

RANDOMISED PLACEBO-CONTROLLED DOUBLE BLIND TRIAL ON "ESSENTIAL" PHOSPHOLIPIDS IN THE TREATMENT OF FATTY LIVER ASSOCIATED WITH DIABETES

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Fatty infiltration of steatosis occurs in obesity, diabetes, malnutrition, during hyperalimentation and in other conditions including pregnancy, drug therapy and intoxication with alcohol, carbon tetrachloride, etc.

Autopsy studies showed the incidence of fatty liver to be at 20-30 %, compared with 15-22 % in the non diabetic population (4). Therefore steatosis is not specific to diabetes. In most cases fatty infiltration in the so-called simple fatty liver is a reversible benign condition and the liver fat content in obese patients may be changed to normal by reducing diet. Natural history of simple fatty liver is, however, poorly known and the question whether it can progress to cirrhosis is unresolved.

Previously we (Z.G., E.L., non published data) have evaluated one of the so-called hepatoprotective agents in 37 patients with maturity-onset diabetes and uncomplicated fatty infiltration. In all these patients after 6 months of starting therapy, post treatment liver biopsy was performed to compare with pretreatment base line. This prospective placebo controlled double blind study revealed no beneficial effect of the tested drug; however, progression to hepatitis and portal fibrosis in 2 patients in each group was shown. As the condition seems poorly susceptible to pharmacotherapy we see the need for further controlled trials.

Essentiale

Essentiale® forte* is a preparation containing "essential" phospholipids and vitamins. The biochemical and pharmacological action of the "essential" phospholipids (EPL) in this preparation has been documented by numerous investigators (1, 8, 11, 11, 18). Orally administered EPL has both a membrane-stabilising and an anti-hepatotoxic effect. The damaged ultrastructures are reconstructed and restricted membrane functions are normalised. For example by in-vitro studies Neuberger et al. (10) were able to show that the susceptibility of rabbit hepatocytes to antibody dependent cell-mediated cytotoxicity and mitogen induced lymphocyte cytotoxicity is remarkably reduced after oral administration of these poly-unsaturated phospholipids.

Essentiale (2, 3, 5-7, 12-15, 17) has shown efficacy in several liver diseases. Knüchel (5) and Schüller Pérez and San Martín (14) have demonstrated the therapeutic effect of "essential" phospholipids in patients with alcoholic fatty liver; however, no liver biopsy before and after the treatment was performed. Similarly, the results obtained by Pogromow et al. (13) have shown improvement in serum enzymes in 17 patients with fatty liver after 20 days of treatment.

The present study was undertaken to evaluate the therapeutic efficacy of Essentiale forte in diabetic patients with fatty liver.

Material and Method

Thirty patients, HBs Ag negative with maturity-onset diabetes were admitted to the study. All patients gave their consent to participate in the study after a full explanation on its nature and purpose.

Criterion for participation was histologically-proven fatty liver; obesity did not invalidate entry. Patients were excluded if their serum bilirubin concentration was higher than 2 mg/dl, serum aspartate transaminase activity more than twice the upper limit of the normal, or if portal infiltration of cirrhosis was seen in the liver biopsy specimens.

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* Manufacturer: A. Nattermann & Cie GmbH, Cologne, FRG.

Patients on insulin therapy and those who had been treated with corticosteroids, antibiotics or major psychotropic drugs within the last 3 months and patients with unexplained abnormalities in the routine laboratory blood and urine tests were also excluded.

Patients developing ketoacidosis, or any other severe condition during the study had to be withdrawn and treated with the standard therapy for these complications.

Treatment with other liver therapeutics was discontinued 2 weeks before the start of the trial. No other liver drugs were given concurrently throughout the trial. All obese patients were instructed to reduce diet (ca 1200 kcal/day) containing 1 gm per kg protein. There were 5 patients in the placebo and 7 patients in the Essentiale forte group who were treated with tolbutamid (daily dose 1,0 - 1,5).

