Effects of Antiepileptic Drugs on Lipids, Homocysteine, and C-Reactive Protein

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Objective: The widely prescribed anticonvulsants phenytoin and carbamazepine are potent inducers of cytochrome P450 enzymes, which are involved in cholesterol synthesis. We sought to determine whether these drugs have an effect on cholesterol and other serological markers of vascular risk.

Methods: We recruited 34 epilepsy patients taking carbamazepine or phenytoin in monotherapy whose physicians had elected to change treatment to one of the noninducing anticonvulsants lamotrigine or levetiracetam. Fasting blood samples were obtained both before and 6 weeks after the switch to measure serum lipid fractions, lipoprotein(a), C-reactive protein, and homocysteine. A comparator group of 16 healthy subjects underwent the same serial studies.

Results: In the epilepsy patients, switch from either phenytoin or carbamazepine produced significant declines in total cholesterol (-24.8mg/dl), atherogenic (non–high-density lipoprotein) cholesterol (-19.9mg/dl), triglycerides (-47.1mg/dl) (all $p < 0.0001$), and C-reactive protein (-31.4%; $p = 0.027$). Patients who stopped taking carbamazepine also had a 31.2% decline in lipoprotein(a) level ($p = 0.0004$), whereas those taken off phenytoin had a decrease in homocysteine level (-1.7μmol/L; $p = 0.005$). All of these changes were significant when compared with those seen in healthy subjects ($p < 0.05$). Results were similar whether patients were switched to lamotrigine or levetiracetam.

Interpretation: Switching epilepsy patients from the enzyme-inducers carbamazepine or phenytoin to the noninducing drugs levetiracetam or lamotrigine produces rapid and clinically significant amelioration in several serological markers of vascular risk. These findings suggest that phenytoin and carbamazepine may substantially increase the risk for cardiovascular and cerebrovascular disease.

Antiepileptic drugs (AEDs) are utilized extensively in the general population. A recent large survey of ambulatory practice data demonstrated that an AED was mentioned at more than 13% of outpatient healthcare visits in the United States in 2003 to 2004, a proportion that approaches that of penicillins or corticosteroids.[1]

Although many new AEDs have been introduced over the past 15 years, the consensus first choice for focal seizures has traditionally been carbamazepine (CBZ).[2] Moreover, proprietary marketing data and clinical experience indicate that phenytoin (PHT) remains one of the most commonly prescribed AEDs in the United States. Both of these AEDs exhibit potent induction of the cytochrome P450 (CYP450) enzyme system.[3] This has led to questions regarding their potential long-term effects, because CYP450 enzymes are known to figure prominently in numerous important aspects of metabolism.[4] In addition to their well-established effects on drug metabolism, both steroid metabolism and vitamin D metabolism are altered by treatment with enzyme inducers.[5–7]

Another area of metabolism that is worthy of study is that of the potential effects of AEDs on vascular risk. Epidemiological studies suggest that patients with epilepsy have a greater prevalence of cardiovascular and cerebrovascular disease than is seen in the general population.[8–10] Because most patients with epilepsy are treated with AEDs, one must consider whether the drugs might be playing a role in this increased risk.

CYP450 enzymes catalyze key steps in cholesterol synthesis.[4] Previous investigations have suggested that treatment with CBZ is associated with increases in total cholesterol (TC) and various lipid fractions, includ-

ing low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum triglycerides (TRIG).[11–16] The evidence pertaining to this issue is limited by several factors, however. Many of the studies are done in children.[14–17] Some of the data are contradictory.[18–20] There has been little investigation of PHT.[12] Finally, the large majority of the studies are cross sectional, rather than using a repeated-measures within-patient design.[12–14]

Several other serological indices of vascular risk also bear investigation. C-reactive protein (CRP) is a highly important marker for vascular risk that is independent of serum lipids. Nonetheless, because all drugs that reduce cholesterol also significantly reduce CRP,[21] one might wonder whether the enzyme-inducing AEDs, if they affect cholesterol, could also affect CRP. To our knowledge, CRP has never been studied in patients with epilepsy or in any patients taking AEDs.

Lipoprotein(a) [Lp(a)] is also a significant independent risk factor for cardiovascular disease.[22] There is some evidence that CYP450-inducing AEDs may increase serum Lp(a),[11,16,23] though it is unclear why this might occur.

Finally, the prothrombotic amino acid homocysteine (HCY) has been implicated as a risk factor for vascular events.[24] Although some recent studies have raised questions regarding its relevance,[25] it may well be a significant risk factor for stroke[26] and dementia.[27] A few studies have suggested that CBZ may increase serum HCY, presumably by inducing the metabolism of B vitamins, which are essential cofactors for its metabolism.[28,29] These studies too are limited by cross-sectional design.

