THIAMINE METABOLISM IN PATIENTS WITH NERVOUS DISEASES

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Although there is considerable literature on disorders in the central nervous system (CNS) as a result of thiamine deficiency, there are few reports concerning the effect of such disorders on thiamine metabolism. The author carried out such studies and the data obtained are outlined herein.

1. Blood thiamine levels in healthy adults and those with CNS disorders

The mean blood thiamine value in 110 normal adults was $8.3 \pm 1.3 \mu g/dl$. In 22 patients with organic diseases of the CNS such as amyotrophic lateral sclerosis, brain tumor, sequelae following cerebral apoplexy and anterior poliomyelities, the mean thiamine value was $5.0 \pm 1.1 \mu g/dl$, that of 35 schizophrenic patients was $5.7 \pm 1.0 \mu g/dl$, 20 cases of neurosis was $5.3 \pm 1.0 \mu g/dl$ and other psychosis was $6.0 \pm 1.3 \mu g/dl$. These values are significantly lower than in normal patients (Fig. 1). In cases where blood thiamine levels are lower than $6.0 \mu g/dl$, a thiamine deficiency usually exists. The rate of occurrence was thus determined and was found to be $18.2\%$ in normal adults and $60-80\%$ in those with CNS-related diseases.

2. Thiamine deficiency in humans

As it is generally considered that the blood thiamine level depends on the ingestion of thiamine, studies were done to determine to what extent the blood thiamine values change in proportion to the ingestion of thiamine. Figure 2 shows the results in 1 out of 6 cases in which the ingestion of thiamine was limited to approx. $30 \mu g$ for 21 days, a regimen which resulted in a thiamine deficiency. About 10 days after initiation of the thiamine-deficient diet symptoms such as general lassitude, heavy feeling in the lower extremities and anorexia

Fig. 1. Blood thiamine levels.

21-YEAR OLD STUDENT

General lassitude, anorexia, heavy feeling in legs

decrease of patellar tendon reflex, intensity of $P_2$ sounds

Fig. 2. Changes in blood thiamine levels in healthy adults after ingestion of a thiamine-deficient diet.
appeared and in about 15 days, decrease in the patellar tendon reflex and increase in the intensity of P2 sounds followed. The blood thiamine concentration was at a minimum at about 14 days and the lowest decrease was 2.6 µg/dl. On the 21st day, the last day of the experiment, however, there was no further decrease in the value rather a slight increase was observed.

3. Changes in blood thiamine levels in healthy adults after a daily 10 mg injection of thiamine

The experiment was carried out as follows: 10 mg of thiamine was given subcutaneously to 10 normal adults in the early morning everyday for 9 days. During the experiment, 8 subjects were at their usual light work and the other 2 subjects did moderately heavy work. At the time of determination of the blood thiamine levels carried out before the loading with thiamine, on the 4th, 7th and 10th days of the experiment, the blood thiamine levels gradually increased. In the 8 subjects doing light work, the levels increased to 13 to 18 µg/dl on the 10th day, but decreased to levels before the load on the 4th day after discontinuation of the thiamine injection. Thus the blood thiamine levels fluctuate in a range between 2.7 µg/dl and 18 µg/dl according to the difference in the amount of ingested thiamine.

4. Changes in blood thiamine levels in patients with CNS diseases after a daily 10 mg injection of thiamine

Blood thiamine levels in patients with diseases of the CNS are significantly lower than those in the normal adults and such was first shown to be attributed to the small amount of thiamine ingested. To eliminate such a possibility, patients with diseases of the CNS were loaded with thiamine in the same way as normal adults who were consecutively given 10 mg of thiamine subcutaneously and the following results were obtained:

Figure 4 shows the results obtained in 22 cases of organic diseases of the CNS. Increase
in the blood thiamine levels in 19 cases, except for cases 1, 2 and 3, was obviously less than in normal adults. The rate was $15.3 \pm 2.3 \, \mu g/dl$ in normal adults on the 10th day of the load, while it was $9.2 \pm 2.7 \, \mu g/dl$ in patients with CNS disorders. This suggests that in many such cases the blood thiamine levels do not increase as they do in normal adults, although in some cases, the levels did increase to the same extent as in the normal adults. Of the exceptional cases, case 1 was a myelosyphilis and case 2 and 3 were acute anterior poliomyelities; and all recovered with treatment.

