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Antiepileptic Drugs and Markers of Vascular Risk

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Opinion statement

The most-used treatments for epilepsy worldwide are older-generation drugs such as phenytoin, carbamazepine, phenobarbital, and valproic acid, which have prominent enzymatic effects. Our sense of comfort with these treatments is starting to fade, however, as more and more potential long-term consequences of these drugs come to light. Epidemiologic studies demonstrate that ischemic disease of the heart and brain is more common among patients with epilepsy. Enzyme-inducing drugs are associated with elevations in a host of surrogate markers of vascular risk, suggesting that they could be responsible for increased rates of cardiovascular and cerebrovascular disease. The enzyme-inhibiting drug valproate may have adverse consequences of its own pertaining to glucose and lipid metabolism. These effects stand in addition to those well established in the literature regarding bone metabolism, hormonal abnormalities, and drug–drug interactions. Because patients with epilepsy require medication for years, and often for life, it is difficult to justify the long-term use of these agents when there are capable alternatives. Many of the adverse effects of the older drugs appear to be rapidly reversible, prompting consideration of whether patients who are currently treated with these agents should be switched to alternative therapies, even in the absence of obvious side effects. Newer medications without effects on hepatic enzymes likely do not have these chronic metabolic consequences, and we recommend their use over older-generation drugs whenever possible.

Introduction

Patients with epilepsy often require lifelong treatment with medications. Biochemical properties and empiric evidence suggest that some seizure medications may have chronic metabolic effects. In particular, there is growing support for the idea that some treatments for epilepsy are associated with changes in vascular risk markers, prompting us to reevaluate epidemiologic data linking epilepsy to vascular disease and to review the current literature on the relationship between commonly used antiepileptic drugs (AEDs) and markers of increased vascular risk.

Epidemiology of epilepsy and vascular disease

Multiple epidemiologic studies have shown positive correlations between epilepsy and comorbid vascular disease. Patients with epilepsy suffer mildly increased mortality from ischemic heart disease, with standardized mortality ratios (SMRs) between 1.2 and 2.5 in several studies in developed countries [1,2]. One Chinese study demonstrated an SMR of 10.7 for myocardial infarction [3], and comorbid myocardial ischemia as reported on death certificates was positively correlated with epilepsy with an odds ratio of 16 [4]. Nonfatal

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ischemic heart disease is also significantly elevated 34% to 63% above controls [1,5]. Stronger correlations between epilepsy and cerebrovascular disease are seen, with mortality ratios 3.7 to 5.3 [2,6] and morbidity close to 7 in one study [5]. The latter correlation is to be expected, as stroke is a known causative factor for epilepsy. Whether having epilepsy increases subsequent cerebrovascular risk is more difficult to demonstrate in the literature, as the cross-sectional nature of most studies makes it difficult to infer causation.

Very little data exist regarding the effects of specific AEDs on the incidence of vascular events. One Finnish study found a lower prevalence of ischemic heart disease in epilepsy patients, and furthermore found that patients who were on enzyme-inducing AEDs had 29% lower mortality due to heart disease [7]. When a Norwegian group performed a survey of coronary risk profiles on patients with epilepsy and controls, however, they found no significant differences [8]. It is possible that the Finnish study reflects genetic variants in the isolated, homogeneous Finnish population, as Finnish studies of serologic risk factors also yield different results than those in other populations (as discussed below).

Mechanism of enzyme induction effects on serum cholesterol

The enzyme-inducing AEDs phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), and primidone (PRM) increase the activity of the hepatic cytochrome P450 system, which is involved in synthesis of serum cholesterol. Animal data show that a particular enzyme, CYP51A1, catalyzes the conversion of lanosterol into cholesterol intermediates [9].When these intermediates build up through inhibition of the enzyme, they in turn inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and slow the synthesis of cholesterol [10]. It follows that induction of CYP51A1 should therefore increase cholesterol production through metabolism of these intermediates and reduced feedback inhibition. While the pathway has not been explicitly studied in humans to our knowledge, this mechanism engenders some predictions regarding the effects of certain AEDs in patients. For example, an enzyme-inducing AED such as CBZ should increase serum cholesterol. On the other hand, valproic acid (VPA), an enzyme-inhibiting medication, should decrease metabolism of intermediates and increase feedback inhibition, thereby decreasing production of cholesterol. One might also conjecture that pharmacogenetic heterogeneity of these effects could result in varying effects of a given AED on lipids in different patients.

