

Relation between serum Vitamin B₁₂ level and duration of treatment with carbamazepine in epilepsy patients

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Abstract

Vitamin B₁₂ levels in the serum of 58 epileptic patients receiving only carbamazepine for at least 6 months were measured. Same number of epilepsy patients with no history of taking antiepileptic medicine were taken as control. The mean level of vitamin B₁₂ in carbamazepine-treated epileptic patients was 265.5 pg/mL whereas it was 478.3 pg/mL in control. Increased duration of treatment of carbamazepine in epilepsy caused significantly decreased level of serum vitamin B₁₂ (Pearson correlation coefficient, $r = -0.9$, $p < 0.0001$). In conclusion, serum vitamin B₁₂ level significantly decreased in relation to duration of carbamazepine treatment in epileptic patients.

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures of cerebral origin, with episodes of sensory, motor or autonomic manifestation with or without loss of consciousness.¹ Antiepileptic drugs are the simplest and the safest means of controlling epilepsy. Several studies have suggested that treatment with distinct antiepileptic medicines like valproate, carbamazepine or phenytoin is associated with reduced mean serum levels of folate and vitamin B₁₂. However, long-term administration of antiepileptic medicine has a number of adverse effects, one of which is the lower level of serum vitamin B₁₂.¹

While the reason for this reduced vitamin B₁₂ level remain obscure, several mechanisms have been proposed. One hypothesis is the increased pH of the small intestine, inhibiting the intestinal conjugate activity and impairing the intestinal absorption of vitamin B₁₂. Other hypotheses include direct competition between folate and antiepileptic drug for uptake sites, inhibition of vitamin B₁₂ interconverting enzymes by antiepileptic medicine, increased catabolism of vitamin B₁₂ by induction of vitamin B₁₂ catabolic enzymes, inhibition of central appetite centers by antiepileptic medicine decreasing food intake, thereby leading to decreased tissue vitamin B₁₂ concentrations.²

However, there are very few reported studies which estimate the serum vitamin B₁₂ concentration in epileptic patients receiving carbamazepine for less than 6 months. Therefore, our

study goal was to explore the level of serum vitamin B₁₂ in epileptic patients receiving carbamazepine therapy for at least 6 months duration.

Materials and Methods

This study was conducted on 116 epileptic patients from July 2013 to December 2015. Half of the patients were receiving carbamazepine and the rest half were still not on any antiepileptic medicine. Epileptic patients were selected irrespective of sexes seeking treatment at the outpatient department. Patients were selected on the basis of inclusion and exclusion criteria. Patients aged between 14 to 60 years, diagnosed as epilepsy and receiving only carbamazepine for at least 6 months were included. Epileptic patients with other systemic diseases: Chronic liver disease, kidney disease, hypothyroidism, leukemia, inflammatory bowel disease and psoriasis or patients taking antitubercular medicines, other antiepileptic medicines, folic acid supplement, receiving vitamin B₆, vitamin B₁₂ or on folate antagonists, smokers and pregnant lady were excluded from this study.

Detailed history and clinical examination were carried out for each patient using predesigned proforma. Baseline investigation of serum vitamin B₁₂ level was collected.

Selected patients were send to the Department of Biochemistry of the same University for assessment of serum vitamin B₁₂ level. The



venous blood was collected after 6 hours of fasting.⁶ Assessment of serum vitamin B₁₂ level was done by Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols referred to as chemiflex.

After collection of sample, patients were grouped as follows: Group 1: Patients on carbamazepine; Group 2: Patients of control group.

Statistical analysis

Statistical analysis was performed Statistical Packages for Social Sciences (SPSS-21). Association between categorical variables were analyzed by chi-squared test and continuous variable by independent sample t-test used for normal distribution. Correlation was done by Pearson correlation coefficient test, as for normal distribution. Normality of distribution was seen by Shapiro-Wilk test. For all statistical tests, we considered p value <0.05 as statistically significant.

Results

The parameters of these two groups were more or less same (Table I). The mean age was found 25.3 years in patients and mean age was 25.8 years in control. The mean duration of illness was 62.3 months. The duration of diagnosis was 51.4 months while duration of treatment was 35.3 months.

The level of serum vitamin B₁₂ in patient of Group 1 was 265.5 pg/mL whereas it was 478.3 pg/mL in control. The differences were highly significant. In epileptic patients with carbamazepine therapy, normal level of serum vitamin B₁₂ was found in 32 patients which accounted 55.2% and decreased level in 26 patients or 44.8%. On the other hand, in control group, 100% had normal value of serum vitamin B₁₂.

The distribution of patients according to low and high level of vitamin B₁₂ (pg/mL). Median serum vitamin B₁₂ was 333 pg/dL. This value was taken as cut off value. As per this cut off value, serum vitamin B₁₂ was low in 45 patients and high in 13 patients in case. Serum vitamin B₁₂ was low in 14 patients and high in 44 patients in control. There was statistical significant difference between this two groups.

