Original Article

VALPORIC ACID: IS IT SAFE TO USE IN EPILEPTIC PEDIATRIC PATIENT?

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ABSTRACT

Objective: To evaluate the effects of a 3-month low dose valporic acid treatment (20 mg/kg/day) on liver function tests, hematologic parameters, serum lipids and lipoprotein (a) levels in children.

Methodology: Twenty-one newly diagnosed epileptic pediatric patients, nine female and 12 male, aged between 18 months and 14 years old (mean age 6.3±4.3 years), were enrolled in this study. valporic acid treatment was started with a dose of 20 mg/kg/day. To evaluate the effects of valporic acid on liver function tests, hematologic parameters, and serum lipids and lipoprotein levels were measured in pre-treatment and post-treatment 3rd month and values in pre-treatment were compared with values in post-treatment 3rd month.

Results: There were no statistically significant differences between pre-treatment and post-treatment 3rd month values regarding liver function tests, hematologic parameters, and serum lipids ($p>0.05$). But lipoprotein (a) levels in the post-treatment 3rd month (40.71±50.73 mg/dl) were significantly higher than the pre-treatment levels (25.86±36.54 mg/dl) ($p<0.01$).

Conclusion: It was demonstrated that low dose of valporic acid treatment did not have any significant effects on liver function tests, hematologic parameters and serum lipids after three months. On the other hand it caused an increase in lipoprotein (a) levels. We consider that although these are the initial results for lipoprotein (a) levels and further studies should be undertaken on a larger sample size to confirm our observations, epileptic pediatric patients receiving low dose of valporic acid should not be routinely checked for liver function tests, hematologic parameters and serum lipid profiles, but serum levels of lipoprotein (a) may be monitorized carefully.

KEY WORDS: Valporic acid, Liver function tests, Hematologic parameters, Serum lipids, Lipoprotein (a).

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INTRODUCTION

Valporic acid (VPA) is a widely used and well-tolerable drug in epileptic pediatric patients.[1] However, VPA has many adverse effects which may be dose-related or not.[2] It has been associated with acute, not rarely fatal hepatotoxicity.[3,4] However, reversible increases in liver enzymes have been detected in 15–30% of VPA treated patients.[5] It has been reported that VPA can cause hematologic side effects

as thrombocytopenia, deficiency of coagulation factors, hypofibrinogenemia, acquired von willebrand disease, and decreased protein C (ProC) levels.[6-8] In addition VPA may increase lipoprotein (a) (Lp (a)) levels which is an independent risk factor for atherosclerosis.[9]

In this study we aimed to investigate the effects of low dose VPA treatment on liver function tests, hematologic parameters, serum lipids and Lp (a) levels in post-treatment 3rd month.

METHODOLOGY

This study was conducted at Gülhane Military Medical Academy Children Hospital, Department of Pediatric Neurology with the approval of the Institutional Ethics Committee and in conformity with Helsinki Declaration, ICH/GCP and local regulations.

Twenty-one pediatric patients with idiopathic epilepsy were included in the study. The patients who received any other drugs, or who had any neurological, renal, thyroid, hepatic, cardiac, neurometabolic or other chronic diseases were excluded. Diagnostic tests of the patients including brain magnetic resonance imaging, tandem-mass spectrophotometry, amino acid and organic acid screening in blood and urine were normal. Idiopathic epilepsy was defined according to the International League Against Epilepsy. The dose of the VPA was chosen according to generally accepted guidelines. Patients were started on VPA with a dose of 20mg/kg/day. To evaluate the effects of VPA on liver function tests, hematologic parameters, and serum lipids and lipoprotein levels were measured in pre-treatment and post-treatment 3rd month and values in pre-treatment were compared with values in post-treatment 3rd month.

Biochemical assays: Venous blood samples were obtained after 12 hour fasting in early morning, between 8.00 and 10.00 a.m. and they were collected from each subject into tubes without anticoagulant (for preparation of serum) and into tubes with ethylenediaminetetraacetic acid (EDTA) or citrate. Blood samples with citrate or without anticoagulant were centrifuged at 4000 rpm in room temperature for 10 minutes, and serum or plasma samples were stored at –80 °C until the time of the assay. Blood samples with EDTA were immediately studied for platelet counts (PLT) and mean platelet volume (MPV).

