Eur Arch Psychiatr Neurol Sci (1990) 239:218–220

European Archives of Psychiatry and Neurological Sciences



# Thiamine Tetraphydrofurfuryl Disulfide in Nutritional Polyneuropathy

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**Summary.** An open trial with thiamine tetrahydrofurfuryl disulphide (TTFD) was carried out on 44 patients with nutritional polyneuropathy who were admitted to the Neurological Department, Dr. Soetomo Hospital, Surabaya, Indonesia, Thirty-four patients showed improvement of their motor functions ($P < 0.01$) with slight restoration of sensory function and reflexes ($P < 0.1$). Of the 18 patients who were re-examined electrophysiologically 3 months later, 6 showed remarkable improvements. No side-effects were observed during TTFD treatment. It seemed that nutritional polyneuropathy in our low socio-economic patients was mostly caused by thiamine deficiency.

**Key words:** Thiamine tetraphydrofurfuryl disulphide – Nutritional polyneuropathy – Beriberi – EMG findings

## Introduction

In 1985 nutritional polyneuropathy constituted 4.3% of the 1015 neurological admissions to the Dr. Soetomo Hospital in Surabaya, Indonesia. It affected the low socio-economic patients seven times more frequently than the middle and high socio-economic patients.

The diet of the low socio-economic Indonesian consists mainly of machine decorticated rice, which contains a low amount of protein. It seems likely that nutritional polyneuropathy in our low socio-economic patients is caused by a lack of thiamine. Our study was intended to determine if our low socio-economic polyneuropathic patients suffered from thiamine deficiency.

We chose thiamine tetrahydrofurfuryl disulphide (TTFD) because it has the following advantages in comparison with ordinary thiamine HCl. TTFD gives a higher blood concentration with both oral and parenteral administration and the high level is maintained longer. Its tissue affinity is much greater compared with that of ordinary thiamine. It is rapidly converted to the activated form of thiamine cocarboxylase and it is very little affected by thiaminase [1].

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## Materials and Methods

The subjects examined were 44 patients who had been admitted to the Neurological Department of the Dr. Soetomo Hospital, Surabaya, Indonesia, between August 1986 and August 1987. Their ages ranged from 14 to 65 years, with a mean age of 25.9, SD 12.7 years. Most of the patients came from Surabaya and surrounding areas. All patients were from low socio-economic families with incomes ranging from 5.5 to 55 U.S. dollars a month. They were given $2 \times 25$ mg TTFD intravenously daily for 6 weeks in an open trial.

The criteria for patients to be in this study were as follows:

1. Symmetrical impairment or loss of motor, sensory and reflex functions, usually affecting the legs earlier and more severely than the arms and their distal segments more than the proximal ones.
2. Exclusion of other polyneuropathies, e.g. diabetes mellitus, uraemia, leprosy, Guillain-Barré syndrome and intoxication.
3. History of nutritional deficiency.
4. Electroneuromyographic parameters indicative of polyneuropathy, as for instance prolonged nerve conduction velocities, denervation activity and reduced interference patterns especially in the leg muscles, based on the normal values mentioned in Notermans [8].
5. No cells or increase of protein in the cerebrospinal fluid.

Routine examination included electrocardiogram, radiography of the chest, blood, urine, stool and cerebrospinal fluid tests and other blood sugar, liver and kidney function tests, total serum protein, serum albumin and serological tests for syphilis were performed. To achieve an objective evaluation of their neurological status all patients were uniformly scored with a modification of Gilroy's Scoring [3].

The scoring method allows a maximum of 100 points for a neurologically intact person, i.e. as follows: normal cranial nerves, 20 points; normal reflexes, 18 points; normal sensory functions, 10 points; and normal motor functions, 52 points.

This scoring system was devised to express the severity of loss of function. The method is relatively simple and highly

reproducible, even if the same patient is scored by different neurologists. The patients were graded as follows: a score of 30–50 means that the neurologic status is poor; a score of 50–70 indicates that it is fair; a score of 70–90 indicates that it is good; and a score of more than 90 that it is excellent.

On admission all patients were classified into four distinct stages: stage 0, normal (score 100); stage I, mild (score 70–90); stage II, moderately severe (score 50–70); stage III, severe (score 30–50).

## Results

There were 20 patients with severe nutritional polyneuropathy (stage III); 12 were males and 8 were females. Their ages ranged from 14 years to 65 years, with a mean age of 24 years. The mean score on admission was 39 (poor) and after 6 weeks TTFD treatment it had become 59 (fair).

