*Clinical trial***Treatment of alcohol-related liver disease with thioctic acid: a six month randomised double-blind trial**

A W MARSHALL, R S GRAUL, MARSHA Y MORGAN,* and SHEILA SHERLOCK

From the Departments of Medicine and Histopathology, The Royal Free Hospital, London

SUMMARY A randomised double-blind trial of thioctic acid (α -lipoic acid), 300 mg/day versus placebo was carried out in 40 patients with pre-cirrhotic alcohol-related liver disease over a six month period. Twenty patients received the active drug and 20 placebo. Twenty-two of the 40 patients (55%) abstained from alcohol and showed significant improvements ($p < 0.01$) in mean values for serum aspartate transaminase, serum gamma glutamyl transpeptidase, and mean corpuscular volume. Seventeen of the 22 (77%) showed overall histological improvement on liver biopsy. The remaining 18 patients (45%) continued to drink but significantly reduced their mean daily alcohol intake ($p < 0.001$). No significant changes occurred in their laboratory indices, but five of the 18 (28%) showed overall histological improvement. Changes occurred irrespective of treatment with thioctic acid, which suggested that, over six months, this drug did not influence the course of alcohol-related liver disease.

In patients with alcohol-related liver damage the major factor determining outcome is abstinence from alcohol. In normal circumstances no other manoeuvre is necessary. As abstinence, however, is often difficult to achieve, it has been suggested that hepato-protective agents may have a place in the management of alcohol-related liver disease.¹ Colchicine² and (+) – cyanidanol-3³ have been used to modify the course of alcohol-related liver disease but with disappointing results.

Thioctic acid (α -lipoic acid) is a cofactor in oxidative decarboxylation and was first isolated in 1951.⁴ It may also have anti-inflammatory properties as it stimulates prostaglandin cyclooxygenase, thus increasing prostaglandin synthesis.^{5,6} Thioctic acid has been advocated for the treatment of a variety of liver diseases^{7–10} but no controlled clinical trials of its use have been reported. This paper reports a prospective double-blind randomised trial of thioctic acid versus placebo in 40 patients with pre-cirrhotic alcohol-related liver disease over six months.

Methods**PATIENTS**

The study group comprised 40 patients (32 males: eight females) admitted consecutively who had consumed alcohol in excess of 80g daily for three or more years and in whom the liver biopsy showed pre-cirrhotic and hence potentially reversible alcohol-related liver disease. For the purpose of this study a pre-cirrhotic liver lesion was defined as any combination of fatty infiltration, alcoholic hepatitis, or fibrosis without nodule formation. All patients had been abusing alcohol up to the start of the trial.

An initial inpatient assessment was made of the drinking history, the physical condition, and of various haematological and biochemical measures. Particular note was made of the serum bilirubin, serum aspartate transaminase (AST), serum gamma glutamyl transpeptidase (γ GTP), and mean corpuscular volume (MCV). Liver biopsies were examined blindly looking for centrizonal and portal inflammation, fatty infiltration, Mallory bodies, centrizonal liver cell damage, central and portal fibrosis, siderosis, and cholestasis. Each feature was graded as 0 = absent, 1 = mild, 2 = moderate, or 3 = severe.

* Address for correspondence and reprints: Dr M Y Morgan, Medical Unit, Royal Free Hospital, Hampstead, London NW3 2QG.

Received for publication 18 March 1982

The 40 patients were then randomly assigned to two equal groups of 20. The treated group received the manufacturer's recommended dose of 300 mg thioctic acid daily in three divided doses for 24 weeks, while the control group was given an identically presented placebo for a similar time. All but essential medications – for example, anti-hypertensive agents – were discontinued; vitamin supplements were not routinely prescribed.

After discharge from hospital, patients were reviewed at two, four, six, eight, 12, 16, 20, and 24 weeks. At each visit an assessment of alcohol intake was made as accurately as possible from the patient's own report, reports from family and work contacts, and from random breath ethanol estimations. On the basis of these observations an average daily alcohol intake for the period between visits was estimated. Physical examination and laboratory tests were repeated and a careful note made of side-effects. At 24 weeks patients were admitted for complete re-assessment including a second liver biopsy.

The laboratory data were analysed in two ways. Firstly, broad comparisons were made between the initial and final laboratory tests in the thioctic acid and placebo treated groups. Secondly, the patients were divided into two groups on the basis of whether they had abstained from alcohol or not during the trial. Patients consuming alcohol in any quantity were regarded as continuing to drink, even if they had significantly reduced their alcohol intake. The effects of thioctic acid were then assessed in greater detail by comparing results in the placebo and thioctic acid treated patients in the abstinent and drinking groups.

