Chuang Y-C, Chuang H-Y, Lin T-K, Chang C-C, Lu C-H, Chang W-N, Chen S-D, Tan T-Y, Huang C-R, Chan SHH. *Epilepsia* 2012;53(1):120–128.

**PURPOSE:** Long-term therapy with antiepileptic drugs (AEDs) has been associated with metabolic consequences that lead to an increase in risk of atherosclerosis in patients with epilepsy. We compared the long-term effects of monotherapy using different categories of AEDs on markers of vascular risk and the atherosclerotic process. **METHODS:** One hundred sixty adult patients who were receiving AED monotherapy, including two enzyme-inducers (carbamazepine, CBZ; and phenytoin, PHT), an enzyme-inhibitor (valproic acid, VPA), and a noninducer (lamotrigine, LTG) for more than 2 years, and 60 controls were enrolled in this study. All study participants received measurement of common carotid artery (CCA) intima media thickness (IMT) by B-mode ultrasonography to assess the extent of atherosclerosis. Other measurements included body mass index, and serum lipid profile or levels of total homocysteine (tHcy), folate, uric acid, fasting blood sugar, high sensitivity C-reactive protein (hs-CRP), or thiobarbituric acid reactive substances (TBARS). **KEY FINDINGS:** Long-term monotherapy with older-generation AEDs, including CBZ, PHT, and VPA, caused significantly increased CCA IMT in patients with epilepsy. After adjustment for the confounding effects of age and gender, the CCA IMT was found to be positively correlated with the duration of AED therapy. Patients with epilepsy who were taking enzyme-inducing AED monotherapy (CBZ, PHT) manifested disturbances of cholesterol, tHcy or folate metabolism, and elevation of the inflammation marker, hs-CRP. On the other hand, patients on enzyme-inhibiting AED monotherapy (VPA) exhibited an increase in the levels of uric acid and tHcy, and elevation of the oxidative marker, TBARS. However, no significant alterations in the markers of vascular risk or CCA IMT were observed in patients who received long-term LTG monotherapy. **SIGNIFICANCE:** Patients with epilepsy who were receiving long-term monotherapy with CBZ, PHT, or VPA exhibited altered circulatory markers of vascular risk that may contribute to the acceleration of the atherosclerotic process, which is significantly associated the duration of AED monotherapy. This information offers a guide for the choice of drug in patients with epilepsy who require long-term AED therapy, particularly in aged and high-risk individuals.

### Commentary

Ascertaining the adverse effects (AEs) of an antiepileptic drug (AED) can be a very tricky business. It seems like it should be easy: just give it to a bunch of people and see what happens. That works for some AEs, but for others it can be quite problematic. For example, some AEs are vague and hard to define (e.g., fatigue), and some can be confounded by their relationship to the underlying disease (e.g., cognitive impairment, depressed mood). The clearest way to establish causation is with a randomized trial, which can sometimes address these issues. But there are other side effects that are relatively rare (e.g., aplastic anemia) or that only occur over a protracted period of time (e.g., osteoporosis). For these latter types of AEs,

no randomized trial could be large enough or long enough to establish causation, thereby requiring Plan B.

Plan B can take a number of different forms. In the case of very rare and serious side effects, surveillance of spontaneous reporting systems is often utilized; for example, this was enough to establish the life-threatening effects of felbamate (1). Of course, spontaneous reports will only occur for very dangerous or unusual occurrences, so this isn't suitable for more mundane or common AEs. Another possibility is simply to do a large epidemiologic study of a database to ascertain whether the AE in question occurs more frequently in patients treated with a given drug than in patients not treated with that drug. This may seem like the most straightforward approach, but it is actually greatly complicated by a number of issues, including the appropriate choice of control group, inherent differences in populations, differential prescribing habits, and data limitations in large databases. These concerns make performing such studies deceptively difficult, though it has been done to ascertain the incidence of fractures with enzyme-



inducing AED use (2, 3). Unfortunately, the results have been conflicting, which illustrates the challenge of this approach.

