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TANIGUCHI, HIROSHI

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HIROSHI TANIGUCHI, KAZUSHIGE EJIRI, AND SHIGEAKI BABA

Second Division, Department of Internal Medicine
Kobe University School of Medicine

INDEXING WORDS

autonomic neuropathy; cardiac beat-to-beat variation; uremia; hemodialysis; methylcobalamin

SYNOPSIS

In order to assess the effect of methylcobalamin, the most prevalent analog of vitamin B_{12} in human serum, on autonomic neuropathy in hemodialyzed uremics a daily dosis of 1500 μg methylcobalamin was administered for 3 or 6 months to 8 uremics with abnormal cardiac beat-to-beat variation (BBV). Half of them were diabetic nephropathics. Six non-diabetic uremics with normal BBV also underwent this vitamin administration, while the other six patients without its oral intake entered the study as control. In non-diabetic uremics with normal BBV no significant effect of methylcobalamin was observed. However, in the uremics with impaired autonomic nerve function the vitamin B_{12} analog ameliorated the abnormality 6 months after its administration. These observations indicate that methylcobalamin improves the autonomic neuropathy, a complication of chronic renal failure, either diabetic or non-diabetic in origin.

INTRODUCTION

It has long been known that a peripheral neuropathy develops

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Authors' names in Japanese : 谷口 洋, 江尻一成, 馬場茂明

in chronic renal failure.[1, 7, 12, 30, 40] Besides, various disturbances of the autonomic nervous system have been noticed in patients with chronic renal insufficiency, and these include changes in sweat gland secretions,[10, 14] a reduction of baroreceptor sensitivity,[19, 20] abnormal response to the Valsalva maneuver,[5, 9, 33] reduced elevation in blood pressure in response to sustained hand-grip exercise,[5, 9] nonvolume responsive hypotension during hemodialysis,[5, 16] a reduction in pupillary motor reflex[31] and impotence.[4, 41] However, there have been no established treatments for these complications. Hemodialysis may ameliorate them,[5, 12] but it is unsatisfactory.[12] One of the possible explanations may be loss of water-soluble vitamins caused by frequent hemodialysis and those vitamins have been used since the early stage of application of hemodialysis for management of uremia.[11] Lowered serum concentration of vitamin B_{12}, which is involved in maintenance of the nerve function, has been reported in dialysis compared with nondialysis patients.[2, 23, 32] Serum vitamin B_{12} levels and nerve conduction velocities show a significant correlation[32] and improvement of nerve conduction in dialyzed patients with low serum vitamin B_{12} levels is obtained following administration of this vitamin.[32]

Recently, methylcobalamin, an analog of vitamin B_{12}, has been shown to ameliorate peripheral neuropahy in uremics on hemodialysis.[15] This analog has also been found to improve peripheral neuropathies of various origins other than uremia.[6, 42, 43] However, no observations have been reported regarding its effect on autonomic neuropathy in uremics. In the present communication the cardiac beat-to-beat variation (BBV) as a marker of autonomic neuropathy was examined in the hemodialyzed due to renal insufficiency and the effect of methylcobalamin was assessed in terms of improvement of the autonomic neuropathy in these patients.

SUBJECTS AND METHODS

Twenty chronic uremics, 6 males and 14 females, without arrythmia and cardiac failure were subjected to the study. Their age (mean ± SEM) was 52.6 ± 2.3 years ranging from 34 to 69 and the duration of hemodialysis (mean ± SEM) was 6.5 ± 1.4 years ranging from 0.25 to 28 years. The patients were hemodialyzed 4-6 hours per operation and 3 times weekly. One patient had pyelo-

nephritis, one polycystic kidney and 4 diabetes mellitus as primary disease of the renal failure, while the rest of the patients had glomerulonephritis.

Eight (2 males and 6 females) out of 20 patients showed abnormality in BBV test. All diabetics were included in this abnormality group. Their age was 55.5 ± 4.6 years ranging from 34 to 69 and had been hemodialyzed for 9.4 ± 2.9 years. They were administered 1500 μg methylcobalamin orally for 6 months. Their HbA_1 levels were less than 10.8% over a period of this study and did not change significantly.

On the other hand, 12 subjects (4 males and 6 females) showing normal values in this test were 50.6 ± 2.5 years in age ranging from 37 to 66 and had been hemodialysed for 4.3 ± 1.1 years. No significant difference was observed in age and duration of hemodialysis between the normal and abnormal subjects in the test. The uremics showing normality in the test were divided into two subgroups; one consisting of 6 subjects (2 males and 4 females) with 1500 μg methylcobalamin treatment for 3 months and the other consisting of the same number of subjects with the same sex ratio without the treatment. The age in the former and the latter group was 53.2 ± 3.8 and 48.0 ± 2.5 years, respectively, and the duration of hemodialysis was 4.4 ± 2.0 and 4.3 ± 1.1 years, respectively. There was no statistical difference in both age and duration of hemodialysis between these two subgroups.

