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Scott Mintzer
Thomas Jefferson University, scott.mintzer@jefferson.edu

Christopher T Skidmore
Thomas Jefferson University, Christopher.Skidmore@jefferson.edu

Sara J Rankin
Thomas Jefferson University

Inna Chervoneva
Thomas Jefferson University

Edward Pequinot
Thomas Jefferson University

See next page for additional authors

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Authors

Scott Mintzer, Christopher T Skidmore, Sara J Rankin, Inna Chervoneva, Edward Pequinot, David M Capuzzi, and Michael R Sperling

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CONVERSION FROM ENZYME-INDUCING ANTIEPILEPTIC DRUGS TO TOPIRAMATE: EFFECTS ON LIPIDS AND C-REACTIVE PROTEIN

Scott Mintzer, MD[1*], Christopher T. Skidmore, MD[1], Sara J. Rankin, MS[1], Inna Chervoneva, PhD[2], Edward Pequinot, MS[2], David M. Capuzzi, MD, PhD[3], Michael R. Sperling, MD[1]

[1] Jefferson Comprehensive Epilepsy Center, Department of Neurology, [2] Division of Biostatistics, Department of Pharmacology and Clinical Therapeutics, and [3] Divisions of Cardiology and Endocrinology, Department of Medicine, and Department of Biochemistry, Thomas Jefferson University

*Corresponding author: Dr. Mintzer, 900 Walnut Street, Suite 200, Philadephia PA 19107; e-mail scott.mintzer@jefferson.edu; phone 215-955-1222; fax 215-955-0606

ABSTRACT

Purpose: We previously demonstrated that converting patients from the enzyme-inducers phenytoin or carbamazepine to the non-inducers levetiracetam or lamotrigine reduces serum lipids and C-reactive protein (CRP). We sought to determine if the same changes would occur when patients were switched to topiramate, which has shown some evidence of enzyme induction at high doses. We also examined the effects of drug switch on low-density lipoprotein (LDL) particle concentration.

Methods: We converted 13 patients from phenytoin or carbamazepine monotherapy to topiramate monotherapy (most at doses of 100-150 mg/day). Fasting lipids, including LDL particle concentration, and CRP were obtained before and ≥6 weeks after the switch. A group of normal subjects had the same serial serologic measurements to serve as controls.

Results: Conversion from inducers to topiramate resulted in a -35mg/dL decline in total cholesterol (p=0.033), with significant decreases in all cholesterol fractions, triglycerides, and LDL particle concentration (p≤0.03 for all), as well as a decrease of over 50% in serum CRP (p<0.001). Alterations in cholesterol fractions and CRP remained significant when compared to those seen in normal controls.

Conclusions: Changes seen when inducer-treated patients are converted to TPM closely mimic those seen when inducer-treated patients are converted to lamotrigine or levetiracetam. These findings provide evidence that CYP450 induction elevates CRP and serum lipids, including LDL particles, and that these effects are reversible upon deinduction. Low-dose TPM appears not to induce the enzymes involved in cholesterol synthesis.

INTRODUCTION

Antiepileptic drugs (AEDs) that induce the cytochrome P450 (CYP450) system alter metabolism in a variety of ways that may become apparent when patients are started on or taken off these drugs. Patients switched from the enzyme-inducing agents phenytoin (PHT) or carbamazepine (CBZ) to the non-inducing drugs levetiracetam (LEV) or lamotrigine (LTG) experience a sizable drop in serum lipids, along with changes in other serologic indices of vascular risk, including C-reactive protein (CRP)(Mintzer et al., 2009). Other studies have suggested that patients treated with PHT or CBZ may have higher lipid levels than controls; at least one such study measured before and after treatment and found that CBZ produced significant elevation of lipids(Bramswig et al., 2003; Nikolaos et al., 2004). Furthermore, the potent CYP450 inhibitor ketoconazole has been shown to reduce cholesterol production in experimental animals(Gibbons, 2002), and this effect is corroborated clinically by the finding that patients taking valproate, an AED with CYP450-inhibiting properties, have lower cholesterol levels than controls(Nikolaos et al., 2004). These findings imply that serum lipids — and possibly CRP — parallel the activity of the CYP450 enzyme system, so that treatment with a CYP450 inducing agent increases lipids, and upon withdrawal of the drug they return to the patient's baseline.

