ORIGINAL ARTICLE

THE EFFECT OF LAMOTRIGINE MONOTHERAPY AFTER CONVERSION FROM THE COMBINED THERAPY LAMOTRIGINE AND VALPROIC ACID IN PATIENTS WITH EPILEPSY

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Abstract

This study aimed to investigate the curative effect and safety profile of lamotrigine monotherapy converted from small doses of lamotrigine (LTG) combined with valproic acid (VPA) in epileptic patients. The study included 40 patients with epilepsy whose seizures were completely controlled after six months treatment with small doses of LTG combined with VPA. The doses of VPA were gradually reduced till the patients were converted to LTG monotherapy. The patients were followed-up on a period of six months. LTG plasma concentration, fasting blood glucose, fasting serum insulin, patients' height and weight were measured before converting from drug-combination treatment to monotherapy, a week after VPA was withdrawn and six months after monotherapy. Long-term electroencephalogram (EEG) of 24 h was monitored before converting to monotherapy and after six months' follow-up visit. When VPA was withdrawn for a week and monotherapy was adopted for six months, body mass index (BMI) decreased. There was no difference between insulin resistance indexes according to the homeostasis model assessment (HOMA-IR) a week after VPA was withdrawn and before monotherapy. However, after six months monotherapy, HOMA-IR lowered. No difference was observed in LTG plasma concentrations before monotherapy, a week after VPA was withdrawn and six months after monotherapy. LTG plasma concentration during the switch was higher than before monotherapy. Also, after the therapy conversion, the pharmacologic effect was stable, the spontaneous recurrent seizures were rare, adverse reactions reduced and drug safety increased.

Rezumat

Acest studiu şi-a propus să evalueze efectul curativ şi profilul de siguranţă în cazul monoterapiei cu lamotrigină la pacienţii cu epilepsie, după conversia de la dubla terapie cu lamotrigină şi acid valproic. În studiu au fost incluşi 40 de pacienţi cu epilepsie ale căror crize convulsive au fost controlate complet după şase luni de tratament cu doze mici de lamotrigină plus acid valproic. Dozele de acid valproic au fost reduse treptat până la conversia la monoterapia cu lamotrigină. Pacienţii au fost urmăriţi pe o perioadă de 6 luni de la monoterapie. Concentraţia plasmatică de lamotrigină, glicemia, insulina serică, greutatea şi înălţimea pacienţilor au fost determinate înainte de trecerea de la dubla terapie la monoterapie, la o săptămână după renunţarea la acid valproic şi la 6 luni după monoterapie. Encefalograma înregistrată timp de 24 de ore s-a realizat înainte de conversia la monoterapie şi la 6 luni de la conversie. Indicele de masa corporală (IMC) a scăzut la o săptămână şi la 6 luni de la instalarea monoterapiei. În ceea ce priveşte rezistenţa la insulină, evaluată prin indicele HOMA-IR (*homeostasis model assessement*), nu s-a observat nici o diferenţă între valoarea dinaintea conversiei la monoterapie şi valoarea după o săptămână. La 6 luni după conversie, indicele HOMA-IR a scăzut semnificativ. În ceea ce priveşte concentraţia plasmatică de lamotrigină nu s-au observat diferenţe între valorile dinainte de monoterapie şi cele de la o săptămână şi 6 luni de monoterapie, dar concentraţia plasmatică de lamotrigină în timpul conversiei la monoterapie a fost mai mare. După modificarea terapiei, efectul farmacologic a fost stabil, convulsiile spontane recurente au fost rare, reacţiile adverse s-au diminuat, iar eficacitatea terapeutică a fost îmbunătăţită.

Keywords: lamotrigine, valproic acid, epilepsy, drug combination, monotherapy, adverse reactions, safety profile

Introduction

Epilepsy is a common nervous system disease that affects around 50 - 70 million people worldwide, and accounts for 0.75% of the global burden of diseases [37]. It is a chronic and recurrent central nervous system disease with several causes. Excessive simultaneous discharge of cortical neurons causes paroxysmal, temporary and recurrent central nervous system dysfunction. Sometimes the clinical signs are similar to those in psychoses, requiring differential diagnosis [25].

Nowadays, the main treatment method for epilepsy is through medicines. Since 1980s, most physicians supported the monotherapy [15] because in this way the adverse effects and drug interactions can

be effectively prevented [28]. Studies showed that when treating the new-diagnosed epileptic patients with the first line antiepileptic drugs (AEDs) on monotherapy, morbidity of epileptic seizure is about 53% [26] while treating it with the second line AEDs on monotherapy, morbidity reaches 87% [1, 29]. Besides, when treating the patients with the third line AEDs, the morbidity is 99%. The absorption and distribution of anti-epileptic drugs may be altered by chronic liver disorders such as non-alcoholic fatty liver disease [5], hepatitis with C virus [9] or vitamin K dependent clotting disorders [36].

