TRANSKETOLASE-TPP-EFFECT IN CHRONIC ALCOHOLICS WITH VARIOUS DEGREES OF LIVER CIRRHOSIS*

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Summary A re-investigation of the use of the transketolase-TPP-effect for the assessment of the thiamine status of chronic alcoholics with various degrees of liver cirrhosis was carried out on 36 alcoholics. The extent of the liver damage in these patients was established by clinical examinations and biochemical tests. Fourteen persons showed no significant hepatic abnormalities, 5 patients had compensated liver cirrhosis, 7 slightly decompensated, and 10 patients suffered from severely decompensated liver cirrhosis. This investigation shows that the transketolase-TPP-effect is also present in patients even with severe liver cirrhosis and that a decrease of the TPP-effect can be observed after oral thiamine administration in these subjects. The TPP-effect of patients with compensated liver cirrhosis was markedly smaller than that of the subjects with slightly or severely decompensated cirrhosis. Accordingly a relationship exists between the TPP-effect and the degree of liver damage. No other correlations however could be established in this respect.

Keywords TPP-effect, chronic alcoholics, liver cirrhosis, oral thiamine administration

Chronic alcoholism is frequently associated with deficiencies of vitamins (1–5), mainly of thiamine (6–10). The clinical symptoms of thiamine deficiency are dependent upon the severity of the vitamin deprivation. A mild thiamine deficiency might exist without or with so-called subclinical symptoms. A reliable method for the assessment of the thiamine status is therefore of great importance.

Several methods have been proposed, including: determination of blood pyruvate level (11, 12), thiamine excretion in urine (13, 14), microbiological assay of thiamine in blood (15), and determination of the transketolase activity in red
blood cells. According to various authors (16–18; J. F. de Wijn, personal communication) the transketolase activity itself is not in all cases a good measure for the thiamine status. The enhancement of the enzyme activity resulting from the in vitro addition of thiamine pyrophosphate (TPP) to the hemolyzed blood, i.e., the determination of the TPP-effect gives better results in this respect (19, 20). In our own investigations the determination of the TPP-effect before and after oral thiamine administration represents the more specific test (8, 18).

The determination of the TPP-effect is generally accepted for the assessment of the thiamine status with the exception of certain cases of alcoholics. Fennelly et al. (21) as well as Konttinen et al. (22) reported that the in vitro addition of TPP to hemolyzed blood from alcoholics with liver cirrhosis did not increase the transketolase activity, while the hemolysates from thiamine-deficient patients without liver disease a marked rise of enzyme activity was observed.

As a consequence of these investigations the use of the TPP-effect for the assessment of the thiamine status of chronic alcoholics would in our opinion be rather limited since many of these patients suffer from liver cirrhosis.

A re-investigation of this question seemed to be necessary in subjects in which the extent of the liver cirrhosis had been established by clinical examinations and biochemical tests (Quick, GOT, GPT, and $\gamma$-globulin) by two of the co-authors (Filippini and Monnat). Simultaneously the thiamine status of these patients was determined by the TPP-effect according to our modification (8, 18).

METHODS

Thirty-six alcoholics were investigated: 1) 14 persons (11 males and 3 females) without significant hepatic abnormalities and 2) 22 patients with liver cirrhosis of various degrees a) compensated cases (5 males), b) 7 slightly decompensated (4 males and 3 females), and c) 10 patients with severely decompensated liver cirrhosis (7 males and 3 females). The 14 persons of the first group were under the care of the Advisory and Social Service for Alcoholics in Zurich (Zürcher Beratungs- und Fürsorgedienst für Alkoholgefährdete), but not hospitalized. The 22 alcoholics of the second group were patients of the Medical Department of the General Hospital of Canton Lucerne (Medizinische Abteilung des Kantonsspitals Luzern).

The diagnosis of liver cirrhosis was established in all patients by clinical examination and biochemical tests, i.e., by the determination of $\gamma$-globulins, the Quick values, and/or by liver biopsy or laperoscopy, respectively. Additionally the transaminase activities (GOT and GPT) were measured in the serum of the patients to estimate the degree of the liver cirrhosis.

Classification of the patients into three groups according to the severity was based on the following criteria: ascites as the manifestation of parenchymatic and vascular decompensation; by the Quick value as a recognized measure of the total
liver function and by the symptoms of the liver coma (flapping tremor, disorders of consciousness).

The group of patients with compensated liver cirrhosis (2a) had no ascites and the Quick value was higher than 70%; the second group, patients with slightly decompensated liver cirrhosis (2b) had a small ascites only and the Quick values were between 50 and 70%; patients with severely decompensated liver cirrhosis (2c) suffered from massive ascites, the Quick value was lower than 50% and/or symptoms of liver coma were detected.