The liver biopsy findings at the beginning of the trial and on its completion were compared for each patient without knowledge of either drinking behaviour or drug treatment during the trial period. An overall assessment of change was first made by two observers (AWM, RSG). A more objective measure of change was then made by comparing the numerical scores given to the histological features of

each biopsy.

Laboratory data were compared using Student's *t* test. The values of serum γ GTP were normalised by logarithmic transformation before analysis. A two-way analysis of variance computed by the least-squares method was used to determine the significant factors influencing the absolute changes in the laboratory measures. The overall assessments of histological change were analysed by the Mantel and Haenszel modification of the stratified Chi-squared test.¹¹

Approval for this trial was obtained from the Hospital Ethics Committee. Informed consent was obtained from all patients.

Results

Forty patients completed the trial, 20 in the treated group and 20 in the control group. On admission to the trial the two groups were comparable (Table 1), although patients in the thioctic acid group had a longer history of alcohol abuse.

The initial mean serum bilirubin concentrations were within the normal reference range and remained so throughout the trial period. After six months significant improvements ($p<0.05$) had occurred in the mean serum aspartate transaminase, γ GTP, and mean corpuscular volume values in both the thioctic acid and placebo treated groups (Table 2, Fig 1).

Fifty-five percent of patients (13 thioctic acid, nine placebo) abstained from alcohol and showed significant improvements in mean serum aspartate transaminase, γ GTP, and mean corpuscular volume values, irrespective of whether they were taking active drug or placebo (Table 2, Fig. 2).

Forty-five percent of patients (seven thioctic acid, 11 placebo) continued to drink, though significantly reducing their mean daily alcohol intake ($\pm$ SEM) from 2.8 ± 0.3 to 1.3 ± 0.2 g/kg body weight ($p<0.001$). No significant changes were seen in mean serum aspartate transaminase, γ GTP, or mean corpuscular volume values in this group

Table 1 Details of sex, age, drinking histories, biochemistry, and haematology of 40 alcoholics admitted to thioctic acid trial

Treatment (n)	Sex ratio M:F	Age (yr)	Length of drinking history (yr)	Alcohol intake (g/kg/day)	Bilirubin (μ mol/l) (rr*5–17)	AST (IU/l) (rr 5–15)	γ GTP (μ mol/l) (rr 0–65)	MCV (fl) (rr 80–95)
		Mean $\pm$ SEM						
Thioctic acid (20)	17:3	50.7 $\pm$ 1.9	17.5 $\pm$ 2.7†	2.6 $\pm$ 0.2	16.3 $\pm$ 4.1	38.9 $\pm$ 9.0	272 $\pm$ 71	98.6 $\pm$ 1.0
Placebo (20)	15:5	46.4 $\pm$ 2.7	10.1 $\pm$ 1.7	2.5 $\pm$ 0.3	12.4 $\pm$ 1.1	35.2 $\pm$ 5.5	224 $\pm$ 58	96.5 $\pm$ 1.5

* Reference range for control population.

† Values different from placebo $p<0.05$.

Table 2 Details of laboratory tests at beginning and end of thioctic acid trial

	AST (IU/l)		γ GTP (IU/l)		MCV (fl)	
	Initial	Final	Initial	Final	Initial	Final
	Mean $\pm$ SEM		Mean $\pm$ SEM		Mean $\pm$ SEM	
Thioctic acid:						
Total (20)	39 $\pm$ 9	17 $\pm$ 2	272 $\pm$ 71	125 $\pm$ 31	98.6 $\pm$ 1.0	91.9 $\pm$ 1.3
Abstinent (13)	44 $\pm$ 14	14 $\pm$ 2	319 $\pm$ 107	80 $\pm$ 27	99.2 $\pm$ 1.2	89.4 $\pm$ 1.2
Drinking (7)	30 $\pm$ 5	22 $\pm$ 4	184 $\pm$ 31	208 $\pm$ 63	97.4 $\pm$ 2.0	96.2 $\pm$ 2.0
Placebo:						
Total (20)	35 $\pm$ 6	21 $\pm$ 4	224 $\pm$ 58	172 $\pm$ 93	96.5 $\pm$ 1.5	91.8 $\pm$ 1.1
Abstinent (9)	43 $\pm$ 8	14 $\pm$ 2	219 $\pm$ 60	58 $\pm$ 14	95.9 $\pm$ 2.6	89.0 $\pm$ 1.0
Drinking (11)	29 $\pm$ 8	27 $\pm$ 6	288 $\pm$ 95	266 $\pm$ 167	97.4 $\pm$ 1.8	94.0 $\pm$ 1.5

Fig. 1 Changes occurring in mean (± SEM) serum aspartate transaminase, γ GTP, and mean corpuscular volume values over the trial period in thioctic acid treated and placebo groups (* $p < 0.05$, ** $p < 0.01$).