Enzyme-inducing AEDs and lipid levels

Studies suggest that the enzyme inducers CBZ, PB, PHT, and PRM each lead to increased serum cholesterol levels. Elevated total cholesterol and low-density lipoprotein (LDL) fractions were associated with CBZ use in multiple cross-sectional and prospective studies of children and adults with epilepsy [11–20], and were increased after CBZ use in healthy adult male volunteers [21]. Increases in cholesterol persist after 5 years of therapy [22], but appear to be reversible 1 year after cessation of treatment [15,16]. Much less data are available regarding PHT, with some cross-sectional studies showing modest nonsignificant elevations in total cholesterol along with elevated high-density lipoprotein cholesterol (HDL-C) [23,24]. The only repeated-measures study performed demonstrated that PHT appears to be responsible for elevations of both total cholesterol and atherogenic cholesterol fractions [25••, Class III]. PB similarly has been associated with higher total cholesterol and LDL fractions in children [12–16,26] and adults [19]. PRM, used commonly for treatment of essential tremor, was associated in a single study with higher total cholesterol and HDL-C fractions as well as total cholesterol/HDL-C ratios in children with epilepsy [27]. Thus, enzyme-inducing AEDs increase total cholesterol as would be expected by the enzyme induction hypothesis, with most studies indicating that their effects on specific lipid fractions favor an atherogenic profile (Table 1).

In a crossover study at our center, CBZ and PHT users who were switched to the non-enzyme-inducing agents levetiracetam or lamotrigine had significant decreases in total cholesterol and non-HDL-C fractions [25••, Class III]. This is supportive of the enzyme induction hypothesis and is also in agreement with an earlier study in which patients on CBZ who were switched to oxcarbazepine (which has only weak enzyme-inducing effects) had decreased total serum cholesterol [28]. Further support for this hypothesis is the evidence for the effect of enzyme inhibition on lipids. Several studies have shown that VPA is associated with lower serum LDL and/or total cholesterol in children and adults [13,15,16,19,24,29]. Thus, both enzyme-inducing and enzyme-inhibiting drugs yield data that are consistent with the animal model previously described.

Effects of AEDs on lipoprotein(a), C-reactive protein, and homocysteine

Other vascular risk markers may be negatively affected by enzyme-inducing AEDs as well. Lipoprotein(a) is composed of apolipoprotein(a) linked to an LDL-like particle and is a modest but independent risk factor for coronary heart disease [30]. Elevated lipoprotein(a) has been associated with CBZ treatment in several studies [17,21,25,26], while PHT and PB do not have consistent relationships with lipoprotein(a) levels [14–16,25,26,31]. This suggests that the metabolic effects of inducing AEDs are not uniform. The effects of VPA on lipoprotein(a) remain unclear, with the available evidence conflicting [14–17,26]. C-reactive protein (CRP), an acute phase reactant predominantly synthesized in the liver, is an inflammatory marker that is also a marker of vascular disease. Baseline CRP levels are strongly associated with subsequent cardiovascular events independently of LDL and other known cardiovascular risk markers [32–34]. CRP was elevated in a population on mixed AEDs, compared with normal controls [35•, Class III]. In our own center's study, patients who were switched from inducing to non-inducing agents had sharp reductions in CRP [25••, Class III]. The mechanism through which enzyme-inducing AEDs affect CRP is not certain. Thus, vascular risk markers beyond traditional lipid levels appear to be negatively affected by treatment with various inducing AEDs (Table 1).

Another possible vascular marker is homocysteine (HCY), a nonessential amino acid with prothrombotic properties. Though its role as a causative factor for myocardial infarction is uncertain, there is evidence suggesting that HCY might be a risk factor for stroke and dementia [36]. There are several cross-sectional studies of CBZ and PB use in which the drugs are associated with elevated HCY [37,38,39•, Class III], and a recent study found hyperhomocysteinemia associated with the sometime enzyme-inducing AEDs oxcarbazepine and topiramate [39•, Class III]. Two prospective studies in children found that CBZ raised HCY [40,41]. In our center's recent study, switching to a non-inducing drug from PHT resulted in significantly decreased HCY levels, while switching from CBZ had no effect [25••, Class III]. Studies of VPA have been inconsistent, with some showing that the drug elevates HCY levels [40,41] and others showing a decline in HCY after treatment [42]. Newer drugs that do not affect hepatic enzymes, however, show no correlations with hyperhomocysteinemia [39•, Class III], nor do they appear to affect serum HCY levels [25••, Class III; 42]. It is unknown whether drug-induced hyperhomocysteinemia contributes to increased stroke or dementia risk. Although the effects of hyperhomocysteinemia in the epilepsy population remain to be defined, one investigation found that elevated HCY levels in epilepsy patients may be normalized by folate supplementation [43].

Valproic acid and the metabolic syndrome

The enzyme inhibitor VPA is also associated with adverse metabolic effects distinct from those seen with enzyme induction. Obesity is seen in up to 71% of patients treated with VPA, particularly female patients. Postulated mechanisms include effects on appetite or carnitine

depletion leading to decreased fatty acid metabolism [44]. The metabolic syndrome—abdominal obesity, glucose intolerance, elevated triglycerides, low HDL-C, and hypertension—was found in 41% of women treated with VPA, compared with 5.3% with CBZ and none with lamotrigine or topiramate [45]. A recent prospective study in children who were followed for at least 2 years on VPA found that 40% developed obesity, and of those, 43% developed the metabolic syndrome, whereas non-obese patients did not [46]. Although this evidence supports the notion that drug-induced weight gain drives the development of the metabolic syndrome, Pylvanen and colleagues [47] found that obese VPA-treated patients had higher insulin than obese controls, suggesting that obesity may not be solely responsible for the metabolic syndrome in VPA-treated patients. It is not known whether these adverse metabolic effects contribute to increased vascular risk in VPA-treated patients over the long term.