To evaluate the effects of VPA on liver, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL) and albumin (ALB) levels were measured in pre-treatment and post-treatment 3rd month. To evaluate the effects of VPA on hematologic parameters, PLT, MPV, activated partial thromboplastin time (aPTT), prothrombin time (PT), bleeding time (BT), levels of fibrinogen (FIB), factor VIII (FVIII), factor IX (FIX), von Willebrand Factor (vWF), protein C (pro-C), protein S (pro-S), and antithrombin-III (AT-III) were measured in pre-treatment and post-treatment 3rd month. To evaluate the effects of VPA on serum lipids and lipoprotein levels, triglyceride (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), very low density lipoprotein-cholesterol (VLDL-C), apolipoprotein A (ApoA), apolipoprotein B (ApoB), and Lp (a) were measured in pre-treatment and post-treatment 3rd month.

Pro-C, pro-S, vWF, FVIII, and FIX levels were measured by STA-Compact coagulation analyzer (Diagnostica Stago, France), and FIB, PT, aPTT levels were measured by Amelung Amax CS-190 coagulation analyzer (Sigma Chemical Co., USA). The BT was measured by using the template method (Simplate®, Pediatric, Organon Teknika Corp, Durham, NC, USA). Serum VPA levels were quantified by Abbott fluorescence polarization immunoassay with TDx analyzer (Abbott Laboratories; Abbott Park, IL, USA). Serum TG, TC, HDL-C, VLDL-C and LDL-C concentrations were measured by Olympus AU2700 analyzer (Hamburg, Germany) using its specific kit. LDL-C and VLDL-C were calculated by means of the Friedewald formula. Serum Apo A1, Apo B, and Lp (a) concentrations were determined using an immunonephelometric assay on a BN-ProSpec

Table-I: Comparison of pre-treatment and post-treatment 3rd month liver function tests

	AST(U/L)	*ALT(U/L)*	*TBIL (mg/dl)*	*DBIL(mg/dl)*	*ALB(g/dl)*
Pre-treatment	25.95±5.88	24.43±4.87	0.80±0.17	0.09±0.05	4.78±0.52
Post-treatment	24.95±4.07	24.86±3.66	0.79±0.12	0.08±0.05	4.81±0.45
P value	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

AST:Aspartate aminotransferase; ALT:Alanine aminotransferase; TBIL:Total biluribine; DBIL:Direct biluribine

Nephelometer (Dade Behring, Marburg, Germany).

Statistical Analysis: Data were analyzed by using the package program SPSS for Windows V.10.0. Descriptive data are given as numbers and percents for intermittent variations, and as the mean ± standard deviation. The Wilcoxon signed rank test was used in statistical analyses. Alpha values less than 0.05 were accepted significant.

RESULTS

The study group consisted of 21 epileptic pediatric patients (nine female, 12 male) aged between 18 months and 14 years (mean age 6.3±4.3 year). Mean serum VPA levels in the post-treatment 3rd month was 69.4±15.7 ìg/ml. Serum AST, ALT, TBIL, DBIL, and ALB values were all in normal limits in the pre-treatment and post-treatment 3rd month. There were no statistically significant differences between pre-treatment and post-treatment 3rd month values for serum AST, ALT, TBIL, DBIL, ALB, PLT, MPV, APTT, PT, FIB, BT, FVIII, FIX, vWF, pro-C, pro-S, AT III, TC, TG, VLDL-C, LDL-C, HDL-C, ApoA, and ApoB (all p>0.05) (Tables I, II, III, IV and V). But post-treatment Lp (a) levels were statistically higher than pre-treatment levels (p<0.01) (Table-V).