Patients were randomly assigned to the Essentiale forte or placebo group in a double blind manner. At entry there were 15 patients in each group. Only 1 patient dropped out after 5 months of therapy because of severe hemorrhage from peptic ulcer, and he proved to be in the placebo group. Physical examination, liver size estimation by ultrasonography, clinical laboratory, including liver function tests were performed 1-2 days prior to the beginning of therapy and were repeated on days 28, 91 and 182 (± 2 days). Ultrasonography was performed using a linear array real time scanner (3,5 MHz transducer, model Sigma 20, Kontron, FRG). Longitudinal scan was obtained with the patient supine position and the dimension of the right lobe of the liver in the midclavicular line was measured. After the end of therapy, the patients had to classify their condition as better, unchanged or impaired.

For histological examination of the liver two blind biopsies were performed with Menghini needle: one within 10 days before starting drug therapy and the other within 1-7 days after the end of treatment. Histological evaluation was carried out by the pathologist without any knowledge of the trial and of the results for liver function test.

Hepatocellular fatty infiltration was evaluated as focal or dispersed. The comparative evaluations of hepatocellular changes were denominated as follows: "mar-

ked improvement" = no more fatty infiltrations (score = +2), improvement = at first biopsy dispersed infiltration, at the second biopsy = focal infiltration (score = +1), "no change" = similar hepatocellular fatty infiltration in the first and in the second biopsy (score = 0), "worsening" = first biopsy = focal infiltration, second biopsy = dispersed infiltration (score = -1). Each biopsic specimen was assessed for architectural change, portal cell infiltration and fibrosis (exclusion criteria). If the last changes occurred in the post treatment biopsy they were not scored, but evaluated separately from changes affecting hepatocytes.

Each patient was supplied with coded bottles of capsules of Essentiale forte or placebo (Nattermann, Cologne, FRG). One capsule of Essentiale forte contained 300 mg of "essential" phospholipids, tocopherol and vitamins of the B group. Placebo capsules identical in appearance to the active drug contained rapeseed oil. The code number became the patient's study number. The dosage schedule was two capsules three times daily immediately before the principal meals during 182 consecutive days.

Clinical and biochemical characteristics of the patients at entry and during the treatment are presented in table I and table II.

The mean age was 49 years in the placebo group and 54 in the Essentiale forte group. The respective male to female ratios were 8:7 and 4:11. Both groups, however, were similar in respect of their initial body weight, liver enlargement, laboratory parameters and liver histology as outlined in table I and table II. At entry, out of the variables listed in table II only mean values of the γ -GT activity, triglycerides, and blood sugar were beyond the baseline values, more expressed in the Essentiale forte than in the placebo group; however, the statistical evaluation did not reveal any significant difference.

Statistical analysis

All values were classified in descriptive elementary statistics. The significance of discrepancies in the initial values of both therapy groups was determined by the U-test according to Mann and Whitney (9). For the time series, differences in time starting from the initial values were calculated and, accordingly, the Wilcoxon matched-paired-signed-test (16) was carried out.

Results

Laboratory tests

One month after starting the therapy, significant body weight loss (tab. I) as well as a decrease of blood sugar values (tab. II) were observed in both groups as a result of the ordered dietary regimen. We considered them as positive indicators of patients compliance. Liver size hardly changed in the patients of the placebo group, it did however in those of the Essentiale forte group: there was a significant *reduction in liver size* after 6 months of therapy (tab. I).

Compared with the pretreatment values mean serum γ -GT activity was significantly lowered after 1, 3 and 6 months of Essentiale forte therapy, whereas in the control group the deviations were not statistically significant (tab. II). Quick value, total protein and protein electrophoresis, hemoglobin, ESR, creatinine and BUN remained in their normal range. An increase in β -globulin values

	Placebo group				Essentiale group			
Sex	8M, 7F				4M, 11F			
Age/yr/mean range	49 (32-63)				54 (34-73)			
	Month of treatment							
	0	1	3	6	0	1	3	6
Wheight/kg mean ± SD	87,6 3,2	85,3* 2,8	82,2*** 2,7	83,7* 2,6	82,1 3,7	80,3** 3,4	79,4** 3,8	7 8,4** 3,4
Dimension of the right lobe of the liver/cm mean ± SD	14,63 0,97	14,53 0,95	14,46 0,95	14,40 1,08	14,86 1,08	14,80 1,16	14,40 1,58	13,96 1,67
Clinical characteristics of the patients * - 0,05≥2p>0,01 — ** - 0,01≥2p > 0,001 — *** - 2p≤0,001								

Table I — Clinical characteristics of the patients.