A number of the older AEDs — including PHT, CBZ, phenobarbital and primidone — are well-known to be potent CYP450 inducers, while many of the newer-generation agents — such as LEV, LTG, or gabapentin — clearly have no CYP450 effects. For some of the newer agents, however, the situation with regard to CYP450 effects is less clear-cut. For example, oxcarbazepine (OXC) has been shown to induce CYP3A4 and

3A5, leading to important drug interactions, and it also likely induces the metabolism of vitamin D(Mintzer et al., 2006). Yet it appears not to have effects on lipids like those of CBZ(Isojarvi et al., 1994), suggesting that it shares some of the metabolic effects of enzyme inducing agents, but not all of them.

Here we describe the effects on lipids and CRP when patients are switched from either CBZ or PHT to topiramate (TPM), a newer-generation AED that is widely used for both seizures and migraines. TPM induces at least some CYP450 enzymes at high doses(Rosenfeld et al., 1997), but there is no evidence of any CYP450 induction when it is used at low to moderate doses(Doose et al., 2003). Its effects on lipids relative to those of other AEDs have not been studied but are pertinent to the care of patients who are chronically treated with the drug. In addition to measurements of traditional lipid fractions, CRP, and lipoprotein(a), we also present data on changes in low-density lipoprotein (LDL) particle concentration, as this measure, which is distinct from the measurement of the amount of cholesterol carried by LDL particles (LDL-C), may have independent predictive power for myocardial infarction(Rosenson et al., 2002).

METHODS

Subjects

The study involved 13 patients from the Jefferson Comprehensive Epilepsy Center or Thomas Jefferson University Hospital who were a) being treated with PHT or CBZ in monotherapy for at least 1 month and b) being crossed over to monotherapy with TPM based upon the recommendation of the treating epileptologist at our center. Drug

conversion was undertaken due to incomplete seizure control, side effects, or concerns about the long-term effects of enzyme-inducing AED treatment. Of these 13 patients, one was being treated with fenofibrate (which is not subject to CYP450 induction) and another was taking fluvastatin and ezetimibe; the latter patient was excluded from measurement of traditional lipid fractions. All other patients were taking no lipid-lowering agents. As a comparator group, we utilized the same cohort of 16 normal control subjects described in our previous report who were not being treated with any anticonvulsant or lipid-lowering medications(Mintzer et al., 2009). These subjects provided fasting blood samples for the same serologic measures on two occasions approximately 10 weeks apart.

Protocol

Each subject provided two fasting blood samples: one while still on treatment with the old (enzyme-inducing) AED, and one after switch to TPM monotherapy. The latter sample was obtained at least 6 weeks after the last dose of the old AED to ensure sufficient time for complete de-induction of the CYP450 system. The schedule for conversion from the older drug to TPM was individually determined by the patient's treating epileptologist. The target dose of TPM was also determined by the patient's treating physician based upon perceived clinical need; this was 50-75 mg twice daily in all cases except for a single patient who was titrated up to 150 mg twice daily. Subjects were instructed to fast at least 10 hours prior to each blood draw, and samples were analyzed for lipid factions, lipid particle concentrations, and Lp(a), as well as for the serum level of the AED the patient was taking at that time.

Lipid measurements were performed by a specialty lipid laboratory (Liposcience, Raleigh, NC). The analytical specifications are as

documented in our previous investigation(Mintzer et al., 2009). LDL-C was measured directly rather than being calculated using the Friedwald formula. Lipid particle concentrations were measured using a nuclear magnetic resonance spectroscopy technique, yielding a signal which can resolve the different classes of lipoproteins with a high degree of accuracy. Drug levels were performed at the Thomas Jefferson University Hospital laboratory.

Statistical analysis

Data were analyzed using a general linear model when they were normally distributed; where examination of residuals suggested non-Gaussian distribution due to outliers, which was the case for total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), robust MM regression was utilized instead(Yohai, 1987). Lp(a) is well-known to have a non-normal distribution, so log transformation was used for these data prior to calculation of the change between draw 1 and draw 2. The mean change from draw 1 to draw 2 was calculated for each measure in each subject, with comparison then made between the patients and the normal subjects for each measure. In addition, all models controlled for the baseline (draw 1) value (with slopes permitted to differ among the two groups of subjects if those slopes were found to be significantly different). The numbers reported for within group change from draw 1 to draw 2 reflect the predicted change in an individual measure given the average draw 1 value for the group. Between-group comparison is based on simultaneous testing of the difference in slopes and intercepts of the regression on draw 1 when slopes were found to be significantly different. Otherwise the regression lines are parallel with the same slope and between-group comparison is the usual comparison of the intercepts. No corrections were made for multiple comparisons since many of these

measures are dependent upon each other. Data were analyzed in SAS 9.1 (SAS Institute, Cary, NC) and S-Plus (Insightful Corporation, Seattle, WA).