Of 19 patients in whom a slight increase in the blood thiamine levels was seen, case 4 was an acute myelitis and case 5 a cerebellar tumor, both of whom died; case 6 was a progressive spinal muscular atrophy and case 7 an amyotrophic lateral sclerosis, and in both cases the condition deteriorated. The condition of the remaining patients was unchanged during the observation period. Figure 5 shows the results in 5 cases of sequelae following cerebral apoplexy, of which the cause and symptoms were almost uniform. In all cases, the increase in the blood thiamine levels was slight. Figure 6 shows the results in schizo-

![Fig. 5. Changes in blood thiamine levels after daily injection of 10 mg thiamine.](image5.png)

![Fig. 6. Changes in blood thiamine levels after daily injection of 10 mg thiamine.](image6.png)

![Fig. 7. Changes in blood thiamine levels after daily injection of 10 mg thiamine.](image7.png)
phrenia in which the organic disorder was not clear. Here too the increase in the blood thiamine levels was also slight. Figure 7 shows the results with neurosis. Increase in the blood thiamine levels was slight. Diseases such as liver cirrhosis are those in which increase in the blood thiamine levels is slight despite loading with thiamine. Liver function was tested in the above neurologic diseases, but positive findings were nil.

The fact that increase in the blood thiamine levels is slight even though thiamine loading is continued, is these ascribed to a disorder of the CNS.

5. Urinary thiamine excretion after a daily injection of 10 mg thiamine

Figure 8 shows the mean value of thiamine excreted in the urine when a 10 mg of thiamine was given subcutaneously consecutively to 4 normal adults and data were compared with that of 15 patients with diseases of the CNS. On this regimen, about half of the dose was excreted into the urine. Urinary thiamine excretion in the cases of diseases of the CNS tended to be greater. Figure 9 shows the results when 1 mg of thiamine was given orally. The measurement of the amount of thiamine excreted into the urine by loading with 1 mg of thiamine was previously used in the determination of thiamine deficiency. If thiamine deficiency is present, the urinary thiamine excretion is slight, because most of the thiamine loaded in a dose of 1 mg is utilized for saturation in the body.

The blood thiamine concentration in a normal adult selected as control was 5.8 µg/dl and that in a patient with a disease of the CNS was 5.4 µg/dl. As both levels were less than 6.0 µg/dl, they were included in the category of thiamine deficiency from the viewpoint of the blood thiamine levels alone. In a study of the amount of thiamine excreted into the urine over a 24-hr period when 1 mg of thiamine was given orally and consecutively levels were higher in the patient with a CNS disease than in the normal adult.

Thus, the data in these two experiments support the hypothesis that the ability of retaining thiamine in the body is decreased in the presence of a neurological diseases.
6. Urinary thiamine excretion after discontinuation of consecutive load with thiamine and thiamine propyl disulfide

If the ability to retain thiamine in the body is decreased in cases of neurological diseases, how the blood thiamine levels and urinary excretion of the thiamine are effected by loading with thiamine propyl disulfide (TPD) which has an extremely strong affinity with tissue appeared worthy of study.