Yet another alternative, and one that is particularly salient for slowly developing AEs, is to examine surrogate markers for a given pathologic condition. This approach has been used commonly in the area of bone effects, demonstrating, for example, that there is significantly greater decline in bone mass over time with the use of phenytoin (PHT) (4, 5). Bone density is such a strong surrogate marker for fracture risk that this is tantamount to showing that PHT increases the incidence of fractures.

Vascular effects of AEDs are another area in which the latter approach has been employed. The extensive research into surrogate markers for coronary artery disease provides many opportunities to examine the potential effects of AEDs on vascular health. Among the most well-established markers for vascular disease is serum cholesterol, a measure of such long standing that it has seeped deeply into lay consciousness. This makes it quite easy for patients—and physicians—to understand the implications of the finding that enzyme-inducing AEDs raise cholesterol by an average of 26 mg/dL, to say nothing of the other vascular risk markers that are likewise elevated by enzyme-inducing AED use (6).

Now the next step in the pathologic process of vascular disease has been examined by Chuang et al., with striking results. This group assessed another surrogate marker: the combined thickness of the intimal and medial layers of the carotid artery (CIMT). CIMT is, in essence, a measure of the amount of atherosclerotic plaque on the carotid wall, so it is not surprising to find that it is a strong marker for risk of stroke. But it is also a strong and well-established surrogate marker for myocardial infarction risk (7), presumably because the state of the carotid reflects the state of the rest of the body's vasculature as well.

A previous study by these authors, along with two other studies from different groups, demonstrated that CIMT is elevated in drug-treated epilepsy patients, though there was no separation of individual drugs' effects (8–10). This time, the authors assessed CIMT in epilepsy patients treated with one of four drugs—carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), or lamotrigine (LTG)—in monotherapy. They verified previous findings that serum lipids, homocysteine, and C-reactive protein were all significantly elevated in patients taking the former two enzyme-inducing drugs (6, 11). They also demonstrated, for the first time, that CIMT was significantly elevated in patients taking one of the three older drugs, but not those taking LTG, relative to controls. Even more striking was the finding that duration of therapy with CBZ, PHT, or VPA—but not LTG—was significantly correlated with CIMT, after correction for age and sex.

Thus, the picture this paints is one of drugs that gradually and steadily increase the amount of atherosclerotic plaque over years of use—exactly what one would expect from the serologic data showing increases in lipids and other vascular risk markers. The particular value of this study is that its results, using a surrogate marker separate from those measured in blood, point in a concordant fashion toward the notion that the enzyme-inducing AEDs may well be responsible for accelerated atherogenesis. And, while surrogate markers cannot

fully replace direct examination of the disease state, when multiple lines of evidence converge, the underlying concept becomes that much harder to dismiss.

If there's a wrinkle here, it's with the results vis-à-vis VPA, which has been shown in a number of studies to reduce serum lipids (12, 13). Despite this, the Chuang et al. study shows increased CIMT in patients taking the drug, leaving us with a situation in which two reliable surrogate markers point in different directions. Epidemiologic study of vascular risk has suggested that risk of myocardial infarction and vascular death may be lower in VPA-treated patients (14), implying that the CIMT findings of the present study may be off-base with regard to VPA-treated patients.

The latter point underscores the fact that even well-validated surrogate markers can sometimes lead us astray. The presumptive atherogenic effects of enzyme-inducing AEDs will be more convincingly proved when there is good epidemiologic evidence that the drugs are associated with clinical disease, and very little such data exist at present (15). Nonetheless, the surrogate marker data in this article and in the others discussed here should be cause for concern among all who prescribe these drugs. At present, the only prudent course of action is to perform cardiac screening of some kind—serologic or imaging—in all patients who take enzyme-inducing AEDs. And if doing so unduly increases the cost, worry, and hassle of using these agents, then perhaps it's time to think twice before prescribing them in the first place.

by Scott Mintzer, MD

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