The goal of this research was to examine lipid, HCY, and CRP levels in patients who were being switched from CBZ or PHT to one of the noninducing AEDs lamotrigine (LTG) or levetiracetam (LEV), affording us the opportunity to analyze drug-induced changes using a repeated-measures within-patient design.

Subjects and Methods

Subjects

We recruited adult epilepsy patients from the Jefferson Comprehensive Epilepsy Center and Thomas Jefferson University Hospital who were taking CBZ or PHT in monotherapy and whose physician had decided, for clinical reasons, to cross them over to monotherapy with LTG or LEV. The large majority of patients enrolled had focal epilepsy. We chose LEV and LTG as the noninducing drugs because they are commonly used at our center. Patients taking a lipid-lowering agent were excluded from the study. In addition, patients taking any B-vitamin–containing preparation were excluded from the vitamin and HCY analyses (but were enrolled for analysis of all other study variables).

A group of healthy subjects without epilepsy who were not taking AEDs, lipid-lowering agents, or B-vitamin preparations was recruited for comparison. We age- and sex-matched the healthy subjects with the drug-treated patients as closely as possible in a ratio of approximately 1:2.

Design

After a fast of at least 10 hours, each subject provided a morning blood sample for measurement of the study variables, including TC; LDL-C; HDL-C; TRIG; Lp(a); CRP; folate, pyridoxine (B6), and cyanocobalamin (B12); HCY; and the serum AED concentration.

Each drug-treated patient was then switched from the old drug (PHT or CBZ) to the new drug (LTG or LEV) using a regimen individually determined by the treating physician. The minimum target medication dosage was 100mg twice daily for LTG and 500mg twice daily for LEV.

Each patient was scheduled for follow-up serological studies at least 6 weeks after the final dose of CBZ or PHT had been taken. Although most follow-up studies were obtained at the 6-week mark, a small number were delayed as long as 16 weeks related to subject compliance. For the healthy subjects, the follow-up fasting blood draw was obtained 10 weeks after the first draw to approximate the time between blood samples in the epilepsy patients. Subjects were not informed of any results from the first blood draw until the second draw was completed. At the follow-up, a fasting blood sample was obtained once again for all of the aforementioned serological studies; for the drug-treated patients, this included the serum level of the old drug (to verify compliance with the medication switch) and the serum level of the new drug. Clinical evaluation of response to therapy (eg, occurrence of seizures, side effects) was performed as per typical clinical practice in our center and is to be reported in a separate analysis.

Laboratory Analyses

All samples were allowed to clot for 15 minutes, centrifuged, and then placed on ice (for short-term storage) or refrigerated at −70°C (for longer-term storage, if needed) until processing. Lipid studies were performed by a specialty lipid laboratory (Liposcience, Raleigh, NC). TC, HDL, LDL, TRIG, and Lp(a) were each measured directly on an AU400 analyzer (Olympus, Center Valley, PA). TC was measured using cholesterol oxidase and peroxidase together with 4-aminoantipyrine and phenol to produce a colored quinoneimine product whose absorbance was then measured at 520nm. TRIG was measured using a reagent (Carolina Liquid Chemistries, Brea, CA) that produces breakdown products via a series of enzymes that lead to coupling with 4-aminoantipyrine and measurement at 520nm similar to that described for TC. HDL-C and LDL-C were measured directly using specialized detergents that solubilize only HDL or LDL particles, respectively, releasing only that cholesterol fraction to be measured in the presence of a chromogen at a wavelength of 560nm. Total allowable error for measurements of TC is 5% or less, and total allowable error for HDL-C and directly measured LDL-C is 10%. Lp(a) was measured using an immunoturbidimetric assay (Denka Seiken, San Francisco, CA) that is fairly insensitive to apolipoprotein(a) isoform, resulting in reduced calibration bias; the coefficient of variation for this assay was 1.1 to 2.3%. The same laboratory also performed CRP and HCY mea-

surements, the former using a high-sensitivity chemiluminescent immunological assay on an Immulite 2000 analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY) with a coefficient of variation of 3.1 to 5.2%, and the latter using a competitive immunoassay (Carolina Liquid Chemistries, Brea, CA) on the AU400, with a coefficient of variation of 1.4 to 1.9%. AED levels were performed by the Thomas Jefferson University Hospital laboratory, and the B-vitamin levels by Quest Diagnostics (Horsham, PA).

Statistical Analyses

Individual patient changes from draw 1 to 2 were analyzed in a general linear model if a normal distribution assumption was valid as determined by examination of the residuals. Because the large intersubject variability inherent in the study measures would tend to obscure any effects of the drugs, all models controlled for the baseline (draw 1) value. If violations of normal distribution assumptions were observed because of outlier contamination, robust MM regression was used.[30] The measures of Lp(a) and CRP, which had skewed distributions, were log-transformed before computing the change from draw 1 to 2, and the changes on the log scale were analyzed in a robust regression model.