Cardiac BBV was taken as an index of autonomic nerve function. The test for this determination was described elsewhere.[39] Briefly, the subjects lying supine for at least 10 min were subjected to a ECG recording during 5 successively repeated deep respirations with 5 sec inspiration and 5 sec expiration per respiration. Cardiac beat was calculated from each R-R interval on ECG using a computarized calculator "Autonomic R-105" (M.E. Commercial Corp., Tokyo) developed at our laboratory. Subsequently the difference between the maximal and the minimal cardiac beat during one respiration was obtained and the mean of the differences among 5 repeated respirations was expressed as BBV. The results in this test were evaluated in comparison with those of the age-matched healthy subjects described elsewhere.[38] The test was performed prior to an operation of hemodialysis before and at 3 and 6 months of oral administration of a total daily dose of

1500 μg methylcobalamin.

The results were indicated as mean ± SEM and assessed by a paired analysis of Student's t-test.

RESULTS

In the hemodialized uremics without abnormality in BBV test the control group showed the BBV value of 7.2 ± 1.1 and 7.2 ± 1.7 beats/min (n=6) before and 3 months afterwards, respectively, whereas the experimental group 8.6 ± 1.6 and 9.8 ± 2.0 beats/min (n=6) before and 3 months after initiation of methylcobalamin administration, respectively (Figure 1). In the control group there were 2 patients deteriorating in 3 months, while the other group on methylcobalamin treatment produced one with abnormal BBV in 3 months. However, no significant difference of BBV in this length of period apart was found in either group.

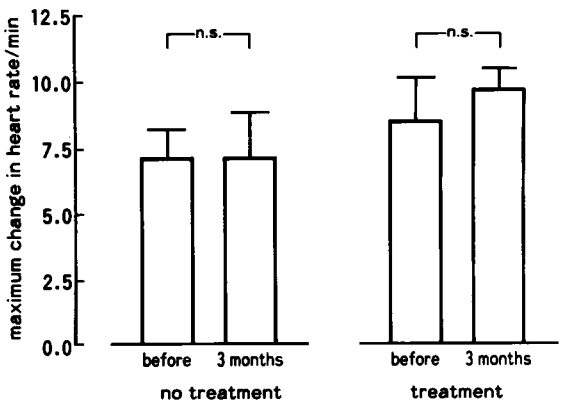

Fig. 1 Cardiac beat-to-beat variation in hemodialyzed non-diabetic uremics with (right panel) and without (left panel) methylcobalamin administration. Twelve non-diabetic uremics with normal beat-to-beat variation were divided to two groups, i.e., 6 with and 6 without daily administration of 1500 μg methylcobalamin for 3 months. The test to determine the cardiac beat-to-beat variation was performed prior to an operation of hemodialysis. The cardiac beat-to-beat variation was assessed before as well as at the termination of the administration, and is indicated as maximum change in heart rate per min on the ordinate.
n.s.: not significant.

The subjects revealing abnormal values in BBV test, i.e., 3.3 ± 0.2 beats/min (n=8), showed an improvement of BBV value, i.e., 5.9 ± 1.1 (n=8) ($p<0.1$) and 5.8 ± 0.5 beats/min (n=7) ($p<0.005$) at 3 and 6 months of the treatment, respectively (Figure 2). In 3 months of administration 5 showed the normal value, out of which 3 were diabetic uremics, while in 6 months 5 out of 7 patients followed-up were in normal range.

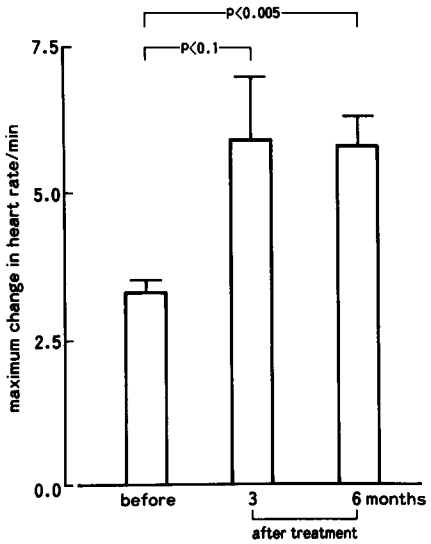

Fig. 2
Effect of methylcobalamin administration on cardiac beat-to-beat variation in uremics on hemodialysis. Eight subjects depicted in the figure were all abnormal in cardiac beat-to-beat variation test before initiation of methylcobalamin administration. Seven took 1500 μg methylcobalamin daily for 6 months, while one for 3 months. The test was carried out prior to an operation of hemodialysis, and the cardiac beat-to-beat variation was assessed before and at 3 and 6 months of the administration. The results are shown as maximum change in heart rate per min.