RESULTS

Baseline characteristics

Of the 13 patients completing the study, 6 were switched from CBZ to TPM and 7 were switched from PHT to TPM. Five of the CBZ-treated patients and 2 of the PHT-treated patients were female. The mean age of the whole cohort was 54 years (range 22 - 88). They had been treated with CBZ or PHT for anywhere between 30 days and 35 years. In the CBZ-treated patients, drug levels at baseline ranged from 5.5 to 10.4 µg /mL (mean: 7.6). In the PHT-treated patients, drug levels ranged from 8.9 to 30.1µg /mL except for a single patient with a level of 3.3µg /dL (mean: 14.0 µg /mL). The second blood draw was always obtained at least 6 weeks after the last dose of the enzyme-inducing AED; the total time between draws also included a period of several weeks to titrate up TPM and then titrate down the old drug. The time between the first and second blood draws in these patients ranged from 76 to 301 days (mean: 169 days). The normal comparator group (n=16), described in the previous publication (Mintzer et al., 2009), was 50% female, with a younger mean age (39 years) than these study subjects; however, neither age nor gender was a significant covariate for any of the study variables, so the reported results are unadjusted for these.

Standard lipid measures

Data on standard lipid measures for patients (n=12) and normal controls (n=16) are presented in the Table. (Note that when the same raw data for normal subjects is analyzed together with a different drug-treated group, the model-predicted values are slightly different; thus, the numbers for the normal subjects differ a bit from those presented in the previous paper, even though it is the same data.) Total cholesterol (TC) declined a mean of 35 mg/dL in the epilepsy patients after switch to TPM (p=0.033; Fig. 1). This decline was significantly reflected in all lipid fractions, including non-HDL-C (-18 mg/dL, p=0.011), LDL-C (-18 mg/dL, p=0.023), serum triglycerides (TRIG)(-54 mg/dL, p<0.001), and HDL-C (-10 mg/dL, p=0.001). The single patient who was switched to high-dose TPM, with one of the higher TPM levels in the study, had a decline of 37mg/dL in TC after switch.

When the changes observed in the drug-treated patients were compared to those seen in the normal subjects, there was a trend toward a larger decline in TC and a strong trend toward a larger decline in non-HDL-C among the patients (p=0.09 and 0.051 respectively), while the changes LDL-C, HDL-C, and non-HDL-C were significantly greater in the patients (p=0.019, 0.024, and 0.051 respectively).

Additional vascular risk markers

Data regarding non-traditional vascular risk markers for patients (n=13) and controls are also presented in the Table. Lp(a) did not decline significantly after drug switch. LDL particle concentration declined significantly in the patients after switch to TPM (-21%, p=0.002). The change in Lp(a) remained marginally significant when compared to the change seen in the normal subjects (p=0.09). CRP dropped by more than

half after switch to TPM (-59%; p=0.001), a change which remained significant in comparison to the change seen in the normal subjects (p=0.018). The decline was highly consistent between patients (Fig. 2).

DISCUSSION

This is, to our knowledge, the first study to directly compare lipid levels under TPM treatment to those obtained under treatment with other AEDs. It is also the first to report CRP levels in TPM-treated patients, and the first to report LDL particle concentration in any epilepsy or AED-treated patients. Our findings indicate that patients switched from the enzyme-inducing drugs PHT or CBZ to the newer-generation agent TPM experience substantial declines in both CRP and serum lipids, including LDL particles. The significance of the findings in spite of the modest sample size attests to the robust nature of the effect.