There are studies showing that the therapeutic effect of lamotrigine (LTG) combined with valproic acid (VPA) is better than that of LTG combined with carbamazepine or dilantin [32, 35]. LTG is a new type of AED, which acts by inhibiting the release of excitatory amino acids (EAA) [34]. VPA is a traditional AED, which can control frequent epileptic seizures and improve patients' compliance [18, 26]. During long term treatment with VPA, many adverse reactions can be developed. In order to solve this problem, the treatment method for epileptic patients controlled by small doses of LTG combined with VPA may be the switch to LTG monotherapy. The present investigated the safety profile of this conversion.

Materials and Methods

Study design

40 patients with epilepsy admitted to the Neurology Department of The Second Affiliated Hospital of Harbin Medical University and Affiliated Hong Qi Hospital of Mu Dan Jiang Medical University (31 from the first one and 9 from the second) from March 2015 to September 2016 were included in the study. There were 18 males and 22 females, aged between 7 to 54 years old, with 1-8 years course of the disease, with an average of 24.34 ± 40.23 months. Before the study, patients and their relatives were informed about the study process and all the subjects included in the study signed an informed consent. In the case of children, the legal tutor signed the informed consent. The study protocol was approved by the Medical Ethics Committees of both hospitals.

Inclusion criteria

Patients with epilepsy without relapse for six months after treatment with small dose of LTG and VPA, patients with epilepsy without abnormalities in blood routine examination and disturbance on hepatorenal function, patients without severe adverse reactions and that are not under treatment with drugs that influence the endocrine system. In the study were included patients with body mass index (BMI) below 25 kg/m^2.

Exclusion criteria

History of drug abuse, alcohol addiction, poor compliance with mental disorders, insulin resistance or abnormal glucose tolerance. From the study were also excluded patients during gestation period or lactation, patients under treatment with growth hormones, steroids and sex hormones, patients with pathologies that determine weight changes, patients with severe mental retardation and severe systemic diseases.

Reagents used in study

Drugs and reagents: standard lamotrigine (The Wellcome Foundation Ltd); Depakine® sodium valproate and valproic acid sustained release tablets (Hangzhou Sanofi Pharmaceutical Co,. Ltd.); octane sulfonic natrium of spectral purity (Tokyo Kase Kogo Co., Ltd.); acetonitrile, phosphate and hydrochloric acid buffer solution of 0.01 M (Changsa Mingrui Chemical Co., Ltd.); double distilled water (Shanghai Yongnuo Bio-Technology Co., Ltd.); methilic alcohol, phosphoric acid and EDTA of analytical purity (Hangzhou Youshun Chemical Co., Ltd.).

Instruments

High performance liquid chromatograph (HPLC) (Surwit Technology Inc.), 24 h dynamic electro-encephalograph (Shanghai Yuezheng Enterprise development Co., Ltd.), computer tomograph (Hebei Aofei Numerical-control Machine Tool Accessory Co., Ltd.), nuclear magnetic resonance spectrometer (Changzhou Sanfeng Instrument Technology Co., Ltd.).

Drug administration protocol

Under combined treatment, initial LTG dosage for adult was 12.5 mg/day and initial VPA dosage was 250 mg twice a day. Initial LTG dosage for children was 0.5 mg/kg/day and initial VPA dosage was 10 mg/kg/day administered twice per day. Two weeks later, LTG dosage for adult was changed to 25 mg/day and VPA dosage was 187.5 mg twice a day. LTG dosage for children was changed to 0.3 mg/kg/day and VPA dosage was 2.5 mg/kg/day administered twice per day. Every two weeks later, VPA was reduced by 1/4 of the original dosage. Two months later, VPA was withdrawn. Five weeks later, for adults, LTG dosage was maintained at 25 mg twice per day and for children LTG dosage was maintained at 1 mg/kg/day. The dosage for monotherapy treatment followed the same pattern.

Observation indexes

The recording of epileptic seizures frequency and adverse reactions of all medications stages was observed in real time. Fasting insulin, fasting plasma glucose level and LTG plasma concentration of all experimental subjects were monitored at different stages such as before converting from drug-combination treatment to monotherapy, a week after VPA was withdrawn and six months

after monotherapy. Experimental subjects' height (accurate to 0.1 cm) and weight (accurate to 0.1 kg) were also measured. Long-term electroencephalograms (EEG) of 24 h were monitored before converting to monotherapy and six months after converting.