Effects of AEDs on carotid intima-media thickness

Although enzyme-inducing medications appear to increase lipids and other serologic markers of vascular risk, the question remains as to whether these changes in risk markers actually increase the incidence of ischemic events in treated patients. Ischemic vascular disease can have many causes, but if inducer-treated epilepsy patients were truly subject to higher rates of myocardial infarction and stroke from the aforementioned serologic alterations, one would expect that vascular disease in these patients would have an atherosclerotic etiology. Carotid intima-media thickness (CA-IMT) as assessed by ultrasound is considered to be a surrogate measure of atherogenesis and has been strongly correlated with risk of both stroke and myocardial infarction in several prospective studies [48–50]. One study of patients treated mainly with enzyme-inducing drugs showed higher CA-IMT relative to controls [51]. Another investigation found that CBZ-treated patients had higher CA-IMT than VPA-treated patients, who in turn had higher CA-IMT than untreated patients with epilepsy [52]. When carotid thickness was studied in children treated with VPA alone, treated patients had significantly higher CA-IMT without a difference in serum lipids [53]. CA-IMT in epilepsy patients appears to be positively correlated with duration of AED therapy [35•, Class III], though these investigators did not separate their findings according to different groups of AEDs. These data confirm that enzyme-inducing AEDs may be associated with increased vascular risk over time, consistent with their effects on serologic markers. However, they also suggest that VPA might increase vascular risk through mechanisms unknown. It is possible that epilepsy itself might increase vascular risk, which might then be further exacerbated by enzymatically active AEDs. Future studies are needed to compare CA-IMT between those treated with newer-generation non-enzyme-inducing agents such as levetiracetam, lamotrigine, and topiramate.

Treatment: Conclusions

The risk of vascular complications from AED therapy is an area of legitimate concern in need of further study. Enzyme-inducing AEDs in particular may pose a risk by increasing atherogenic serum cholesterol fractions. Associations between inducers and other vascular risk markers such as lipoprotein(a), CRP, and HCY might also contribute to a propensity for treated patients to develop vascular disease. These findings might be linked to apparent accelerated atherosclerosis in these patients, as reflected in CA-IMT, and could explain why there is a consistent association of epilepsy with comorbid vascular disease. VPA may also have adverse long-term metabolic consequences, including obesity, insulin resistance, and the metabolic syndrome, via mechanisms that are presumably distinct from those activated by the inducing drugs. Pharmacoepidemiologic studies are needed to determine the long-term vascular effects of both older and newer AEDs.

In the meantime, it behooves physicians to be aware of potential long-term side effects of these drugs and to be receptive to the use of non-inducing drugs, which may be safer alternatives. A

thornier issue remains what should be done for patients already treated with enzyme inducers, particular those under good control. One approach would be to survey for known metabolic complications, which would include not only the vascular risk markers mentioned here, but measurements of vitamin D and bone density, review for potential sexual dysfunction in men, and detailed assessment of potential interactions with co-medications. When all of these are normal, it may be argued that there is no compelling reason to alter therapy, though in our view one must keep in mind the likelihood that further metabolic complications are likely to be revealed in the future pertaining to the use of what are obviously biochemically "dirty" drugs. When metabolic abnormalities *are* found, these may be treated, though in some cases (eg, osteopenia) we lack adequate evidence to ensure that further treatments will suffice, and in other cases (eg, hyperlipidemia) it will consign the patient to additional medications, with their attendant costs and potential side effects. In such cases the authors believe that it may be a wiser choice to consider switching the patient to a non-inducing AED, thereby avoiding complications in therapy. This is also almost certainly the better approach from a cost standpoint, particularly in light of the fact that many of the non-inducing AEDs are now available in lower-cost generic formulations.

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Table 1

Effects of enzyme-inducing and enzyme-inhibiting AEDs on serum vascular risk markers

AEDs by type	Vascular risk marker Total cholesterol	Lipoprotein(a)	CRP	Homocysteine
Enzyme-inducing				
CBZ	↑^	↑^	↑	↑/↔
PHT	↑	↔	↑	↑
PB	↑^	↑/↔	?	↑
PRM	↑	?	?	?
Enzyme-inhibiting				
VPA	↓	↑/↓	?	↑/↓

↑^—increases: evidence from multiple studies, including studies with repeated measures; ↑—increases: evidence from single studies or cross-sectional data only; ↓—decreases: evidence from single studies or cross-sectional data only; ↔—no effect demonstrated; ↑/↔—increased or not significantly changed in several studies; ↑/↓—conflicting data (increases or decreases); ?—not sufficient data; AED—antiepileptic drug; CBZ—carbamazepine; CRP—C-reactive protein; PB—phenobarbital; PHT—phenytoin; PRM—primidone; VPA—valproic acid.

See text for references.