For the determination of the transketolase activity and the TPP-effect respectively the modified method by Schouten et al. (23) was used (8). The TPP-effect was assessed before and after oral administration of 50 mg thiamine in one dose per person per day for 2 weeks, as proposed by Somogyi and Kopp (8, 24). The investigation of each subject lasted in general 5 weeks. During this period the TPP-effect was established 5-6 times at weekly intervals, i.e., two determinations were carried out before oral thiamine administration, two during the administration and further one or two after the last thiamine dose.

RESULTS

The results of the four groups: 1) without significant hepatic abnormalities, 2a) patients with compensated, 2b) slightly decompensated, and 2c) severely decompensated liver cirrhosis are summarized in Fig. 1. In this figure the increase of the transketolase activity after in vitro addition of thiamine pyrophosphate to

![Graph showing TPP-effect of chronic alcoholics with and without liver cirrhosis.](attachment:image.png)

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the hemolyzed blood is expressed by the utilized ribose in µg/ml/h as it was done by Fennelly et al. (21). This should facilitate a comparison of the experiments by Fennelly et al. with our results.

If the increase of the transketolase activity is given in % or ζTKA which is the more usual way, the rise of the transketolase activity is even more obvious (Fig. 2).

These experiments show that an increase of the transketolase activity after addition of thiamine pyrophosphate occurs in patients even with severe liver cirrhosis.

Further we have investigated whether a decrease of the TPP-effect can be observed after oral administration of thiamine in patients with liver cirrhosis in compensated as well as in decompensated cases. The results of oral administration of thiamine, of the clinical examinations and of the biochemical tests are summarized in Tables 1–3.

A marked decrease of the TPP-effect occurred after oral administration of 50 mg thiamine, i.e., from the 7th to 21st day. Patients with compensated liver cirrhosis showed a decrease of the TPP-effect from 15 to 6% (both means of 9 determinations). The initial value of 15% corresponds to a marginal thiamine deficiency (Table 1).

Subjects of the second group with a slightly decompensated liver cirrhosis (Table 2) had an initial TPP-value of 29% which was reduced by daily thiamine doses of 50 mg to 8% (both figures are means of 13 determinations). According to Brin et al. (25) a TPP-effect of over 25% can be considered as a sign of a severe thiamine deficiency.

The mean TPP value of the patients with severely decompensated liver cirrhosis was about as high as that of the second group: 25% (mean of 20
Table 1. Patients with compensated liver cirrhosis (no ascites; Quick > 70%).

| Patient | TPP-effect in % before thiamine intake | TPP-effect in % during thiamine intake | TPP-effect in % after thiamine intake | GOT I.U. | GPT I.U. | % proportion γ-globulins |
|---------|--------------------------------------|---------------------------------------|--------------------------------------|---------|---------|------------------------|
| Name    | Sex       | Birth year | 17 | 17 | 6 | 8 | 7 | 12 | 58 | 38 | 30 |
| B.J.    | M         | 1911       | 21 | 18 | 3 | 5 | 5 | 5 | 13 | 12 | 17 |
| G.A.    | M         | 1924       | 6  | —  | 6 | 0 | 3 | 6 | 63 | 27 | 9  |
| H.A.    | M         | 1910       | 16 | 15 | 4 | 10| 11| 10| 9  | 9  | 23 |
| L.A.    | M         | 1907       | 8  | 10 | 9 | 10| 8 | 8 | 44 | 42 | 29 |

Days 1 7 14 21 28 35

Table 2. Patients with slightly decompensated liver cirrhosis (ascites +; Quick 50–70%).

| Patient | TPP-effect in % before thiamine intake | TPP-effect in % during thiamine intake | TPP-effect in % after thiamine intake | GOT I.U. | GPT I.U. | % proportion γ-globulins |
|---------|--------------------------------------|---------------------------------------|--------------------------------------|---------|---------|------------------------|
| Name    | Sex       | Birth year | 35 | 38 | 12 | 3 | 9 | 10 | 47 | 45 | 29 |
| B.J.    | M         | 1947       | 36 | 27 | 8 | 6 | 5 | 5 | 42 | 14 | 24 |
| B.E.    | F         | 1904       | 26 | 25 | 8 | 4 | 12| 16| 54 | 34 | 29 |
| H.W.    | M         | 1907       |  — | 22 | 12| 9 | 14| 14| 38 | 32 | 23 |
| H.L.    | M         | 1914       | 21 | 21 | 19| 11| — | — | 56 | 23 | 40 |
| S.M.    | F         | 1922       | 46 | 25 | 8 | 7 | 5 | 15| 46 | 29 | 22 |
| Z.T.    | F         | 1937       | 33 | 20 | 3 | 4 | 13| 13| 70 | 37 | 27 |