DISCUSSION

VPA has many adverse effects on liver, hematologic parameters, and serum lipids. It has been associated with acute, not rarely, hepatotoxicity.[3,4] Moreover, reversible increases in liver enzymes have been detected in 15–30% of patients treated with VPA.[5] Rarely, VPA causes fatal hepatotoxicity during the first six months of treatment in children younger than 2 years old.[10] Minor elevations of transaminases related to VPA treatment are frequent and appear to be dose-related and they may be the first sign of hepatotoxicity.[6,11] Occasionally, laboratory test results include increased serum bilirubin levels and abnormal changes in other liver function tests. Rugino et al. found hypoalbuminemia related to VPA treatment in severe disabled patients and albumin levels returned to normal levels after cessation of treatment.[12] Attikilos et al.[13] and Hauser et al.[14] found a downward trend of serum albumin levels after six months of therapy. The pathogenic mechanisms responsible for liver failure in children which is induced by VPA treatment may include: an inborn error of VPA metabolism, induction of VPA reactive metabolites and inhibition of the betaoxidation pathway.[15-17] In our study, there were no statistically significant differences between pre-treatment and post-treatment 3rd month values with respect to liver function tests.

Hematologic advers effects related to VPA treatment in pediatric patients are common. Thrombocytopenia is the most common hematologic adverse effect of VPA treatment with an incidence of 5–40%. Thrombocytopenia typically appears after several months of

Table-II: Comparison of pre-treatment and post-treatment 3rd month values of PLT, MPV, aPTT, PT, FIB and BT

	PLT (10^3/mm^3)	*MPV(fl)*	*aPTT(Sec)*	*PT(sec)*	*FIB(mg/dl)*	*BT(min)*
Pre-treatment	365±119	3.78±0.48	38.75±1.89	11.98±0.64	287.5±62.4	5.58±0.60
Post-treatment	324±106	7.70±0.64	29.29±3.36	11.90±0.61	289.7±69.5	5.60±0.79
P Value	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05

PLT:Platelet count; MPV:Mean platelet volume; aPTT:Active partial thromboplastin time; PT:Prothrombin time; FIB:Fibrinogen; BT:Bleeding time.

Table-III: Comparison of pre-treatment and post-treatment 3rd month values of FVIII, FIX, and vWF

	FVIII (%)	*FIX (%)*	*VWF (%)*
Pre-treatment	90.4% (±31.6)	81.6% (±27.5)	99.8% (±40.0)
Post-treatment	78.0 (±16.8)	72.2 (±16.8)	92.7 (±37.7)
P Value	p>0.05	p>0.05	p>0.05

FVIII:Factor VIII; FIX:Factor IX; vWF: vonWillebrand Factor

therapy. The degree of thrombocytopenia correlates with the levels of valporic acid, with a higher level of thrombocytopenia observed in patients with VPA levels greater than 140mg/ml.[18,19] Ko et al. have reported that thrombocytopenia and prolongation of BT were seen when serum VPA level was high and that they became normal after decreasing the dose of VPA.[20] It is reported that the mechanism of thrombocytopenia may be related to immune mediated destruction. In our study, there were no statistically significant differences between pre-treatment and post-treatment 3rd month values for PLT.

It is reported that VPA treatment may cause reduction in vWF level.[6] Kreuz et al. showed that 67% of patients receiving VPA developed an acquired vWF disease type I which was not related to dose or duration of VPA treatment.[8] Banerjea et al. showed significant correlation between vWF and serum VPA levels especially after 30 days of treatment.[6] Hypofibrinogenemia may be seen during VPA therapy due to unkown mechanisms.[21] Banerjea et al. reported deficiency of FIB in 15% of patients receiving VPA treatment.[6] Gruppo et al. reported that FIB level rapidly increased after discontinuation of VPA treatment.[22] In our study, there were no statistically significant differences between pre-treatment and post-treatment 3rd month values for vWF and FIB.

Some studies reported that FVIII and FIX levels decreased during VPA treatment, but that they returned to normal after discontinuation of treatment.[22] Kreuz et al. reported a significant decrease in FVIII levels during VPA treatment.[8] Gerstnet et al. reported a 7-month old boy who had deficiency of vitamin-K dependent coagulation factors due to VPA treatment.[23] In our study, we found a statistically insignificant decrease in FVIII and FIX levels in post-treatment 3rd month.

It has been reported that VPA treatment might affect the natural anticoagulant levels. Gruppo et al.[22] and Banerjea et al.[6] showed a significant reduction in pro-C levels during VPA treatment. Banerjea et al.[6] also showed a significant reduction in AT-III levels whereas Gruppo et al.[22] found normal AT-III and pro-S levels. In our study, there were no statistically significant differences between pre-treatment and post-treatment 3rd month values concerning the natural anticoagulants.