Duration of treatment (month)			Placebo (n = 14)				Essentiale forte (n = 15)			
			0	1	3	6	0	1	3	6
AST (IU/l)	Normal ranges ≤ 14	mean \pm SD	13,9 1,6	12,1 0,9	10,9* 1,0	11,2 0,8	16,7 3,7	18,0 2,8	13,4 1,9	16,8 2,5
ALT (IU/l)	$\leq 17,5$	mean \pm SD	14,0 1,8	14,2 1,9	10,7* 1,1	11,0* 1,1	18,3 4,3	18,2 5,1	12,7 1,7	16,3 2,8
γ GT (IU/l)	15-106	mean \pm SD	142,0 74,4	104,7 28,8	84,0 35,2	50,4 7,7	166,3 61,5	135** 54,6	83,9** 29,2	117,4* 52,9
Bilirubin (mg/dl)	$\leq 1,0$	\pm SD	0,83 0,09	0,96 0,13	0,83 0,12	0,84 0,10	0,74 0,07	0,74 0,09	0,66 0,08	0,74 0,10
BSP (%)	≤ 5	mean \pm SD	4,0 0,6	3,8 0,8	4,7 0,8	4,3 0,7	5,7 1,6	5,0 1,3	5,8 1,4	6,4 1,4
Cholestérol (mg/dl)	150-230	mean \pm SD	234,4 12,8	222,6 12,6	202,0** 12,5	219,7 18,6	224,4 20,7	212,7 15,3	203,5 12,1	190,9 7,0
TG (mg/dl)	74-172	mean \pm SD	268,5 21,2	240,0 25,4	225,4 24,4	231,8 33,8	219,8 51,1	235,8 49,7	217,7 32,5	177,3 19,0
Glucose (mg/dl)	60-110	mean \pm SD	155,9 11,4	103,4*** 8,9	117,1*** 8,5	116,9** 7,8	161,6 10,9	104,9** 6,7	127,8** 8,4	131,4** 14,0
* = $0,05 > 2p > 0,01$ — ** = $0,01 > 2p > 0,001$ — *** = $2p \leq 0,001$										

Table II — Biochemical tests in patients at entry and during treatment

and a decrease of ALT levels within the normal range were noticed in the placebo group. No further significant changes were found after 6 months in the laboratory test in both groups as compared to the respective pretreatment values (tab. II).

Histology

Table III shows the evaluation of the liver histology. Marked improvement was observed in 4 patients treated with Essentiale forte and in 1 patient of the placebo group. (fig. 1a, 1b). Although no fatty infiltration was seen in the post-treatment biopsy ("marked improvement") of this patient, he developed the feature of progression to cirrhosis. Also in one patient treated with Essentiale

Group	Marked Improvement	Improvement	No change	Worsening
Placebo n = 14 Score = 4	1*	3	9	1
Essentiale forte n = 15 score = 10	4	3	7	1**
* - no fatty infiltration in post-treatment biopsy, but cirrhosis developed. ** - dispersed fatty infiltration and mild portal fibrosis were found.				

Table III — Histopathologic evaluation of therapy.

forte, in whom fatty infiltration was more pronounced at the second biopsy, morphological features of developing discrete fibrosis in portal tract was observed.

None of the patients developed clinical symptoms such as jaundice, ascites, or marked general malaise during the study. No adverse reactions associated with the treatment were observed and none of the patients stopped taking the capsules during the study. Final patients' own opinion is presented in table IV.