The mean change from draw 1 to 2 for each study measure was computed for all patients and then compared with the mean change in healthy subjects. We hypothesized that the change in each study variable would be similar, regardless of whether the patient began the study taking PHT or CBZ. We also anticipated that the choice of target drug (LEV or LTG) would have no impact on the change in each outcome measure. However, the drugs were separately examined so that, if there appeared to be significant differences in the change in any study measure between patients who were taking CBZ and those taking PHT, then the change in that study measure could be analyzed separately by initial drug. When this was not the case, results were pooled to maximize statistical power. Analogously, if there appeared to be significant differences in the change in any study measure between patients switched to LEV and those switched to LTG, then the change in that study measure was analyzed separately by target drug; otherwise, results were pooled. Interaction effects could not reliably be sought because of sample size and the nonrandomized nature of the study. In all models, age, sex, and race (white vs nonwhite) were considered as covariates. They were retained in the model only if significant. Data were analyzed in SAS 9.1 (SAS Institute, Cary, NC) and S-Plus (Insightful Corporation, Seattle, WA).

Results

Baseline Characteristics

Thirty-four epilepsy patients and 16 healthy subjects provided complete data for the study. The mean age of the epilepsy patients was 38.8 (range, 18–64) years, of whom 18 (53%) were women and 28 (82%) were white. Among the healthy subjects, mean age was 38.7 (range, 22–74) years, of whom 8 (50%) were women and 12 (75%) were white. There were no differences between the two groups for these demographics. Of the drug-treated subjects, 15 were taking PHT, 11 of

whom were switched to LEV and 4 to LTG. The remaining 19 epilepsy patients were taking CBZ, of whom 5 were switched to LEV and 14 to LTG. The time between blood draws averaged (± standard deviation) 104 ± 42.5 days in the epilepsy patients (median, 94 days; range, 41–248 days) and 94 ± 36.4 days in the healthy subjects (median, 78.5 days; range, 69–201 days). Only 5 patients, and none of the normal subjects, were smokers. An additional 15 epilepsy patients enrolled and provided a first blood sample but subsequently dropped out of the study for noncompliance, difficulty in returning for fasting phlebotomy, adverse effects on the new AED, or worsening of seizures requiring change in therapy. Baseline data from these patients are not included here.

Lipid Measures

The summary results for serum lipids, together with the other primary outcome measures, are shown in the Table. At baseline, the mean values of all lipid measures except LDL-C were modestly greater in the drug-treated patients than in the healthy subjects, though none of these differences reached statistical significance. This is not surprising, because the study was not powered to detect these unpaired differences. However, baseline Lp(a) levels were greater in CBZ-treated patients than either PHT-treated or healthy subjects ($p = 0.02$, Kruskal–Wallis test).

The change in each vascular risk marker between baseline and second blood draw is also shown in the Table. After controlling for the baseline value, the predicted mean change in TC after switch from inducing to noninducing AED was -24.9mg/dl ($p < 0.0001$). A modest, nonsignificant change of -8.5mg/dl was seen in the healthy subjects ($p > 0.1$) (Fig 1). The difference between the predicted change in the drug-treated patients and the change in the healthy subjects was significant ($p = 0.027$). Changes in the drug-treated patients were similar regardless of initial drug (CBZ or PHT) or final drug (LTG or LEV).

The large majority of the change in TC was attributable to the atherogenic, non-HDL cholesterol fraction, which declined 19.9mg/dl in the epilepsy patients irrespective of initial drug ($p < 0.0001$) but only 6.2mg/dl in the healthy subjects ($p > 0.1$). The difference between these two groups was significant ($p = 0.046$). Declines in HDL-C were minor in the healthy subjects and in those who were taken off PHT but were significant, though modest (-6mg/dl model predicted), in patients switched off CBZ ($p = 0.001$). The comparison among these three groups was not significant, however ($p > 0.1$).

Although overall atherogenic (non-HDL) cholesterol declined notably, the drug-related decline in LDL-C was considerably smaller (-7.8mg/dl model predicted), yielding only a trend toward significance ($p = 0.097$)

