

RESEARCH

ANTIEPILEPTIC DRUG THERAPY AND SERUM CARNITINE LEVELS IN CHILDREN PRIOR TO AND FOLLOWING TREATMENT

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Abstract:

Background:

The physiologic function of carnitine, oxidation of fatty acid and lipid metabolism, is severely affected in carnitine deficiency, secondary forms of which lead to renal tubular disorders and chronic renal failure. Reduction in serum carnitine has been frequently reported in patients and experimental animals treated with antiepileptic drugs, one of which, valproic acid has consistently been found to cause the deficiency; the antiepileptic drugs, valproic acid, has consistently been found to cause the deficiency. Previous results, however, regarding the effects of other antiepileptic drugs have been less consistent. Considering the controversial results available in literature, the aim of this study was to determine the effect of Valproic acid, Carbamazepine and Phenobarbital on serum carnitine levels in epileptic children.

Methods:

In the present study, serum carnitine levels were randomly monitored before and six months after therapy in 39 epileptic patients receiving the antiepileptic drugs mentioned. Patient blood samples were taken before and six months after treatment and L-carnitine level was determined using the UV enzymatic test (Rouche Kit) spectronic Genesis 2, 340 nm.

Results:

Results showed a significant fall in the L-carnitine levels of epileptic children taking these drugs ($P < 0.01$).

Conclusion:

Considering the reducing effect of antiepileptic drugs on serum carnitine levels, it is recommended that a carnitine supplement be administered in pediatric epileptic patients to prevent the deficiency and related consequences caused by such therapies.

Keywords: Carnitine / Epilepsy – in children / Valproic Acid / Phenobarbital/ Carbamazepine

Introduction

The amino acid derivative carnitine is present in most human tissues; its major sources are the diet and de novo synthesis. Blood carnitine increases during the first month of life and remains in the body in adequate amounts for life. The first

known physiologic function of carnitine is the transport of long-chain fatty acids across the mitochondria for beta oxidation (1,2). A subnormal concentration of total carnitine may result from decreased biosynthesis, inadequate dietary intake, inadequate absorption, defective tissue transport, excessive renal excretion or inborn errors of metabolism (3).

A number of clinical studies have shown a significant decrease in blood carnitine concentration in patients taking multiple antiepileptic drugs (AED), including Valproic acid (VPA), Carbamazepine (CZB), Phenobarbital (Ph) (4). In most studies, serum carnitine levels of patients treated with antiepileptic drugs have been compared with levels of control subjects, but not with level in the same patients before treatment. This may lead to erroneous interpretations, since in some epileptic patients serum carnitine concentrations may be affected by underlying metabolic or nutritional states (5-7). Reductions in serum carnitine levels have been frequently reported in patients and experimental animals treated with antiepileptic drugs (4,8-10). In the work reported here, serum carnitine levels were monitored in epileptic children, before and 6 months after treatment using antiepileptic drugs, viz. the three antiepileptic drugs Valproic acid, Carbamazepine, and Phenobarbital used in this study; and the effects were studied.

Materials and methods:

Thirty-nine children, aged between 1 month and 18 years,

were enrolled in the study. All had been referred to the neuropediatrics division of the Ekbatan hospital in Hamadan. Patients with metabolic disorders (such as amino acidopathies, organic acidopathies , or suspected mitochondria disease) , or with serious encephalopathy or malnutrition , were excluded (11). The patients were divided into three groups, depending on treatment received: (11) Group 1 consisted of 13 patients aged 2.5 years to 18 years (mean 7.9 4.8 years) , 10 with generalized seizures including 4 with typical absence seizures , 6 with tonic clonic seizures , 2 with complex febrile seizures and 1 with complex partial seizures received valproic acid , group 2 of 13 patients aged between 1 to 6 years (mean 3.34 1.62) , all with partial seizures including 9 with simple partial seizures and 4 with complex partial seizures received carbamazepine, and group 3 of 13 patients aged between 1 to 36 months (mean 13.15 12.19 months) 4 with tonic clonic seizures , 7 with complex febrile seizures, 1 with simple partial seizures and 1 with complex partial seizures , received Phenobarbital .

Serum carnitine level was randomly monitored before and six months after therapy. Blood samples, obtained with informed parental consent, were taken early in the morning after fasting for 8 hours for determination of L-carnitine level, using the UV enzymatic test (Rouche Kit) spectronic Genesis 2 , 340nm; analyses were done in the biochemistry department , faculty of medicine, Hamadan university.

