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Influence of antiepileptic drugs on serum lipid levels in adult epilepsy patients

Yoshiaki Yamamoto[a,b,*], Kiyohito Terada[a], Yukitoshi Takahashi[a,b], Katsumi Imai[a], Yoshiyuki Kagawa[b,c], Yushi Inoue[a]

[a] Department of Clinical Research, National Epilepsy Center, NHO, Shizuoka Institute of Epilepsy and Neurological Disorders 886, Urushiyama, Shizuoka, 420-8688, Japan
[b] Department of Clinical Pharmaceutics, Graduate School of Pharmaceutical Sciences University of Shizuoka 52-1, Yada, Shizuoka, 422-8526, Japan
[c] Laboratory of Clinical Pharmacokinetics and Drug Safety, Shizuoka General Hospital 4-27-1 Kita Ando, Shizuoka, 420-8527, Japan

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ABSTRACT

The aim of this study was to evaluate the influence of antiepileptic drugs (AEDs) on lipid levels in adult epilepsy patients. We retrospectively reviewed blood data of 5053 patients with epilepsy (aged 20–94 years) and divided them into 3 groups: non AED group (without AED treatment), non-inducer group (using non-inducer AEDs), and inducer group (taking inducer AEDs; phenytoin (PHT), phenobarbital (PB), and carbamazepine (CBZ)). As a marker of dyslipidemia, the level of non-high-density lipoprotein cholesterol (non-HDL-C) was calculated by subtracting HDL-cholesterol from total cholesterol. The mean non-HDL-C level of non AED group, non-inducer group, and inducer group was 124, 130, and 138 mg/dL, respectively. In inducer group, patients using CBZ had a higher non-HDL-C level than patients taking PHT or PB. When a non-HDL-C level exceeding 180 mg/dL was defined as dyslipidemia, use of CBZ was associated with a significantly higher risk of dyslipidemia (adjusted odds ratio (OR); 2.6: 95% confidence interval (CI): 1.8–3.8) in comparison with non AED group. Use of valproic acid (VPA) was also associated with a higher non-HDL-C level (OR; 2.1: 95% CI: 1.4–3.2). An elevated non-HDL-C level was associated with increasing age, increasing BMI, and male gender, and use of inducers enhanced the risk of dyslipidemia. We recommend routine monitoring of the non-HDL-C level when using VPA and inducers, especially CBZ. While CBZ and VPA are first-line AEDs, medication should be selected by considering risk factors for dyslipidemia, such as age gender, and obesity.

1. Introduction

In patients with epilepsy, the risk of cardiovascular death is 1.5–2.5 times higher than in the general population (Brodie et al., 2013). Dyslipidemia is related to the development of cardiovascular disease. In particular, high levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C), as well as low high-density lipoprotein cholesterol (HDL-C), are related to cardiovascular mortality.

Cholesterol is synthesized from acetyl CoA via mevalonic acid and lanosterol. In this pathway, cytochrome P450 lanosterol 14α-demethylase (CYP51A1) plays a role in the synthesis of cholesterol from lanosterol (Keber et al., 2013). Lopinto-Khoury and Mintzer (2010) hypothesized that treatment with hepatic enzyme inducers (inducers), such as phenytoin (PHT), phenobarbital (PB), and carbamazepine (CBZ), could lead to induction of CYP enzymes and a consequent increase of the serum cholesterol level. In fact, many studies have demonstrated that administration of PHT, PB, or CBZ is associated with elevation of total cholesterol and LDL-C (Calandre et al., 1992; Zeitlhofer et al., 1993; Isojärvi et al., 1993; Erminio et al., 1994; Sudhop et al., 1990; Luef et al., 2002; Pylvänen et al., 2003; Bramswig et al., 2003; Nikolaos et al., 2004; Pylvänen et al., 2006; Hamed et al., 2007; Luef et al., 2009; Mintzer et al., 2009; Svalheim et al., 2010; Chuang et al., 2012; Phabphal et al., 2012).

The extent of enzyme induction is known to differ among PHT, PB, and CBZ, with PHT being the strongest inducer of CYP3A4 and UDP-glucuronosyltransferases (UGTs) (Yamamoto et al., 2012, 2014). However, the extent of CYP51A1 induction by each of these inducers is unclear, and there is limited information regarding the effects of different inducer regimens on the lipid profile. Further-

* Corresponding author at: Department of Clinical Research, National Epilepsy Center, NHO, Shizuoka Institute of Epilepsy and Neurological Disorders 886, Urushiyama, Shizuoka, 420-8688, Japan.
E-mail address: yamamoty-3@hosp.go.jp (Y. Yamamoto).

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more, there have been no studies comparing lipid levels in patients treated with mono-inducer or poly-inducer regimens (Vyas et al., 2015). It is well known that valproic acid (VPA) causes weight gain and insulin resistance, resulting in an increasing of triglyceride levels. However, varying effects of VPA on total cholesterol have been identified by previous studies. For example, Nikolaos et al. (2004) reported that VPA reduced the total cholesterol level, but Erminio et al. (1994) found elevation of cholesterol by VPA. Lipid levels can be influenced by many factors, such as the age, gender, and body mass index (BMI), so a multivariate model including these factors needs to be developed for investigations.