Figure 10 shows the results obtained in a 46-year-old patient with spastic spinal paralysis. In this patient, 10 mg of thiamine was injected subcutaneously for 18 days. The fasting blood thiamine concentration in the early morning was 9.5 μg/dl on the 19th day as shown in the bottom of the figure, and the urinary excretion of thiamine immediately decreased when loading with thiamine was discontinued. In this patient, 50 mg of TPD was given orally for 7 days and the fasting blood thiamine concentration in the early morning was increased to 9.1 μg/dl, almost the same level as in the case of the subcutaneous injection of thiamine, on the 8th day. Urinary thiamine excretion after discontinuation of the oral administration of TPD was 6 mg on the 4th day and 10 mg on the 8th day. It can be seen from this result that thiamine is retained in the body by loading with TPD in greater quantities than those presumed from the increase in the blood thiamine concentration.

Figure 11 shows a patient with amyotrophic lateral sclerosis. In this patient, oral administration of TPD in a daily dose of 50 mg was continued for 18 days. The blood thiamine concentration remarkably increased to 17.1 μg/dl on the 19th day, but the urinary thiamine excretion decreased rapidly to 8 mg on the 4th day and to 3 mg on the 8th day after discontinuation of TPD. In this case, therefore, thiamine was not retained in the body to the extent presumed from the blood thiamine levels and the patients condition worsened.

TPD having a stronger affinity to tissue than thiamine increases the thiamine concentration in the tissue to a higher extent than the increase in the blood thiamine concentration. In the patient in whom thiamine concentration is
increased more in the tissue with TPD administration, thiamine may be retained in large amounts in the body. In such a patient, the prognosis is favorable, while in cases where thiamine is retained in smaller amounts, the prognosis is less favorable.

7. Thiamine propyl disulfide effective in CNS disorders

Table 1 shows the result in the case of spastic spinal paralysis mentioned above. Oral administration of TPD was continued and the patient was almost completely cured of the disease.

This patient was initially almost unable to walk. Oral administration of TPD in a daily dose of 50 mg was continued. Foot and patellar clonus were strikingly improved from about the 4th week and he began to walk. The blood thiamine concentration was increased from the initial 5.4 μg/dl to 14 μg/dl. In the 9th week, he recovered to the extent that he could walk about outside the hospital. The blood thiamine concentration increased further to 21 μg/dl. He was discharged at the 10th week.

Since spastic spinal paralysis is a disease classified as an amyotrophic lateral sclerosis in a broad sense, TPD, was used later in 6 cases of amyotrophic lateral sclerosis patients but was not so effective. Some neurologists are of opinion that when a neurologic disease diagnosed as amyotrophic lateral sclerosis was completely cured, such may not have been a true case. In view of the symptoms, this case, however, was a type of amyotrophic lateral sclerosis.

Kimura (3) reported that TPD is effective in the treatment of amyotrophic lateral sclerosis, an endemic disease in Wakayama Prefecture and that the disease is associated with deficiency of minerals such as Ca and Mg. Itokawa (4,5) reported that thiamine to a certain plays a role in the metabolism of Ca and Mg. It is assumed that not only is thiamine increased in tissue but Ca also increases in tissue when TPD is given, thus leading to an improvement is seen in nervous function.

CONCLUSION

Blood thiamine levels in disease of the CNS were significantly low and even after consecutive subcutaneous injections of 10 mg of thiamine the increase was only slight when compared with that of normal adults. Those in whom the increase in blood thiamine level was the same as in the controls had a favorable prognosis. Regarding urinary excretion of thiamine after consecutively loading with thiamine, higher rates were seen in patients with CNS diseases. It would thus appear that the ability to retain thiamine is generally decreased.

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Table 1. A case of CNS disease successfully with TPD.

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Blood thiamine level (μg%) 5.4 10.7 12.2 13.3 13.7 13.7 14.0 14.1 21.5 18.0

a 46-year-old male.
b Daily dose of 50 mg TPD.
c ++++: signs most remarkable.
in patients with diseases of the CNS.

When TPD which has stronger affinity with tissue than thiamine was given orally, thiamine levels in the body increased to a greater extent than presumed from the increase in the blood thiamine levels. The ability to retain thiamine in the body is lower in the patients with an unfavorable prognosis in the disease of the CNS, while it is higher in those with a favorable prognosis.

REFERENCES