Table. Mean Change in Each Outcome Measure between Draws 1 and 2

Outcome (units)	Group	N	Baseline Value (mean ± SD)	Mean Change (predicted)	95% CI	p (within group)	p (between groups)
Total cholesterol (mg/dl)	CBZ/PHT	34	217.9 ± 45.5	−24.8	−32.9 to −16.7	**<0.0001**	**0.027**
	NML	16	203.3 ± 43.9	−8.5	−20.2 to +3.2	NS	
Non-HDL-C (mg/dl)	CBZ/PHT	34	154.5 ± 43.8	−19.9	−27.3 to −12.4	**<0.0001**	**0.046**
	NML	16	148.9 ± 40.5	−6.2	−17.1 to +4.7	NS	—
HDL-C (mg/dl)	CBZ	19	64.6 ± 21.1	−6.0	−9.2 to −2.7	**0.001**	NS
	PHT	15	59.0 ± 16.3	−1.1	−4.6 to +2.4	NS	NS
	NML	16	54.4 ± 12.6	−2.5	−6.0 to +0.9	NS	—
LDL-C (mg/dl)	CBZ/PHT	34	129.9 ± 42.8	−7.8	−17.1 to +1.46	0.097	NS
	NML	16	136.9 ± 39.3	−9.0	−22.3 to +4.30	NS	—
TRIG (mg/dl)	CBZ/PHT	34	141.8 ± 125.9	−47.1	−58.6 to −35.6	**<0.0001**	**0.016**
	NML	16	118.3 ± 69.7	−21.8	−38.6 to −5.0	**0.012**	—
Lp(a)[a] (mg/dl)	CBZ	19	30.6 ± 21.8	−30.6%	−42.3% to −16.4%	**0.0004**	**0.03**
	PHT	15	26.5 ± 38.0	−10.0%	−26.5% to +10.1%	NS	NS
	NML	16	17.3 ± 19.8	−5.6%	−22.4% to +14.8%	NS	—
CRP[a] (mg/L)	CBZ/PHT	33	4.2 + 5.3	−31.4%	−50.9% to −4.3%	**0.027**	**0.037**
	NML	16	4.0 + 5.0	+7.9%	−74.1% to +33.2%	NS	—
HCY (μmol/L)	PHT	12	13.1 ± 6.6	−1.7	−2.7 to −0.6	**0.005**	**0.04**
	CBZ	15	11.1 ± 4.2	+0.3	−1.3 to +0.8	NS	NS
	NML	16	11.5 ± 5.3	+0.1	−1.2 to +1.0	NS	—

Mean changes reported are those predicted by the model, which corrects for the baseline value. For lipoprotein(a) [Lp(a)] and C-reactive protein (CRP), mean changes and confidence intervals are expressed in percentages because logarithmic transformation was used to analyze the data. The penultimate column gives the p value for the change within an individual group from baseline to second blood draw, whereas the last column gives the p value for the difference in the mean change between the drug group and the healthy subjects. CRP in one patient was excluded as an outlier. Statistically significant values ($p < 0.05$) are shown in bold.
[a]Geometric mean, standard deviation (SD) on log scale.
CI = confidence interval; CBZ/PHT = carbamazepine- and phenytoin-treated patients combined; NML = healthy subjects; NS = nonsignificant ($p > 0.1$); HDL-C = high-density lipoprotein cholesterol; PHT = phenytoin-treated patients; CBZ = carbamazepine-treated patients; LDL-C = low-density lipoprotein cholesterol; TRIG = triglycerides; HCY = homocysteine.

and showing no difference from the similar small decline seen in the healthy subjects ($p > 0.1$). There was a sizable decline in TRIG seen after switch to noninducing AED (−47.1mg/dl model predicted from baseline value, $p < 0.0001$). Healthy subjects also showed a decline in TRIG at the second measurement relative to the first (−21.8mg/dl predicted; $p = 0.012$), but the change was significantly smaller ($p = 0.016$). These results were similar regardless of which drug the patient was taking initially, and none of the lipid measures was affected by the choice of final (noninducing) AED.

In contrast, changes in Lp(a) differed greatly depending on the initial AED. Patients taken off PHT had no change in Lp(a), nor did the healthy subjects (both $p > 0.1$), whereas patients taken off CBZ had a mean decline in Lp(a) of about one third ($p = 0.0004$). The decline in the latter group was significant relative to the change seen in the healthy subjects ($p = 0.03$). Once again, these results were similar regardless of whether the patient was switched to LEV or LTG.

Figures 2 and 3 show the changes in cholesterol fractions and Lp(a) in each individual subject between the baseline and second blood sample. For cholesterol frac-
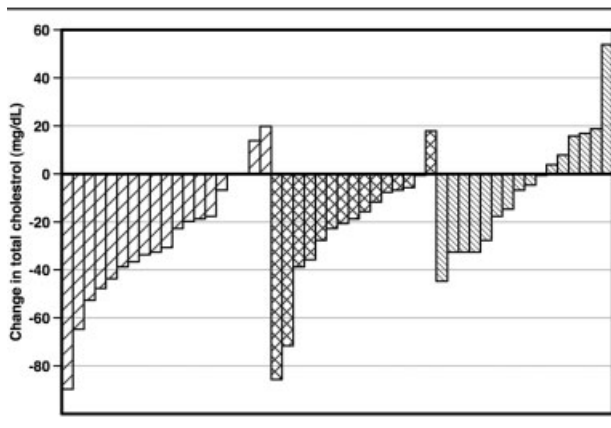
Fig 1. Change in total cholesterol seen in each subject at the second blood draw relative to the baseline value. Subjects are arranged numerically within each group, starting with the largest decline. Carbamazepine-treated patients on the left; phenytoin-treated in the center (cross hatched), normal subjects on the right (narrow diagonals).