Lipid levels in TPM-treated neurological patients have been examined in few previous investigations, only one of which was in adults with epilepsy; that study included only female patients(Franzoni et al., 2007; Kocer et al., 2008; Genc et al., 2010). These studies found no change in TC after TPM treatment; one found a small decline in HDL-C only(Genc et al., 2010). Thus, it is unlikely that TPM itself produces a significant effect upon serum lipids. Furthermore, the results of the present study are quite comparable to those seen when patients are switched from inducers to LEV or LTG(Mintzer et al., 2009), two drugs which are both structurally and biochemically unrelated to TPM. This provides additional strong evidence in a separate group of patients in favor of the hypothesis that CYP450-

inducing agents increase lipid levels, so that switching to non-inducing drugs results in deinduction and a return to baseline values.

Additionally, these data, combined with those of previous studies, suggest that TPM at the doses studied here (predominantly 100-150 mg daily) may not affect the activity of the CYP450 system, at least with regard to the enzymes responsible for cholesterol synthesis. This is clinically relevant, since TPM has been found to induce the metabolism of oral contraceptive hormones at high doses, but not at low doses(Rosenfeld et al., 1997; Doose et al., 2003), making it unclear whether its effects on the CYP450 system are dose-dependent, enzyme-specific, or both. It is noteworthy that the single patient in the study who was switched to high-dose TPM (300mg daily), and who had one of the higher TPM levels in the patient cohort, nonetheless had a drop of 37mg/dL in TC, suggesting that the drug may not affect the cholesterol synthetic pathways even at high doses. It is possible that the CYP450-inducing effects of TPM are both enzyme- and concentration-specific, occurring only for certain enzymes, and even then only at certain serum levels. Targetted study of patients taking high-dose TPM is clearly needed to establish this.

While involvement of the CYP450 system in cholesterol synthesis and metabolism is well-established, this is not the case for the synthesis of CRP, whose metabolic pathways remain somewhat obscure. CRP has recently been shown to be elevated in patients with epilepsy relative to controls(Tan et al., 2009), but our previous investigation, to our knowledge, is the only one that has examined this phenomenon in a drug-specific fashion(Mintzer et al., 2009). The current findings reinforce those of the previous study, demonstrating that conversion of patients from inducers to TPM results in sharp declines in CRP similar to those seen when patients are switched to LTG or LEV. As with lipids, this indirectly but strongly supports the idea that CYP450 induction increases CRP, and that CRP

levels decline after switch to a non-inducer through de-induction. It remains unclear whether the rise in CRP prompted by enzyme-inducing agents reflects broader upregulation of inflammatory pathways or an isolated epiphenomenon.

This is, to our knowledge, the only study that has ever examined LDL particle concentration in patients with epilepsy or in patients taking AEDs. The measurement of LDL particles is likely a more accurate reflection of an atherogenic diathesis than the standard measurement of LDL-C(El Harchaoui et al., 2007); the latter is, in effect, a surrogate marker for the former, which until relatively recently was not measurable in an economically feasible manner. The analogy is sometimes made to automotive travel, with LDL particles carrying cholesterol the way cars carry passengers; measuring LDL-C is like measuring the number of *people* traveling on a highway, when what one really wants to know is the number of *vehicles*. In a similar vein, evidence suggests that LDL particle concentration has predictive power for cardiovascular events over and above that provided by the measurement of LDL-C and other traditional risk factors(Rosenson et al., 2002; Cromwell and Otvos, 2004). The present data demonstrate that there is a significant decline in LDL particle number when patients are switched from inducers to TPM, corroborating that there is a significant improvement in atherogenic lipid fractions following CYP450 deinduction.

One factor that is unique to TPM among available AEDs is its proclivity to reduce body weight(Verrotti et al, 2011). Weight loss itself may have a modest downward effect on serum lipids and CRP, so that it is possible that some of the effects observed in the present study could be due not just to CYP450 de-induction, but also to positive effects of TPM on these markers. Unfortunately some of our study subjects provided blood samples at outside laboratories because they lived too far away to return to

our center, and this precluded the implementation of body weight measurement into our protocol. But the results obtained in the present patients are similar to those seen in other patients who were switched to LTG or LEV, both of which are weight-neutral drugs(Mintzer et al., 2009). Thus, we believe it is unlikely that the weight loss effects of TPM are a major contributor to our findings.