Fig. 2 Changes occurring in mean (± SEM) serum aspartate transaminase, γGTP, and mean corpuscular volume values in drinking (—) and abstinent (---) patients on thioctic acid or placebo over the trial period. (* $p<0.05$, ** $p<0.01$).

(Table 2, Fig. 2).

The effects of drinking and treatment on laboratory indices are shown in Table 3. Significant improvements were seen in the patients who stopped drinking irrespective of treatment with thioctic acid. The changes that occurred were due entirely to abstinence and there was no evidence of a treatment effect or an interaction of treatment with drinking status.

At the beginning of the trial the patients in both groups showed similar degrees of liver damage with comparable mean histological scores (thioctic acid, 5.0 ± 0.9 ; placebo, 4.7 ± 1.0). The results of the overall assessment of histological change are shown in Table 4. The number of patients showing histo-

Table 3 Mean fall (± SEM) in laboratory tests during thioctic acid trial

Drinking status and treatment group (n)	AST* (IU/l)	$\log_{10}\gamma\text{GTP}^\dagger$	MCV‡ (fl)
Abstinent (22)			
Thioctic acid (13)	29.6 ± 13.3	0.53 ± 0.09	9.7 ± 1.1
Placebo (9)	29.0 ± 8.6	0.54 ± 0.11	6.9 ± 2.3
Drinking (18)			
Thioctic acid (7)	8.6 ± 4.2	0.05 ± 0.11	1.1 ± 0.9
Placebo (11)	2.1 ± 3.2	0.06 ± 0.10	2.9 ± 1.5

For the difference between drinkers and non-drinkers in the analysis of variance:

* $F = 15.0$, $df = 1,36$, $p<0.01$

† $F = 5.7$, $df = 1,36$, $p<0.05$

‡ $F = 27.1$, $df = 1,36$, $p<0.01$

Table 4 Overall histological change in 40 alcoholics during treatment with thioctic acid or placebo over six months in relation to their drinking habits

	Overall histological assessment					
	Deterioration (no.) (%)		Unchanged (no.) (%)		Improved (no.) (%)	
Thioctic Acid:						
Whole group (20)	1	5	5	25	14	70
Abstinent (13)	—		2	15	11	85
Drinking (7)	1	14	3	42	3	42
Placebo:						
Whole group (20)	1	5	9	45	10	50
Abstinent (9)	1	11	—		8	89
Drinking (11)	—		9	82	2	18

logical improvement was similar: 14 of 20 (70%) patients on active drug and 10 of 20 (50%) on placebo. Improvement was seen predominantly in patients who abstained from alcohol and thioctic acid had no effect on liver histology ($z=0.263$). The histological pattern of improvement was similar in both the thioctic acid and placebo treated patients.

Thioctic acid was well tolerated in a dose of 300 mg/day and no side-effects were seen.

Discussion

There is some experimental¹² and clinical evidence^{13 14} to suggest that thioctic acid may be useful in treating the liver failure caused by *Amanita phalloides* poisoning. Its use in other forms of liver disease is anecdotal^{7 8 10} but, despite this, it is widely used as a hepato-protective agent. In alcoholics ethanol oxidation is accompanied by an increase in the NADH: NAD ratio¹⁵ which results indirectly in reduction of citric acid cycle activity.¹⁶ Thioctic acid is a cofactor in the pyruvate dehydrogenase and α -ketoglutarate dehydrogenase enzyme complexes which form part of the citric acid cycle.¹⁷ Thus thioctic acid might prevent the changes in citric acid cycle activity which accompany ethanol oxidation and could benefit patients with alcohol-related liver disease. Within the confines of the present trial, however, thioctic acid had no effect on the course of pre-cirrhotic alcohol-related liver disease.

Significant improvements in various laboratory tests were seen in the patients in this study who abstained from alcohol but not in those who continued to drink even in reduced amounts. Morgan *et al*¹⁸ have shown that a combination of the values of serum aspartate transaminase, γ GTP, and mean corpuscular volume is useful for following drinking patterns in an alcoholic population and,

indeed, the patients in this trial who continued to drink showed a rise of at least one of these indices.