tions, some variability was seen in the healthy subjects, presumably reflecting the inherent fluctuation in the measures themselves. However, the degree of variability seen in the drug-treated epilepsy patients was more pronounced. For example, although most patients had moderate declines in atherogenic (non-HDL) cholesterol, others had enormous declines of 70mg/dl or more, whereas still others changed minimally or even increased. Similar variability was seen in other cholesterol fractions. For Lp(a), less variability was seen, and the effect of taking patients off CBZ was remarkably consistent; this is best appreciated when the data are analyzed using a logarithmic scale (see Fig 3B).

Nonlipid Measures

CRP values were similar in the groups at baseline. After accounting for the baseline value, both CBZ- and PHT-treated patients had an average reduction in CRP of approximately one third (see the Table) after switch to either of the two noninducing drugs ($p = 0.027$). The healthy subjects showed no change at the second measurement, and the difference between the two groups was significant ($p = 0.037$). The choice of noninducing AED had no bearing on these results. Individual patient data are shown in Figure 4.

A secondary analysis was done to determine whether the change in CRP was related to the change in any of the lipid factors. The change in CRP was found to be significantly correlated with the change in HDL-C ($r = 0.327$; $p = 0.023$) and the change in Lp(a) ($r = 0.43$; $p = 0.002$) but not with any of the other lipid measures (all $p > 0.1$).

Analysis of changes in HCY showed a notable difference between the two enzyme-inducing drugs. At baseline, the healthy subjects and the CBZ-treated pa-
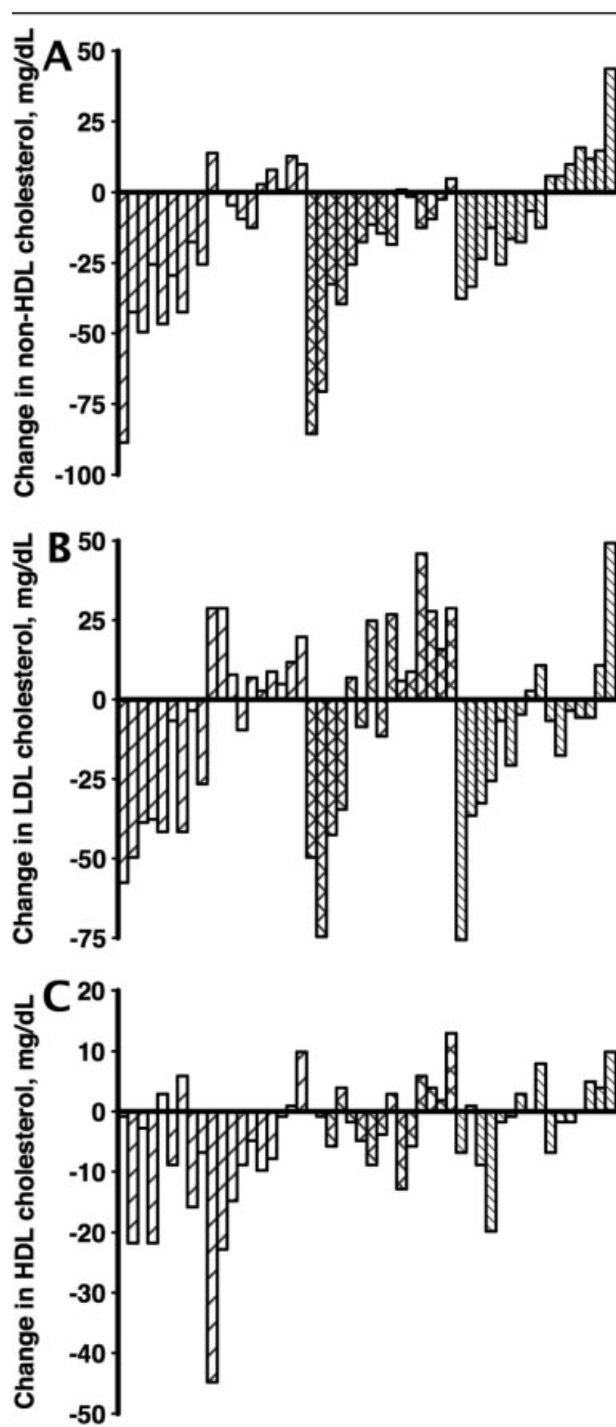