DISCUSSION

In recent years distinct peripheral neuropathy in uremics has not been encountered frequently because of development of hemodialysis and its extensive application. However, its incidence is still high according to the sophisticated electrophysiological studies.[7, 15] Besides, autonomic neuropathy is noticed even on hemodialysis; impaired response to the Valsalva maneuver,[9, 33] abnormal baroreceptor response to rise in blood pressure[25, 29] and hypotension during hemodialysis.[16] This autonomic neuropathy is sometimes so serious as to induce cardiorespiratory arrest[20, 26] and therefore its early detection and management is an important issue in uremic on hemodialysis.[22] Among various

methods devised for examination of the autonomic nerve function, measurement of BBV from ECG recordings during deep respirations is becoming popular[27, 28, 36] because of its simplicity, non-invasiveness as well as sensitive and quantitative detection of disturbance of the nervous dysfunction.[27, 28, 36, 38, 39] Using this method high frequency of autonomic disorder has been recognized in diabetics.[13, 27, 38] In the present study all diabetics tested revealed the autonomic abnormality and even in the non-diabetic uremics on hemodialysis 25% of them were autonomically abnormal. A recent report has revealed impaired function by BBV test in 69% of patients with chronic renal failure.[21]

The mechanism for the development of neuropathy remains unclear, though various hypotheses have been advocated.[37] Vitamin deficiency has long been suggested as one of plausible explanations of diabetic neuropathy, but some controlled studies show no amelioration of the neuropathy by administration of vitamins B_1, B_6 and B_{12}, indicating little role of these vitamins in the pathogenesis of the nerve dysfunction.[37] However, methylcobalamin, the most prevalent form of vitamin B_{12},[34] has been found decreased to one half that of non-diabetic controls,[35] and observed to prevent degeneration of peripheral nerves in diabetic animals[42] as well as to recover the peripheral neuropathy in humans.[43] Thus, a certain form of vitamins might be involved in the peripheral nerve disturbance.[37] In the uremic peripheral neuropathy an improvement of ulnar nerve excitability has been recognized after administration of 1500 μg methylcobalamin for 3 months.[15] These observations suggest another possibility, i.e., a favorable effect of methylcobalamin on autonomic neuropathy, but no studies relevant to this have been reported to our knowledge. In our current investigation this vitamin analog recovered the autonomic dysfunction in 62.5 and 71.4% of diabetics at 3 and 6 months of the administration, respectively, and especially in the non-diabetic uremics the recovery rate was 50 and 75%, respectively. This implies that much longer administration of methylcobalamin may be more effective, although the duration of the neuropathy might be taken into consideration as a factor to hinder this effect. Furthermore, 33.3% of uremics with normal BBV values became abnormal in an interval of 3 months, whereas 16.7% of them

did when treated with methylcobalamin. Although these figures are not statistically different, this vitamin may prevent the deterioration of the autonomic function in uremics.

Vitamin B_{12} level is reported to be lowered in the renal failure,[32] whereas some observations indicate no remarkable difference in the level between the hemodialyzed and the healthy control[23] as well as between before and after hemodialysis.[18] Recently it has been observed that methylcobalamin constituting around 70% of total serum vitamin B_{12} in the healthy subjects[34] is lowered to 40.4 - 54.2% in the hemodialyzed patients.[17] The relative proportion of methylcobalamin increases to around 84% by the oral administration of 1500 μg methylcobalamin for 3 months.[34] These findings support the explanation that an elevation of serum methylcobalamin in uremic patients with probable decrease of methylcobalamin may be involved in the improvement of autonomic nerve function. This understanding is consistent with the current recovery of BBV observed in uremia whether it was diabetic or non-diabetic in origin.

Besides the afore-mentioned possibility dialysis itself might ameliorate the autonomic lesions. Although it is the case in non-diabetic renal insufficiency, a detelioration of the nerve function is observed in diabetic uremia.[13] Furthermore, no significant correlation between BBV and duration of dialysis[3] and our recent observations of unchanged BBV before and after an operation of hemodialysis[8] suggest that the present correction of BBV might not be caused solely by dialysis.

Normalization of metabolism, mainly of blood glucose, is one of the most important factors for the recovery of neuropathy in diabetes mellitus.[21, 24] In a course of the present investigation the HbA_1 level was not significantly varied in each diabetic. However, it should be carefully discussed whether the amelioration of the neuropathy in the present study was merely due to the probable increase of methylcobalamin.

Methylcobalamin, though a tiny amount, is a vitamin physiologically present in the humans. It is widely applied clinically and no serious adverse effects have been reported. Considering these with the current observations, methylcobalamin is one of the agents to be tried for the management of autonomic as well as peripheral neuropathy in uremics, either diabetic or non-diabetic.

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