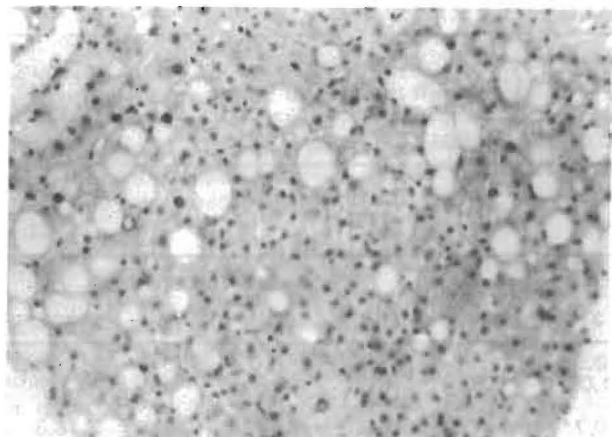


Fig. 1a — Patient M.L. Essential group - First liver biopsy - diffuse fat accumulation in the liver. Hematoxylin - eosin stain.

Group	Improvement	No change	Worsening
Placebo n = 14	1	13	0
Essentiale forte n = 15	8	7	0

Table IV — Final patients' own evaluation of their condition.

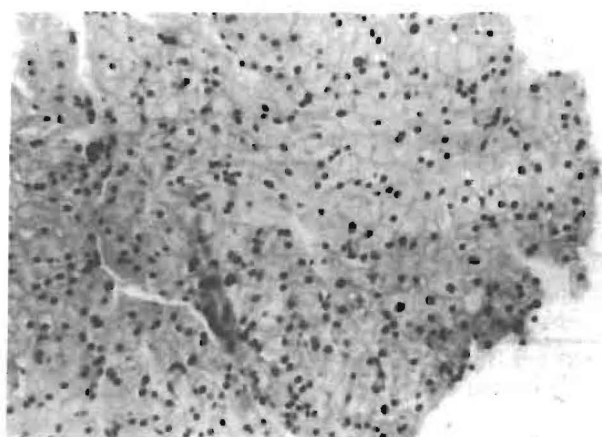


Fig. 1.b. — Second liver biopsy - there are no fatty degenerative changes. Hematoxylin - eosin stain.

Discussion

It is widely believed that fatty liver requires no other therapy than that of the underlying condition such as alcoholism, obesity and others. In some cases, however, as seen in one patient of the Essentiale forte group in this trial as well as in four patients of another study mentioned in the introduction, histological evidence of hepatitis and cirrhosis may occur within 6 months. Therefore it can be concluded that this condition may lead to more serious damage of the liver and more active therapy should be required.

As evident from table I, Essentiale forte was significantly effective in reducing liver size probably as a result of reducing liver fat content. This is supported by histological examinations of post treatment biopsies which showed actually no fatty infiltration in 4 patients in the Essentiale forte group only. It is unlikely that weight loss influenced the changes of liver size as it was very similar at the end of both placebo and Essentiale forte treatment. Only one patient from the control group showed no fatty infiltration in the second biopsy; however, as a matter of fact there was "marked worsening" because of progression to cirrhosis, and that is why the sum of the scores of 4 (tab. III), obtained from the placebo treated patients was somewhat better than it really should be. Altogether there were 7 patients in the Essentiale forte group and 4 under placebo (including the patient with developing cirrhosis), in whom steatosis improved

histologically during the study.

Histology is the most relevant criterion in the evaluation of efficacy in a fatty liver therapy. It is known that no or only mild abnormalities in the liver function test usually occur in these patients. Our trial included patients with uncomplicated fatty liver, all others with initial histological or laboratory findings of hepatitis or cirrhosis had been excluded. At entry only serum γ -GT activity, triglycerides and blood sugar values were considerably elevated, similarly in both groups. Although serum γ -GT is of little value in the differentiation of liver diseases, its measurement is of great value as a broad index of hepatic dysfunction.

Increased γ -GT activity may be present as the only evidence of liver damage. Compared with pretreatment values mean γ -GT levels were significantly lowered just after 1 and 3 and also after 6 months in patients treated with Essentiale forte while they were not lowered in the placebo group: this may be interpreted as biochemical evidence of effective therapy.

The results from this study indicate that Essentiale forte is effective in long-term treatment of fatty liver. As this condition sometimes progresses to cirrhosis, the use of Essentiale forte may be an advance in the medical prevention of this irreversible liver disease.

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