Fig 2. Change in various cholesterol fractions seen in each subject at the second blood draw relative to the baseline value. Each vertical column represents the same patient in each of the three charts, with the patients arranged in the same order as in Figure 1. HDL = high-density lipoprotein; LDL = low-density lipoprotein. Carbamazepine-treated patients on the left, phenytoin-treated patients in the center (cross-hatched), normal subjects on the right (narrow diagonals).
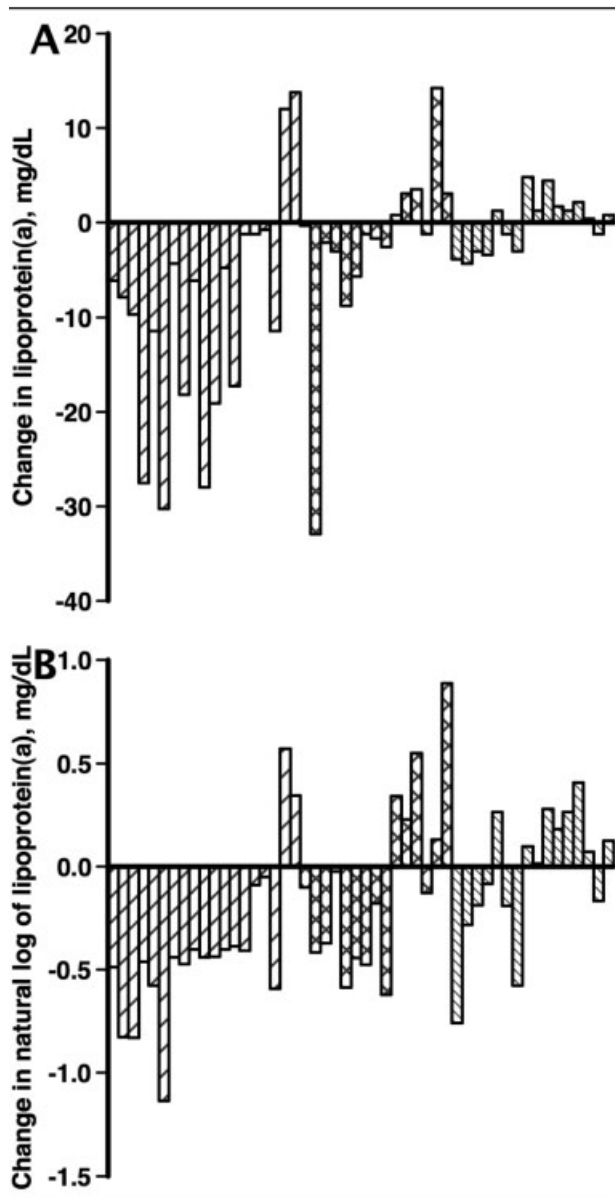
Fig 3. Change in lipoprotein(a) seen in each subject at the second blood draw relative to the baseline value. (A) Absolute change is shown, with patients arranged by value within each group; (B) same data as in (A) (with the subjects in the same order) plotted using a logarithmic scale. Carbamazepine-treated patients on the left, phenytoin-treated patients in the center (cross-hatched), normal subjects on the right (narrow diagonals).

healthy subjects ($p = 0.04$). Again, the choice of non-inducing target AED had no impact on the results.

A secondary analysis was done to determine whether

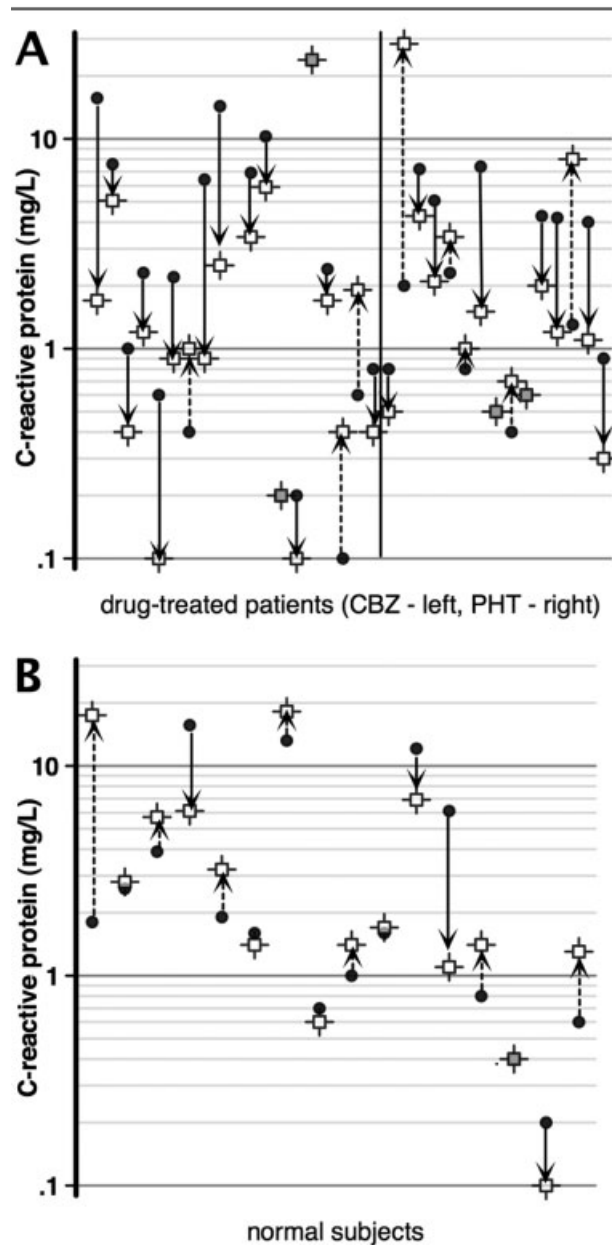drug-treated patients (CBZ - left, PHT - right)