In the moderately severe stage (stage II) there were 18 patients. Nine were males and nine were females. Their ages ranged between 15 and 53 years, with a mean of 29.5 years. The initial and final mean scores were 64 (fair) and 75 (good) respectively. Statistical analysis showed that the effect of treatment on the motor functions in stage II and III patients was significant ($P<0.01$ and $P<0.05$ respectively), whereas the sensory functions and reflexes did not improve.

There were only 6 patients with mild nutritional polyneuropathy, all of whom were females with a mean age of 22 years. Their mean score on admission was 79 (good) and at the end of the 6th week it had reached 83 (good). Unfortunately, the number of cases was too small for statistical analysis. The outcome of treatment in all the patients is shown in Table 1.

On admission all patients were examined electrophysiologically, whereas only 18 patients were reexamined at the end of the trial 3 months later (see Table 2). It seemed that the largest percentage of recovery was seen in the electromyogram at voluntary contraction (40%), followed by the motor nerve conduction velocities (peroneal nerve 20%, posterior tibial nerve 16.7%); F-response (20%); H-reflexes (16.7%) and sensory nerves (sural nerve 16.7%). These findings correlate with the clinical outcome. No side-effects were observed during TTFD treatment.

**Table 1.** Outcome of treatment with TTFD

| | No. of patients | Summated score | No. of improved patients | Summated score | *P* (Wilcoxon) |
|---|---|---|---|---|---|
| Cranial nerves | 44 | 880 | – | 880 | – |
| Reflexes | 44 | 112 | 7 | 170 | $P<0.1$ |
| Sensoric functions | 44 | 290 | 9 | 329 | $P<0.1$ |
| Motoric functions | 44 | 1144.5 | 34 | 1674 | $P<0.01$ |
| Total score | | 2426.5 | | 3053 | $P<0.01$ |
| Mean score | | 55.1 (Fair) | | 69.4 (Good) | |

## Discussion

The low socio-economic Indonesian people consume machine-milled rice which is distributed by the Indonesian government. It is stored for a long time in humid places, so that a considerable amount of thiamine is lost. It is also common usage to discard the water after soaking and boiling the rice which also reduces the thiamine content. It is estimated that about 85% of the thiamine is lost by this method of cooking [10].

Additional precipitating factors, such as infections (e.g. chronic hepatitis), pregnancy and bad sanitation were predominant in our patients. Thiaminase may also have played a role. Antithiamine factors (thiaminase) are found in products such as tea, blue berries, red chicory, blackcurrents, red beet root, Brussels sprouts, red cabbage, mussels, oysters, crabs and ferns [4, 13]. Thiaminase is also produced by the thiaminolytic bacillus and thiaminolytic clostridium [6, 7]. 3% of the beriberi cases in Japan are caused by the presence of thiaminolytic bacillus [7]. The use of TTFD in our study has the advantage that it is not decomposed by thiaminase.

It is generally thought that beriberi is most commonly found in association with malnutrition. However, most of our patients had normal serum albumin and globulin levels.

The body contains only 30 mg thiamine – 30 times the daily requirement – and deficiency starts about 1 months sooner on a thiamine – free diet than with any other vitamin deficiency. The requirement is proportional to the non-fat intake [11].

In experimental Bl-hypovitaminosis in human beings, it was found that a thiamine supply of 0.2 mg/day (0.1 mg/1000 calories) for 110 days produces severe polyneuropathy [2].

One of the authors (W. Djoenaidi; unpublished data found that chickens fed with distributed polished rice and fresh vegetables developed a severe polyneuropathy after 3 weeks on such a diet.

Abnormal H-reflexes are frequently one of the earliest signs of polyneuropathy [8]. All of our patients showed abnormal H-reflexes with prolonged interval latency time and low amplitude. In severe cases they were non-elicitable.

Abnormalities of the electromyogram were found in 91.1% of the cases. They consisted of fibrillation potentials, positive, sharp waves and increased insertion activity in the distal small hand and foot muscles. Sometimes fasciculations were seen. The interference pattern was reduced during maximal effort and in severe cases there were only single motor unit potentials. The duration of the motor unit action potentials was prolonged and their amplitudes were higher. In mild cases an increase in the percentage of polyphasic muscle action potentials was found. In metabolic-nutritional neuropathy the sensory nerves are affected earlier than the motor nerves, especially in the lower extremities. The sensory nerve action potential of the sural nerve is more commonly or severely affected than the motor nerve action potential [5]. In 88.9% of our cases abnormalities of the sural nerve action potentials were present, whereas in only 72.2% of the cases was prolonged motor nerve conduction velocity of the peroneal nerves found.