The effects of VPA treatment on serum lipids and lipoprotein levels have been demonstrated in many studies.[11,24-27] The results of these studies contradict each other for serum lipid levels related to VPA treatment.[11,27-30] Franzoni et al. reported a reduction in TG and LDL-C levels and an increase in HDL-C levels.[25] Eiris et al. demonstrated a reduction in levels of TC, LDL-C, Apo-A1, Apo B, and HDL-C.[27] Tekgul et al. reported a significant decrease in TG levels after two years of VPA treatment.[31] Verrotti et al. reported a decrease in levels of LDL-C, and TG and an increase in HDL-C levels following VPA treatment.[30] But the effects of VPA on lipid profile remains unclear. In our study, there were no statistically significant differences between pre-treatment and

Table-IV: Comparison of pre-treatment and post-treatment 3rd month values of pro-C, pro-S, and AT- III

	Pro-C (%)	*Pro-S (%)*	*AT-III (%)*
Pre-treatment	83.52 ± 17.73%	83.52 ± 17.73%	83.52 ± 17.73%
Post-treatment	88.57 ± 22.38%	87.33 ± 22.37%	100.4 ± 16.13%
P Value	p>0.05	p>0.05	p>0.05

Pro-C: Proteine C; Pro-S: Proteine S; AT-III: Antithrombin III

Table-V: Comparison of pre-treatment and post-treatment 3rd month values of TC, TG, VLDL-C, LDL-C, HDL-C, ApoA, ApoB, and Lp (a)

	TC (mg/dl)	*TG (mg/dl)*	*LDL-C (mg/dl)*	*VLDL-C (mg/dl)*	*HDL-C (mg/dl)*	*Lp (a) (mg/dl)*	*Apo A1 (mg/dl)*	*ApoB (mg/dl)*
Pre-treatment	140.61±49.16	119.33±64.72	82.55±35.48	30.60±20.75	48.57±15.37	25.86±36.54	129.95±34.21	83.76±8.59
Post-Treatment	152.76±44.59	96.47±51.75	89.00±38.19	23.01±20.28	47.14±11.06	40.71±50.73	136.66±20.36	75.40±32.70
p value	p>0.05	p>0.05	p>0.05	p>0.05	p>0.05	p<0.01	p>0.05	p>0.05

TC: Cholesterol; TG: Triglycerids; LDL-C: Low density lipoprotein; VLDL-C: very low density lipoprotein; HDL-C: High density lipoprotein; Lp (a): Lipoprotein (a); Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B

post-treatment 3rd month values for TG, TC, LDL-C, HDL-C, and VLDL-C.

Lipoprotein (a) is a low-density lipoprotein and an independent risk factor for premature coronary heart disease.[32] It is reported that elevation of Lp (a) and LDL-C levels may be an early sign of atherosclerosis.[33-35] Verrotti et al. reported that VPA treatment had no effect on serum Apo-A, ApoB and Lp (a) levels.[30] But some studies reported an increase in Lp (a) levels during VPA treatment.[11,36] Voudris et al. showed a significant early and persistent increase in Lp (a) levels related to VPA treatment.[9] On the contrary, Castro-Gago et al. showed a reduction in Lp (a) levels following VPA treatment.[37] The relevant mechanism of elevated serum Lp (a) level in pediatric patients is unclear and possibly multiple factors are involved. In our study, we found a statistically significant increase in Lp (a) levels in post-treatment 3rd month. These are initial results for VPA's effect on serum Lp (a).

In our all results demonstrated that low dose VPA treatment did not have any significant effects on liver function tests, hematologic parameters and serum lipids. But this situation may be related to small of duration of treatment period and the serum VPA levels that were in normal therapeutic range.

In conclusion, it was demonstrated that a 3-month low dose of VPA treatment did not have any significant effects on liver function tests, hematologic parameters and serum lipids but it caused an increase in Lp (a) levels. We consider that epileptic pediatric patients receiving low dose of VPA should not be routinely checked for hepatologic, hematologic and serum lipid profiles, but serum levels of Lp (a) may be monitored carefully. We do not at all mean to bring into disrepute the efficacy of valporate but we suggest further studies with larger groups and long duration, in order to make a statement whether to carefully monitor serum Lp (a) levels which is important risk factor for atherosclerosis.

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