normal subjects

Fig 4. Values of C-reactive protein (CRP) in each subject at baseline (solid circle) and the second blood draw (open box with whiskers). Each subject's two data points are shown in a single vertical column, with the points connected by a solid downward-facing arrow (if CRP declined at the second measurement) or a dotted upward-facing arrow (if it increased). Patients whose values remained essentially unchanged are shown with overlapping symbols and no arrow. (A) Drug-treated patients, with carbamazepine (CBZ)-treated patients left of the solid black line and phenytoin (PHT)-treated patients to the right. (B) Normal untreated subjects. Note the logarithmic scale.

tients had similar values; PHT-treated patients were modestly (but insignificantly) greater. Both the healthy subjects and the patients switched off CBZ showed no change in HCY at the second measurement. In contrast, patients who were taking PHT showed a mean model-predicted decline of -1.7μmol/L in HCY after switching to LEV or LTG, which was significant both in itself ($p = 0.005$) and in comparison with the

changes in B-vitamin levels could be responsible for the PHT-related change seen in HCY. No differences between the groups were seen for vitamin B6 levels. Vitamin B12 levels declined in the healthy subjects at the second draw (predicted -57pg/ml after adjustment for baseline value; $p = 0.02$), whereas they increased in the CBZ- and PHT-treated patients (predicted $+57$pg/ml, $p = 0.01$; $p = 0.001$ for the difference between the drug-treated and healthy subjects), but this cannot explain the disparity between the two drugs for HCY. Folate levels were virtually unchanged in the healthy subjects and in the CBZ-treated patients, but showed an increase in patients taken off PHT ($+2.7$ng/ml predicted, $p = 0.069$). The comparison among the three groups was not significant, however.

Discussion
Switching epilepsy patients from the inducing AEDs PHT or CBZ to the noninducing drugs LTG or LEV results in significant declines in both atherogenic cholesterol and CRP. In addition, patients switched away from CBZ experience a large decline in Lp(a), whereas those switched off PHT experience a decline in HCY. The total of these changes would be expected to result in a sizable decline in the risk for ischemic vascular disease. Furthermore, all of these changes occur within 6 weeks of discontinuing PHT or CBZ.

These findings are largely consistent with and significantly extend those of other investigations. Studies of CBZ-treated patients have mostly demonstrated increased TC levels compared with a control group, with most also showing increased LDL-C and HDL-C in this population.[11–17] Our findings regarding TC and HDL, though not LDL, are similar to those other investigations. In addition, we found that PHT has similar effects. For the other measures, some studies have suggested CBZ-induced increases in Lp(a),[11,16] whereas others have not.[17] We found that CBZ exerts a substantial effect on Lp(a), whereas PHT has none. Our results regarding HCY are in contrast with previous studies showing increases with CBZ treatment.[28,29] In this study, the difference between the effects of CBZ and those of PHT on HCY may be attributable to the differential effects of the drugs on serum folate, though there was only a trend toward significance, probably because of limited statistical power. Lastly, to our knowledge, this is the first study to examine CRP in patients with epilepsy, or among those taking AEDs for any indication.

The large majority of studies in this area have been cross-sectional rather than using a repeated-measures within-patient design. This can be a significant limitation because the variation in a given measure within the population under study can be so large as to obscure the effects of drug treatment. This may be responsible for some of the apparent contradiction be-

tween investigations in this area, not only for studies of lipids and vascular risk factors, but also for studies of bone metabolism and other metabolic effects of AEDs.

A large amount of interindividual variability was seen in each of the main study measures. It is possible that the range of drug-induced responses seen in Figures 1 to 4 reflects pharmacogenetic differences. This too could be an important cause of apparently contradictory data regarding AED effects. If there are prominent pharmacogenetic effects at play, it may become necessary to consider the effects of the drugs on each individual patient rather than relying on population averages.