Days 1 7 14 21 28 35

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Table 3. Patients with severely decompensated liver cirrhosis (ascites +++; Quick <50% and/or liver coma).

| Patient | TPP-effect in % before thiamine intake | TPP-effect in % during thiamine intake | TPP-effect in % after thiamine intake | GOT I.U. | GPT I.U. | % proportion γ-globulins |
|---------|----------------------------------------|----------------------------------------|----------------------------------------|----------|----------|----------------------------|
| E.M.    | 32 25                                  | 3 3                                    | 1 —                                    | 71       | 32       | 38                          |
| G.M.    | 57 35                                  | 6 4                                    | 14 13                                  | 71       | 45       | 39                          |
| M.H.    | 13 14                                  | 5 3                                    | 10 —                                   | 22       | 16       | 33                          |
| N.E.    | 27 17                                  | 11 5                                   | 10 11                                  | 48       | 18       | 45                          |
| N.V.    | 49 23                                  | 8 10                                   | 2 —                                    | 11       | 5        | 25                          |
| R.A.    | 13 11                                  | 2 —                                    | 9 —                                    | 22       | 18       | 14                          |
| S.J.    | 22 19                                  | 8 1                                    | 11 —                                   | 96       | 86       | 45                          |
| S.K.    | 10 15                                  | 9 6                                    | 11 —                                   | 28       | 10       | 33                          |
| W.A.    | 8 7                                    | 4 2                                    | 12 —                                   | 72       | 24       | 44                          |
| W.J.    | 34 47                                  | 8 4                                    | 18 —                                   | 66       | 30       | 33                          |

Days
1 7 14 21 28 35 42
determinations). This decreased to 5% (mean of 20 determinations) after daily oral administration of 50 mg thiamine. Three patients of this group (M.H., R.A., and W.A.) had a lower initial TPP-value (7–14%) than the other patients which naturally depressed the mean of the whole group. In spite of this the mean TPP-value was rather high (25%) corresponding to a severe biochemical thiamine deficiency (Table 3).

The results show that the TPP-effect of patients with compensated liver cirrhosis (group 2a) is markedly smaller than that of the subjects with decompensated liver cirrhosis (group 2b and 2c). No other correlations could be established between the TPP-effect and the activity of the liver cirrhosis determined by the transaminase values and by the increase of γ-globulins. Our results correspond—with the exception of the γ-globulin values—in general with the investigations by Hell and Six (10). In all the three groups especially in the groups 2b and 2c pronounced decrease of the TPP-effect occurred after daily oral administration of 50 mg thiamine during 2 weeks. From this follows that the phosphorylation of thiamine to thiamine pyrophosphate takes place even in patients with severely decompensated liver cirrhosis.

DISCUSSION

We found that A) the transketolase-TPP-effect is also present in patients with severe liver cirrhosis—this in contrast to Fennelly et al. (21) and to Konttinen et al. (22) and B) a decrease of the TPP-effect has been achieved after oral thiamine administration (50 mg/day and person) in these subjects. From this follows that the transketolase-TPP-effect can be applied for the assessment of the thiamine status of such patients.

These results seem to be important because older (see bibliography in Refs. 18 and 24) as well as newer investigations (26, 27) reveal that “dietary factors can modify the effect of alcohol on the liver” in humans and especially in rodents. Severe vitamin deficiency potentiates the effect of alcohol and on the other hand chronic alcohol consumption interferes with the absorption, utilization, and storage of various vitamins, especially of thiamine. In this connection it is interesting to mention that also the composition of the food influences the spontaneous alcohol preference (28, 29; H. R. Mühlemann and J. C. Somogyi, unpublished results).

Due to the interrelation between dietary factors (e.g., thiamine), alcohol intake and changes in the liver function, it is important to assess the nutritional status of chronic alcoholics in general and the thiamine status especially besides the usual clinical examinations and biochemical tests.

According to our findings it is rather likely that also in cases of severely decompensated liver cirrhosis activable apoenzyme is formed (see A) and phosphorylation of thiamine in the organism and red blood cells takes place as it is shown by the decrease of the TPP-effect after oral thiamine administration (see B).
However higher intake of thiamine as previously reported (8, 24) is necessary. There are various possibilities to explain these latter results, for instance the insufficient supply of the cells with thiamine due to a reduced intestinal absorption and/or a decreased membrane transport.

These investigations seem not to support the "hepatocentric" hypothesis on the primary role of the liver for the phosphorylation of thiamine.

It would be rather interesting and important to attempt further clarification of the changes of various enzyme reactions in chronic alcoholics.

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