Blood glucose levels (GLU) were assayed using the glucose oxidase method in a Hitachi 902 auto-analyser and fasting insulin levels were measured with a chemiluminescent automated method (CLIA) Access (Beckman Coulter, Brea, CA, USA) in the Endocrinology Laboratory of the Second Affiliated Hospital of Harbin Medical University and Affiliated Hong Qi Hospital of Mu Dan Jiang Medical University. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated according to formula = fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5, as proposed by Matthews *et al*. [21].

Statistical analysis

Statistical software SPSS19.0 was used for all statistical calculation. The measured data were tested for normal distribution by the normality test. If the data was normally distributed, it was expressed as mean ± standard deviation. If data were normally distributed, it was used the median. Comparison between means was performed using Student t test and significance level was set to 0.05.

Results and Discussion

Preliminary analysis of the results

During the whole process from VPA dose reducing to six months' follow-up visit, there were 3 patients that did not complete the follow-up and 37 patients that completed the follow-up visit. Among them, 4 patients had epileptic seizures after converting to LTG monotherapy treatment and the epileptic seizure was controlled by increasing dosage of LTG or adding VPA.

Electroencephalogram (EEG): before converting to monotherapy, there were 4 patients with abnormal EEG, including a case of focal epileptiform discharge, a case of moderate diffuse anomaly, a case of bilateral symmetry spike and slow wave complex of 3 Hz, a case of bilateral sharp wave and a case of local (left temporal region) abnormality.

Imaging examination: there were five patients with abnormal imaging examinations, including a case of lacunar infarction, a case of left front-parietal encephalomalacia, a case of asymmetry temporal horn of lateral ventricle, a case of softening focus of left frontal occipital lobe and a case of asymmetry hippocampus. There were no abnormalities of the other 35 cases of patients.

Regarding the previous history, there were 3 patients with anoxia at birth, 2 cases with hyper-pyretic convulsion and 2 cases with cerebral trauma.

Safety

From Table I it can be seen a significant difference between BMI before monotherapy, a week after VPA withdrawn and six months after monotherapy ($p < 0.05$). Also, we registered significant differences between HOMA-IR levels before monotherapy, a week after VPA withdrawn and six months after monotherapy ($p < 0.05$).

Table I

Patients' BMI and HOMA-IR at different time points

	Before monotherapy	A week after withdrawn VPA	Six months after monotherapy
BMI(kg/m^2)	21.22 ± 3.43	20.62 ± 3.61*	20.06 ± 3.23*
Blood glucose levels (GLU) (mmol/L)	5.20 ± 0.30	5.12 ± 0.27	5.09 ± 0.28
Fasting insulin levels (mIU/L)	6.14 ± 0.76	5.63 ± 0.82	4.69 ± 0.71*
HOMA-IR	1.42 ± 0.56	1.28 ± 0.77	1.06 ± 1.03*

*$p < 0.05$

LTG plasma concentrations

It can be seen from Table II that differences between plasma concentration of LTG before monotherapy during therapy change, a week after VPA withdrawn and six months after monotherapy were significant ($p < 0.05$). Differences between LTG plasma concentration before monotherapy, a week after VPA withdrawn and six months after monotherapy have no statistical significance ($p > 0.05$).

It can be observed from Table III that under LTG monotherapy, differences between plasma concentrations of 4 cases of patients with recurrence and the other patients without recurrence have no statistical significance ($p > 0.05$).

Table II

Comparison of LTG plasma concentration at different time points (μg/mL)

	Plasma concentration of LTG	p value
Before monotherapy	4.52 ± 1.71	-
Medicine transformation period	5.02 ± 2.28	0.032*
A week after withdrawn VPA	4.85 ± 2.71	0.382
Six months after monotherapy	4.34 ± 1.85	0.252

* statistical significance; Medicine transformation period: the period of change from combined treatment to monotherapy treatment.

Table III

Comparison of plasma concentration (μg/mL) between epileptic patients with recurrence and patients without recurrence

	Plasma concentration of LTG	p value
Plasma concentration of patients with recurrence	3.91 ± 1.45	0.12
Plasma concentration of patients with no recurrence	4.38 ± 1.91	

Adverse reactions

Among the 40 patients, there was one case with rash during therapy change period, which was developed accidentally and discontinuous and disappeared after withdrawing VPA without the need of special treatment. The occurrence of rash is closely related to relatively high initial dose, overdose and the combined treatment with VPA. There was one case with chickenpox, which developed two months after increasing dosage of LTG. There was one case with headache six months after converting to LTG monotherapy, which disappeared gradually with no special treatment. Also, there was a case with anaemia, with a haemoglobin value of 65 g/L. He was treated accordingly to the haematology clinicians' recommendations.