In mild cases there was a mild reduction in the conduction velocity but not below 70% of normal. In general there was a progressive reduction in amplitude and dispersion of the evoked response on distal stimulation. In severe cases there was a pronounced slowing of conduction or failure to evoke a response. The primary lesion in nutritional polyneuropathy is one of axonal degeneration, the myelin changes being secondary [12].

In many neuropathies of the metabolic-nutritional type abnormalities of the F-response can be demonstrated in individual patients in the same nerve where conventional methods of motor and sensory conduction do not show any abnormality. The F-response provides additional information regarding the function of the alpha motor axons [19]. F-response changes were found in 64.4% of our cases.

**Table 2.** Electrophysiological findings before and after treatment with TTFD (18 patients)

| Procedure | | On admission No. of abnormal cases | After treatment No. of improved cases |
|---|---|---|---|
| MCV | H-reflex | 18 (100%) | 3 (16.7%) |
| | Peroneal nerve | 15 (83.3%) | 3 (20%) |
| | Post.tib. nerve | 18 (100%) | 3 (16.7%) |
| | Median nerve | 9 (50%) | 3 (33.3%) |
| | Ulnar nerve | 0 | 0 |
| SNAP | Median nerve | 9 (50%) | 3 (33.3%) |
| | Ulnar nerve | 6 (33.3%) | 0 |
| | Sural nerve | 18 (100%) | 3 (16.7%) |
| F-Wave | | 15 (83.3%) | 3 (20%) |
| EMG | | 15 (83.3%) | 6 (40%) |

MCV = Motor nerve conduction velocity; SNAP = sensoric nerve action potential

In our trial we found that the improvements of motor function were statistically significant, whereas the reflexes and sensory functions did not improve significantly (see Table 1). These data were in accordance with the neurophysiological findings in which the largest percentage of improvement was established in the electromyogram, followed by improvements of the motor nerve conduction velocities, H-reflexes and sensory nerves respectively (see Table 2). It seems likely that the spindle afferent fibres, which induce the monosynaptic reflex via the sensory nerves, are more vulnerable than the motor nerves.

*Acknowledgment.* The authors express their gratitude to Takeda Chemical Industries Ltd., Surabaya, Indonesia, for the generous supply of TTFD (Alinamin-F) injections.

## References

1. Baker H, Thomson AD, Frank O (1974) Absorption and passage of fat and water soluble thiamine derivatives into erythrocytes and cerebrospinal fluid of man. Am J Clin Nutr 27:676–680
2. Erbsloh F, Abel M (1970) Deficiency neuropathies. In: Vinken PJ, Bruyn GW (eds) Diseases of nerve, part I. Handbook of clinical neurology, vol 7. North Holland Elsevier, Amsterdam, pp 558–571
3. Gilroy J, Barnhart MI, Meyer JS (1969) Treatment of acute stroke with dextran-40. JAMA 210:293–298
4. Leevy GB, Habba SF (1987) Beriberi (Thiamine [viatmin B1] deficiency). In: Rakel RE (ed) Conn's current therapy. Saunders, Philadelphia pp 435–436
5. Lefebvre D'amour M, Shahani BT, Young RR (1979) The importance of studying sural nerve conduction and late responses in the evaluation of alcoholic subjects. Neurology 29:1600–1604
6. Matsukawa D, Chang S, Fujimiya M (1965) Studies on thiamine deficiency due to bacterial thiaminase. III. Further investigations on thiaminase disease. J Vitaminol 2:1
7. Murata K (1965) Thiaminase. In: Shimazone N, Katsura E (eds) Review of Japanese literature on beriberi and thiamine. Kyoto University, Faculty of Medicine, Kyoto, p 220
8. Notermans SLH (1984) Polyneuropathies: In: Notermans SLH (ed) Current practice of clinical electromyography. Elsevier, Amsterdam pp 279–312
9. Shahani BT, Young RR (1980) Studies of reflex activity from a clinical view point. In: Aminoff MJ (ed) Electrodiagnosis in clinical neurology. Churchill Livingstone, New York, pp 297–298
10. Tmangraksatve S, Srisukii S (1955) Thiamine in Thai rice. J Pharm Assoc Thailand 8:8
11. Truswell AS (1985) Vitamins I. Br Med J, 291:1033–1035
12. Victor M (1984) Polyneuropathy due to nutritional deficiency and alcoholism. In: Dyck PJ, Thomas PK, Lambert EH (eds) Peripheral neuropathies, vol 2, 2nd edn. Saunders, Philadelphia, pp 1899–1907
13. Vimokesant SL, Nakornchai S, Dhanamitta S (1974) Effect of tea consumption on thiamine status in man. Nutr Rep Int 9:371–376

Received March 14, 1989