Figure 1 shows correlation between serum vitamin B₁₂ and duration of treatment of carbamazepine in epilepsy patients. As both serum vitamin B₁₂ and duration of treatment were continuous variables and distribution normal, so Pearson correlation was done between them. Here, we found a negative and highly significant correlation coefficient ($r = -0.959$, $p < 0.0001$). Therefore, we can conclude that increase duration of treatment of carbamazepine in epilepsy patients causes significantly decrease level of serum vitamin B₁₂.

Table I		
Parameters of patients		
	Case	Control
Age (year), mean	25.3	25.8
Sex		
Male	42	34
Female	16	24
Type of epilepsy		
Generalized-primary	35	24
Complex partial	0	3
Secondary generalized	23	31
Duration of illness (month)	62.3	4.6
Duration of diagnosis (month)	51.4	Newly diagnosed
Duration of treatment (month)	35.3	-

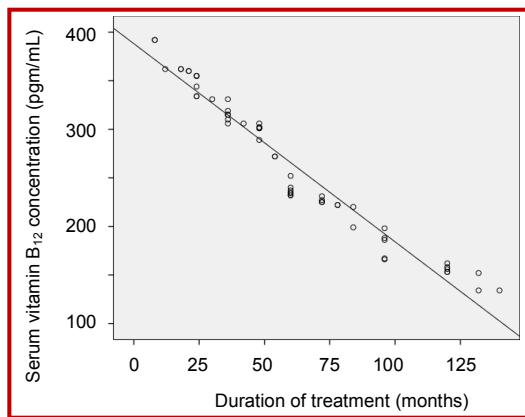


Figure 1: Correlation between serum vitamin B₁₂ and duration of treatment of carbamazepine in epilepsy patients

Discussion

The main focus of this research work was to explore serum vitamin B₁₂ level. Out of all epileptic patients using only carbamazepine as antiepileptic drugs found highly statistically decreased mean value of serum vitamin B₁₂ than control group. Moreover, range of serum vitamin B₁₂ level in carbamazepine treated patients was 134 to 392 pg/mL whereas that of 255 to 736 pg/mL in control group.

In a study it was found 6 months of carbamazepine therapy did not cause significant change in serum levels of vitamin B₁₂; mean vitamin B₁₂ at recruitment and at 6 months are in accordance with our findings.¹⁵ In another study it was found low vitamin B₁₂ level in patients which was comparable to this study.^{6,16} Another study concluded as in

carbamazepine group serum vitamin B₁₂ levels were lower than control group.⁶ Another study showed that mean serum level of vitamin B₁₂ was significantly higher in all epileptic patients, whereas, its mean serum level was no significantly higher in antiepileptic drug users when compared to control.¹⁷ On the contrary, in a study showed that serum vitamin B₁₂ concentration were elevated in all patients.¹¹ Increased circulating vitamin B₁₂ level, however, served as a sensitive biochemical index of hepatic damage due to anticonvulsants¹⁸. Prolonged drug treatment was possibly the cause of the slightly impaired ability of the liver to store vitamin B₁₂.¹⁹

Considering normal level of vitamin B₁₂ of 239-931 pg/mL²⁰, decreased level found in 44.8% in epileptic patients with only carbamazepine therapy and normal level in 55.2%. Whereas in control group, all had normal value of serum vitamin B₁₂ which was highly statistically significant ($p < 0.0001$). In addition, on consideration of median value 333 pg/mL as cut off point, statistical significant difference was found between case and control group in frequency of patients. In a study it was found that 17.8% patients had low vitamin B₁₂ levels.¹⁶ Nonetheless, on account of correlation between serum vitamin B₁₂ and duration of treatment of carbamazepine in epilepsy patients, we found a negative and highly significant correlation coefficient ($r = -0.959$, $p < 0.0001$). In epileptic patients using only carbamazepine as antiepileptic drugs, the mean (SD) value of serum vitamin B₁₂ found 265.52 (74.28) pg/mL which significantly decreased value in context of control patients 478.34 (145.93) pg/mL ($p < 0.0001$).

Conclusion

Increase duration of treatment of carbamazepine in epilepsy causes significantly decrease level of serum vitamin B₁₂. As it is well known that reduced level of vitamin B₁₂ related with hyperhomocystenemia whereas homocysteine is an atherogenic agent.

Ethical Consideration

The aim of the study along with its procedure, risk and benefits was explained to the respondents in easily understandable local language and informed written consent was taken from each patient. It was assured that all information and record would be kept confidential and the result of the study would be helpful both for the physicians and patients in making rational approach of the management of epilepsy. Approval from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University was obtained prior to the commencement of this study.

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