Published researches show that the clinical therapeutic effect of treating epilepsy patients with LTG combined with VPA is remarkable [30]. Some studies showed that the clinical therapeutic effect of treating myoclonic seizure and infantile spasm with LTG combined with VPA was efficient and with only few adverse reactions [19, 20]. Brandt *et al* showed that the successful rate of treating epilepsy with LTG monotherapy is around 35 - 62% [4]. The present study shows that when treating the patients with reduced dosage of VPA and doubled dosage of LTG, 35 patients out of 40 did not develop seizure during the six months' follow-up visit, which means that after treatment was converted to LTG monotherapy, a stable therapeutic effect was maintained for most patients. In conclusion, LTG can be used as first-line drug for monotherapy and add-on therapy to treat epileptic of adult, infant and teenage.

There is a complex interaction between LTG and VPA. Researches showed that LTG plasma concentration and the clinical therapeutic effect can be greatly improved by the treatment with small doses of LTG and VPA [23, 24]. VPA is an inhibitor of liver metabolic enzymes, therefore it is able to increase its plasma concentration and prolong its half-life [6]. Rowland A. studied the interaction between VPA and LTG in humans and showed that these effects occur due to VPA inhibition on UGT287 [31]. Others showed that if LTG plasma concentration is the same and VPA is added, the clinical effect of LTG can be enhanced, which means that when combining VPA and LTG, there is a positive pharmacodynamic interaction and this is related to their anti-epileptic mechanism [11]. VPA is able to decrease the nervous excitability [10, 33] and LTG is able to inhibit the pathological release of excitatory amino acids (EAA). When combining them, complementary mechanisms enhance the anti-epileptic effect [2]. Statistical analysis of plasma concentrations found that LTG plasma concentration change is increased and is higher than that of combined treatment, which means VPA is inhibiting LTG metabolism. When the dose of LTG was doubled and treatment was converted to monotherapy, the influence of VPA on LTG metabolism disappeared, LTG plasma concentration was maintained constant and the pharmacologic effect was stable. Besides, there were 4 cases of patients who had epileptic seizures after converting to LTG monotherapy and their plasma concentration during seizure was obviously lower than that of patients without seizure ($p > 0.05$). Thus, it can be inferred that when LTG is combined with VPA, there is a positive pharmaco-dynamic interaction because some patients are more suitable for the combined treatment.

A range of side effects are caused by the long-term use of VPA, such as weight increasing, female hyperandrogenism and insulin resistance [8, 11, 16]. Biton V. studied 133 cases of epilepsy patients in treatment with LTG or VPA and the research results showed that after ten weeks of VPA, weight was obviously increased and it increased continuously even to the end of the study, in the 32nd week [3]. Hameda *et al*. [17] found that the insulin levels of patients in VPA group was higher than that of patients in the control group and serum insulin level was related to VPA dosage and treatment time. Our research showed that differences of BMI and HOMA-IR at six months after converting to monotherapy and before switching to monotherapy had statistical significance ($p < 0.05$). This means that after converting to monotherapy, patients' weight increased, insulin resistance reduced and adverse reactions of the combined treatment of LTG and VPA were avoided.

The main adverse reactions caused by LTG are tremor, nausea, emesis, diplopia, rash, headache and dizziness, and the most common one is rash [21, 39]. In the earlier stage, there were no patients with rash, due to the low doses of LTG. However, it was one case of patient with rash during therapy conversion. It developed accidentally and dis-continuously and disappeared a week later with no

special treatment. At that moment, LTG plasma concentration was 3.7 μg/mL which means rash was caused by the relatively high LTG plasma concentration. Thus, when increasing LTG dosage, plasma concentration and adverse reaction should be closely monitored. If there are adverse reactions, subsequent visit is needed in time. Besides, adverse reactions in drug combination period did not occurred during LTG monotherapy, which means adverse reactions caused by the long-term use of VPA can be avoided by LTG monotherapy.

There are studies showing that epileptic patients' electroencephalogram (EEG) is closely related to the clinical effect. Research of Murakami T. showed that after LTG was added to the epilepsy treatment, there were 19 cases of patients with brain alpha band reaction and beta wave amplitude was selective enhanced in the attention test [24]. Electroencephalogram (EEG) monitoring results showed that the improvement rate of electro-encephalogram (EEG) was 60%, which is consistent to other research results [7, 14].

Conclusions

In epileptic patients, when switching from small doses of LTG combined with VPA to LTG monotherapy, the curative effect is relatively stable and adverse reactions are obviously reduced. Therefore we report a study that proves the safety of therapy conversion. However our results are limited due to the small number of cases. Further researches are required in order to validate the switch.

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