Non-high-density lipoprotein cholesterol (non-HLD-C) is calculated by subtracting HDL-C from total cholesterol, and it includes LDL-C and very low-density lipoprotein (VLDL). Recent studies have demonstrated that non-HDL-C can be clinically useful for estimating the risk of cardiovascular disease, being similar or superior to total cholesterol, and non-HDL-C has the advantage of not being susceptible to diet (Tanabe et al., 2010; Kitamura et al., 2011). However, there has only been one report about the effects of antiepileptic drugs (AEDs) on the non-HDL-C level (Mintzer et al., 2009), although a number of studies have evaluated the influence of AEDs on HDL-C. Several authors have reported that the use of inducers is associated with elevation of HDL-C (Calandre et al., 1992; Hamed et al., 2007), but others have not found a significant difference (Pylvänen et al., 2006; Chuang et al., 2012). The results obtained may have been inconsistent because the AED group included fewer than 100 patients in most of the previous studies.

Therefore, we evaluated a large cohort of adult epilepsy patients in the present study in order to identify the risk factors for dyslipidemia associated with AED therapy.

2. Material and methods

2.1. Subjects

The protocol of this study was approved by the ethical committee of the National Epilepsy Center (Shizuoka, Japan). We retrospectively reviewed 5053 adult patients with epilepsy aged from 20 to 94 years who underwent measurement of serum cholesterol and HDL-C between January 2007 and December 2014. Blood samples were collected from the patients at 2–6 h after a meal. Serum levels of total cholesterol and HDL-C were measured using a VITROS5600 autoanalyzer (Ortho Clinical Diagnostics, Tokyo, Japan). If multiple measurements were performed in a single patient during the study period, the highest cholesterol level was used. The non-HDL-C level was calculated by subtracting the serum HDL-cholesterol level from the serum total cholesterol level.

We defined PHT, PB (including primidone), and CBZ as inducers (enzyme-inducing AEDs), while all other AEDs were classified as non-inducers. Patients were excluded from this study if they had diabetes, a body weight <30 kg, or were using lipid-lowering agents (statins, fibrates, ezetimibe, and polyunsaturated fatty acids) or immunosuppressive drugs (steroids, tacrolimus, and everolimus). Patients were also excluded if they had commenced AED therapy or had changed their AED regimen (addition or discontinuation of AEDs) within 8 weeks before blood sampling. We divided the patients into the following three groups. The non-AED group comprised 585 patients who were not taking AEDs because they had newly diagnosed epilepsy, suspected epilepsy, or had completed AED therapy (control group). In addition, the non-inducer group included 1254 patients treated with non-inducers and the inducer group was composed of 3214 patients receiving one or more inducers.

2.2. Statistical analysis

To investigate the association between lipid levels and use of AEDs, we compared the three groups by using analysis of variance (ANOVA) with a post-hoc Scheffe's multiple comparison test. Comparison of lipid profiles among AED regimens was performed by analysis of covariance (ANCOVA) with adjustment for age, gender, and BMI, and the significance of intergroup differences was evaluated with a post-hoc Bonferroni test. We then performed multivariable analysis using non-HDL-C as the dependent variable to determine the factors influencing this lipid parameter. Moreover, multiple logistic regression analysis was performed to calculate adjusted odds ratios for dyslipidemia, which was defined as a non-HDL-C level exceeding 140 or 180 mg/dL. Cut-off values for non-HDL-C were set with reference to a previous study of non-HDL-C levels in 8132 Japanese subjects (Kitamura et al., 2011). Results are expressed as the mean ± standard error and all analyses were conducted with SPSS software Ver 22.0.

3. Results

3.1. Patient characteristics

Table 1 compares clinical characteristics and lipid profiles among the three groups of patients. There were significant differences of age, gender, and BMI among the three groups, with the inducer group showing marked male predominance (60.4%). The mean total cholesterol and HDL-C levels were significantly higher in the inducer group than in the non-AED group and the non-inducer group. A non HDL-C level exceeding 140 mg/dL was found in 35.0% and 43.7% of the non-inducer and inducer groups, respectively, which was a higher proportion than in the non-AED group (30.6%). Also, a non HDL-C level exceeding 180 mg/dL was found in 6.0%, 10.4%, and 14.1% of the non-AED, non-inducer, and inducer groups, respectively.

3.2. Influence of inducers on the lipid profile

Table 2 compares lipid levels among the inducer regimens. There were significant differences among three mono-inducer regimens, with non-HDL-C and total cholesterol levels being higher in patients using CBZ than in patients receiving PHT or PB. Also, use of CBZ or PHT was associated with a significantly higher HDL-C level in comparison with use of PB ($p < 0.001$). When PHT and/or PB was combined with CBZ, a significant increase of HDL-C was observed. Furthermore, poly-inducer regimens including CBZ (e.g., PHT + CBZ, PB + CBZ, and PHT + PB + CBZ) were associated with higher total cholesterol and non-HDL-C levels than the same regimens without CBZ, but there was no significant difference in comparison with CBZ alone. Thus, AED regimens including CBZ were associated with significantly increased lipid levels.

3.3. Influence of VPA on the lipid profile

Table 3 displays the effects of VPA on lipids in patients with or without inducers. Treatment with VPA significantly reduced the HDL-C level regardless of the concomitant use of inducers. In the absence of inducers, VPA significantly increased the non-HDL-C level, with a resultant increase of total cholesterol. In contrast, the non-HDL-C level was unchanged when VPA was combined with inducers, while the HDL-C-lowering effect of VPA led to a decrease of total cholesterol. In the non-inducer group (with VPA), there were no differences of lipid levels between patients using VPA alone and those taking VPA plus non-inducers.