Based on the cardiovascular epidemiological literature, the changes in serological measures seen here with CBZ or PHT treatment would be expected to increase the risk for an ischemic vascular event by approximately 36% (see Supplementary material). This is consistent with epidemiological data, most of which demonstrates that patients with epilepsy have increased cardiovascular mortality and morbidity rates.[8–10] Furthermore, carotid intima-media thickness, a well-validated surrogate marker for cardiovascular and cerebrovascular risk, is significantly increased in patients with epilepsy, particularly among those taking CBZ.[23,31] This further reinforces the relevance of atherosclerotic vascular disease risk as an important and disproportionate problem in this population.

Contradictory data do exist. One group has produced a series of studies suggesting that inducing AEDs reduce serum cholesterol.[18,19] In addition, one case–control study suggested that patients treated with inducing AEDs are actually at lower risk for dying of vascular causes relative to the general population.[32] It is worth noting that all of these contradictory data come from Finland, raising the possibility of a variant pharmacogenetic effect in that relatively homogeneous population. If true, this would reinforce the need to evaluate metabolic AED effects on an individual patient basis.

It is highly likely that the changes in lipids seen in this study relate to the effects of CYP450 induction. There is ample basis for the belief that deinduction of the CYP450 system after withdrawal of CBZ or PHT would reduce lipid values. Experimental animals given the antifungal agent ketoconazole, a potent *inhibitor* of CYP450 enzymes, develop reductions of more than 50% in the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, with a consequent decline in serum cholesterol.[33] This appears to be mediated by inhibition of CYP51A1, another crucial enzyme in the cholesterol synthetic pathway, causing upstream feedback inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase.[33] Human patients treated with the AED valproate, another potent CYP450 inhibitor,

have lower cholesterol levels than healthy control subjects.[12,14,34] One would, therefore, expect that CYP450 *induction* should reduce feedback inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and *increase* cholesterol. Though direct studies are needed, our findings are wholly consistent with this hypothesis.

The finding that CBZ and PHT affect CRP was unexpected. The full clinical implication of this finding remains to be determined; although CRP is an independent risk factor for ischemic vascular disease,[35] the question remains whether CRP is a direct cause of disease or simply an epiphenomenal marker for other pathological processes. Nonetheless, evidence from a recent genetic study tying allelic variants in the CRP gene to increased vascular disease risk suggests a direct pathological role for CRP.[36] The fact that CRP reductions were similar regardless of which inducing or noninducing drug the patient was taking strongly implies that CYP450 induction is responsible for CRP level increase. It is unclear whether this is a direct effect or a secondary effect, however. Because all drugs that reduce cholesterol also appear to reduce CRP,[21] we performed secondary correlational analyses to ascertain whether changes in lipid fractions might be linked to changes in CRP in individual patients. We found significant positive correlations between changes in CRP and those in HDL and Lp(a), though the significance of these is entirely unclear. Although the effects of CBZ and PHT on cholesterol fractions and CRP were similar, the two drugs appear to differ sharply in some other effects, including those on Lp(a) and HCY, indicating that their effects are not uniform. Our results should prompt further study into the underlying pharmacological properties of these two widely used agents, as well as other CYP450-inducing drugs.

This investigation has a number of important limitations. The rather modest sample size could have limited our ability to detect significant relations. Yet this makes our findings all the more striking for their significance and attests to their robustness. Furthermore, obtaining a much bigger sample would be quite challenging given the considerable clinical complexities involved in systematically altering AED therapy in a large number of patients.

The latter point suggests another limitation: an imperfect comparator group. The ideal control would have involved taking a group of CBZ- and PHT-treated patients and randomizing them to either continue on their existing drug or switch to a noninducer; such a study is impossible within the bounds of reasonable clinical practice, however. Another limitation is that we studied the metabolic effects of change in AED therapy only among patients coming *off* inducing drugs. We were unable to study patients starting on inducing drugs because this is not compatible with our typical clinical practice. We plan to directly address this limitation in an ongoing study.

This work addresses only the short-term effects of AED switch. It is possible that the changes seen here may be only transient in nature. Some preliminary data in a small sample of our patients suggest that this is not the case, and examination of the longer-term effects of AED switch is a part of our ongoing studies.

Even pending further investigation, we believe the clinical implications of these findings are considerable. Lipid and CRP metabolism can now be added to the list of CYP450-dependent processes that are known to be adversely affected by enzyme-inducing AEDs. Recent drug development has resulted in the availability of a number of AEDs that lack substantial effects on the CYP450 system, yet are equal in efficacy to the older drugs.[37,38] As a consequence, we believe that the constellation of metabolic findings from our investigation and others casts significant doubt on the use of CBZ and PHT as first-line agents for the long-term treatment of epilepsy, and we suggest that it might be prudent for those who treat seizures to eschew their use in favor of other agents. In addition, in light of the potential for chronic adverse medical consequences, the practice of switching patients from inducing to noninducing AEDs may be worth consideration.

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