Table 1 : Mean serum carnitine levels before and during antiepileptic therapy with valroic acid , carbamazepine or phenobarbital

Anti epileptic drug in this study	Serum carnitine level before treatment (mg/l) Mean±SD	Serum carnitine level after treatment (mg/l) Mean±SD	Mean difference	S.E	95% confidence interval	t	P. value*
Valproic acid	4.2±2.2	1.9±0.97	2.34	0.41	1.43~3.24	5.63	P=0.000 Significant
Carbamazepine	3.4±1.7	3.12±1.3	1.28	0.29	0.63~1.92	4.31	P=0.001 Significant
Phenobarbital	3.7±1.4	1.85±0.77	1.81	0.4	0.93~2.7	4.5	P=0.001 Significant

* Paired Samples test

As is shown in table (2) based on ANOVA parametric test, no difference was observed regarding to consumption of the mentioned drugs ($P>0.05$).

Table 2: The comparison of the reduction of serum carnitine levels in epileptic children before and six months after treatment with (mentioned drugs)

Antiepileptic drugs in study	N	Carnitine reduction level in serum (mg/l) mean \pm SD	SE	95% confidence interval	F	P.value
Valroic acid	13	2.34 \pm 1.5	0.41	1.43~3.34	2.057	P=0.143 Non significant
Carbamazepine	13	1.28 \pm 1.06	0.29	0.63~1.92		
Phenobarbital	13	1.81 \pm 1.39	0.40	0.93~2.7		

* One way analysis of variances (ANOVA)

Statistical analysis: Data were expressed as mean \pm standard deviation. Independent samples t-test was used to compare blood L-carnitine level in the patients before and six months after treatment. One-way analysis of variances was used to compare the amount of reduction of serum carnitine level in epileptic children. Statistical significance was considered to be a P. value of less than 0.05.

Results:

Table 1 shows serum carnitine levels in epileptic children before and six months after treatment with antiepileptic drugs. We observed that serum carnitine level reduced significantly in comparison with pretreatment levels and the difference based on the t-test was statistically significant ($P<0.01$).

Discussion:

Reduction in serum carnitine levels have been frequently reported in patients and experimental animals treated with antiepileptic drugs (12). Because of controversial research results, further research in humans in the field is warranted. The present results indicate that a drop serum L-carnitine level (with respect to pretreatment levels in the same patient) occurs not only in patients treated with valproic acid, but also in patients treated with carbamazepine or Phenobarbital and the difference is statistically significant ($P<0.01$).

Fung EL, et al reported that carnitine levels were lower in patients taking valproate. They concluded that routine monitoring of carnitine level was justified in pediatric patients taking valproate (13). In a study done by Zelink et al serum carnitine was measured longitudinally before and after therapy in patients receiving valproic acid, 14 patients receiving carbamazepine and patients receiving Phenobarbital. The patients who received valproic acid showed a significant reduction in carnitine ($P<0.001$). Such an effect however, was not found in patients receiving carbamazepine or phenobarbital (9). Gastro Gago et al reported serum levels of free, acyl, and total carnitine were determined in 32 patients with seizures, before and after treatment with valproic acid (17 patients), carbamazepine (10 patients), or Phenobarbital (5 patients). In all the three treated groups, carnitine levels showed a significant decline with respect to pretreatment levels (11). These findings suggest a need to monitor serum carnitine levels in children treated with any of these drugs. Hiraoka A. reported that reduction in the blood free carnitine (FC) level as a side effect of sodium valproate given to epileptic patients was pharmacokinetically studied in connection with changes in the VPA disposition. The serum FC level in patients taking at least one of Phenobarbital or phenytoin (PHT) or carbamazepine in addition to VPA was significantly lower than in controls given only any one of these antiepileptic drugs. Patients medicated only with VPA also tended to

have a lower serum free carnitine level than the controls, although the difference was not significant (4). Comparing the reduction of serum carnitine level in epileptic children, based on ANOVA parametric test, no difference was observed regarding consumption of the mentioned drugs ($P>0.05$). We did not find any significant correlation between age and serum carnitine levels, although such a correlation (level increasing with age) has been detected in a previous large sample study (14).

Conclusion:

The present results thus recommend the monitoring of serum levels of free and total carnitine not only in children undergoing treatment with valproic acid, but also in those undergoing treatment with carbamazepine or phenobarbital. Monitoring should ideally begin before treatment starts, so that subjects may act as their own controls. This is important, since serum carnitine level may differ from one individual to another because of certain factors including age, nutrition and metabolic status (15-17). In case of confirmation of carnitine deficiency or insufficiency, one recommendation would be to administer an oral L-carnitine supplement.

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