The histological changes tended to reflect drinking patterns and were not influenced by thioctic acid. Seventy-seven percent (17/22) of patients who stopped drinking showed histological improvement. Histological improvement was also seen in 28% (5/18) of patients who continued to drink, probably because they had significantly reduced their alcohol intake. The most consistent histological change seen was a reduction in steatosis.

Only 20–30% of alcoholics develop significant liver disease¹⁹ and these cannot be distinguished at an early stage of their drinking careers. While the concept of hepato-protective drugs is interesting, their use would be superfluous in 70% of alcoholic patients. In those patients who might be considered suitable for such agents the problem of alcoholism remains with its psychosocial sequelae and physical effects on other organs.

We thank Professor P J Scheuer for help with interpretation of liver biopsies, Mr B McGuinness for statistical advice, and Dr J C Colman for help with the initial clinical assessments. AWM is supported by the Medical Council on Alcoholism.

References

- 1 Thomson AD, Majumdar SK, Rowe AE, Shaw GK. Observations on hepato-protective drugs in alcoholic liver disease. *Br J Alc Alcohol* 1980; **15**: 58–77.
- 2 Kershenobich D, Uribe M, Suarez GI, Mata JM, Perez-Tamayo R, Rojkind M. Treatment of cirrhosis with colchicine. A double-blind randomized trial. *Gastroenterology* 1979; **77**: 532–6.
- 3 Colman JC, Morgan MY, Scheuer PJ, Sherlock S. Treatment of alcohol-related liver disease with (+) – cyanidanol-3: a randomized double-blind trial. *Gut* 1980; **21**: 965–9.
- 4 Reed LJ. Metabolic functions of thiamine and lipoic acid. *Physiol Rev* 1953; **33**: 544–59.
- 5 Marnett LJ, Wilcox CL. Stimulation of prostaglandin biosynthesis by lipoic acid. *Biochim Biophys Acta* 1977; **487**: 222–30.
- 6 Egan RW, Gale PH, Beveridge GC, Phillips GB, Marnett LJ. Radical scavenging as the mechanism for stimulation of prostaglandin cyclooxygenase and depression of inflammation by lipoic acid and sodium iodide. *Prostaglandins* 1978; **16**: 861–9.
- 7 Moller E, Brinkman W, Weber O, Wildhirt E. Behandlung chronischer leberkrankheiten mit thioiktsäure. *Med Klin* 1967; **62**: 380–4.
- 8 Dittrich H, Seiffert E. Die klinische verwendbarkeit der thioiktsäure. *Munchen Med Wochenschr* 1962; **104**: 2053–6.
- 9 Thompson CM, Gambescia JM, Lisan P, Fuchs M.

- Addition of thiotic acid to a plan for management of hepatic insufficiency. *Am J Med* 1956; **21**: 131–2.
- 10 Glaeser J. Erfahrungen mit thioctacid bei lebererkrankungen in einer allgemeinpraxis. *Therapiewoche* 1980; **30**: 5585–6.
  - 11 Snedecor GW, Cochran WG. *Statistical methods*. 6th ed. Iowa: Iowa State University Press, 1967.
  - 12 Frimmer M, Waldovogel G, Weil G. Schutzwirkung von thioctsaure gegen die kalium-freizetzende wirkung des phalloidins an der isoliert perfundierten rattenleber. *Klin Wochenschr* 1968; **46**: 1288–9.
  - 13 Zulik R, Bakó F, Budavari J. Death cap poisoning. *Lancet* 1972; **2**: 288.
  - 14 Editorial. Mushroom poisoning. *Lancet* 1980; **2**: 351–2.
  - 15 Lieber CS. Liver adaptation and injury in alcoholism. *N Engl J Med* 1973; **288**: 356–62.
  - 16 Lieber CS. Alcohol and the liver. In: Bittar EE, ed. *The biological basis of medicine*. Vol 5 London: Academic Press, 1965: 317–44.
  - 17 Stryer L. *Biochemistry*. 2nd ed. San Francisco: WH Freeman, 1980.
  - 18 Morgan MY, Colman JC, Sherlock S. The use of a combination of peripheral markers for diagnosing alcoholism and monitoring for continued abuse. *Br J Alc Alcohol* 1981; **16**: 167–77.
  - 19 Salaspuro MK, Lieber CS. Alcoholic liver disease. In: Wright R, Alberti KGMM, Karran S, Millward-Sadler GH, eds. *Liver and biliary disease. Pathophysiology, diagnosis, management*. London: Saunders, 1979: 735–73.