In sum, our results demonstrate that patients taking CBZ or PHT experience substantial declines in multiple markers of vascular risk when switched to TPM, similar to those engendered by switch to LEV or LTG. There are declines in HDL-C as well, but these are likely to be overwhelmed by the negative effects on pro-atherogenic markers (non-HDL-C, TRIG, LDL particles, CRP). Thus, patients may be at higher risk for ischemic co-morbidities while under treatment with the former agents than while under treatment with TPM or other newer-generation, largely non-inducing drugs. Epidemiologic studies will be necessary to determine whether these serologic changes correspond to increases in endpoint clinical events such as myocardial infarction or stroke. Based upon our data, there is no reason to believe that the use of low-dose TPM in neurologic practice would increase the risk of ischemic vascular disease. Thus, there is good reason to believe that the differences between AEDs in serologic risk factors demonstrated here (and in previous studies) are clinically important.

DISCLOSURES

Dr. Skidmore has engaged in promotional speaking for UCB Pharma.

Dr. Sperling been a consultant for Dainippon Sumitomo Pharma and has engaged in promotional speaking for UCB Pharma and Pfizer.

Dr. Capuzzi has been a consultant for Abbott Laboratories and has engaged in promotional speaking for Glaxo SmithKline and Merck Schering Plough

In addition, Drs. Mintzer, Sperling and Skidmore have engaged in contracted research through Thomas Jefferson University with UCB Pharma, Lundbeck, Marinus, Ovation, Sepracor, Medtronic, NeuroPace, and Vertex.

Dr. Chervoneva, Ms. Rankin and Mr. Pequinot have nothing to disclose.

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TABLE

Table: Lipid data in patients switched from an enzyme-inducing antiepileptic drug to topiramate

Outcome (mg/dL except as indicated)	Group	N	Draw 1 Mean (95% CI)	Change from Draw 1 to Draw 2 (95% CI)	p-value (within group)	p-value (between groups)
Total Cholesterol	Normals	16	203 (180, 227)	-9 (-35, +17)	0.473	
	Patients	12	227 (201, 253)	-35 (-66, -3)	**0.033**	0.090
Non-HDL-C	Normals	16	149 (127, 170)	-5 (-17, +6)	0.371	
	Patients	12	173 (151, 195)	-18 (-31, -4)	**0.011**	0.051
LDL-C	Normals	16	137 (116, 158)	-11 (-24, 3)	0.115	
	Patients	12	143 (121, 166)	-18 (-34, -3)	**0.023**	**0.019**
HDL-C	Normals	16	54 (48, 61)	-1 (-6,+ 4)	0.664	
	Patients	12	54 (45, 62)	-10 (-16, -4)	**0.001**	**0.024**
Triglyceride	Normals	16	118 (81, 155)	-11 (-32, 11)	0.305	
	Patients	12	182 (125, 238)	-54 (-78, -29)	**<0.001**	0.518
Lp(a)[†]	Normals	16	11 (7, 18)	-3% (-20%, +17%)	0.713	
	Patients	13	17 (8, 33)	-13% (-30%, +8%)	0.196	0.557
LDL Particles[†] (nmol/L)	Normals	16	1266 (1067, 1503)	-4% (-14%, +9%)	0.539	
	Patients	12	1574 (1346, 1841)	-21% (-31%, -9%)	**0.002**	0.090
C-reactive protein[†] (mg/L)	Normals	16	1.93 (0.97, 3.82)	+7% (-27%, +57%)	0.717	
	Patients	13	5.60 (2.14, 14.70)	-59% (-73%, -37%)	**<0.001**	**0.018**

† Lp(a), LDL particle, and C-reactive protein data log transformed; means are geometric, with differences expressed as percentage change of ratio (draw 2/draw 1). Between-group p-values are as compared to the untreated subjects.

HDL-C - high-density lipoprotein cholesterol. LDL - low density lipoprotein. LDL-C - low-density lipoprotein cholesterol. Lp(a) - lipoprotein(a).

FIGURE LEGENDS

Figure 1: Change in total cholesterol in patients switched from enzyme-inducing AEDs to topiramate and in normal subjects.

Each bar shows the percent change in total serum cholesterol between the first and second draws for a single subject, with drug-treated epilepsy patients shown in blue, and normal subjects not taking AEDs in yellow.

Figure 2: Change in C-reactive protein in patients switched from enzyme-inducing AEDs to topiramate and in normal subjects.

Each bar shows the percent change in serum C-reactive protein between the first and second draws for a single subject, with drug-treated epilepsy patients shown in blue, and normal subjects not taking AEDs in yellow. (Note the one outlier whose CRP increased by 867%.)

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