EFFECTS OF ACAMPROSATE /DISULFIRAM ON SERUM LIPID PROFILE IN CHRONIC ALCOHOLICS

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ABSTRACT

Aim: To measure the effect of Acamprosate/Disulfiram on serum lipid profile and lactate dehydrogenate. Methods: Participants were identified by screening through Alcohol Use Disorder Identification Test (AUDIT) with 8 or more than 8 score. Total 89 patients of 20-60 years with DSM IV criteria were enrolled with history of alcohol consumption without de-addiction treatment. They were admitted and detoxified for 3 weeks. Enrolled participants were randomized among three groups consisting placebo, acamprosate and disulfiram. At baseline, serum lipid profile and LDH were measured and same were measured at the end of 4th and 8th week of treatment. Biochemical values were expressed as mean ± SD and intergroup and time changes were expressed using "t test". One way Analysis of Variance F-Test was used to compare biochemical values among three groups. Results: Serum LDH value was found to be decreased compared to baseline in all treatment groups without intergroup variation. LDL, Triglyceride and total cholesterol were decreased in groups treated by acamprosate or placebo with statistical significance (P <0.01). It was continued to decrease till 8th week of treatment while they were significantly increased in disulfiram treated group. Triglyceride and total cholesterol were significantly increased in disulfiram group at 8th week of treatment than 4th week, moderately affecting lipid metabolism. Conclusion: Disulfiram is found detrimental to cardiovascular system by inducing atherosclerosis through hyper-lipidemia; physicians should be precautious in prescribing disulfiram in chronic alcoholics.

INTRODUCTION

Alcoholism is a devastating addictive disorder affecting multiple body systems. Being an irritant, alcohol affects every system, right from its ingestion complicating gastrointestinal system to its elimination involving renal system. Ethanol a common form of alcohol gets distributed to body after it gets metabolized in liver through dehydrogenase enzymes. As, it metabolizes 90% through hepatic enzymes, it unleashes liver as a potential site of harm in chronic alcoholics. Moreover, ethanol is Central Nervous System (CNS) depressants conferring behavioural abnormalities in chronic alcoholics.

Chronic use of alcohol in a greater amount is proven to be hazardous to heart. This produces cardiovascular failure, cardiomyopathy, stroke and arrhythmias. The above effects are mediated through complex changes induced in plasma lipoprotein lipase (LPL), lecithin-cholesterol acyltransferase (LCAT) and hepatic lipase. This can be well-grounded by formation of acetaldehyde, toxic metabolites of ethanol, produces foam cell and progresses to atherosclerosis[1,2]. Confounding factors include diet, liver function[3, 4], weight[5, 1], drinking pattern, exercise[6], age and sex[7].

The treatment of chronic alcoholism contains pharmacotherapy in forms of

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disulfiram, acamprosate and opioid antagonists-naltrexone. Non-pharmacological therapy includes psychotherapy, motivational & behavioural lessons and group therapy. Disulfiram acts as inhibitors of aldehyde dehydrogenase in the pathway of alcohol metabolism, increases blood concentration of aldehyde[8,9,10]. This produces aldehyde syndrome, which makes patient hypotensive, weak and aversion to alcohol. Acamprosate affects NMDA subtype of glutamate receptors, present in Brain where alcohol acts other than GABA receptor. Acamprosate decreases craving after cessation [11,12,13]. Naltrexone acts on opioid peptides and reduces the rewarding effects of alcohol.

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All abstinence medications need metabolism by liver microsomal enzymes. Hepatic functions in alcoholics are already compromised by alcohol biotransformation in a way, that abstinence therapy metabolism can also lead to lipemic disorder. Hyper-lipidemia is detrimental to the cardiovascular system inferring it to the atherosclerosis. It was contemplated that small amount of ethanol daily would act as cardio-protective, as it increases HDL level and thus decreases jeopardy of myocardial infarction[14,15,16]. On the contrary, consumption of ethanol in a large amount increases risk of hyper-triglyceridemia and cardiac disorders by cardiomyopathy and hypo-contractibility. By contributing to the multisystem wasting, ethanol does soft tissue trauma and deprives tissues from glucose. As a result, pyruvate and lactate increases in tissues and makes molecular and microvasculature injury[17]. Hence Chylomicrons, VLDL, LDL, HDL and LDH need continuous observation in chronic alcoholics under treatment. This was aimed in present study to contemplate the effect of medication on serum lipid profile and lactate dehydrogenase.

MATERIAL AND METHODS

Objective

To study the effect of Acamprosate / Disulfiram on serum lipid profile and lactate dehydrogenase.

Patient screening

Alcohol Use Disorder Identification Test (AUDIT) was used to screen patients to be included in the study (Annexure I). Those patients with a score of 8 or more were included in the prospective randomised placebo controlled study.

Inclusion criteria

1. History of chronic alcoholism as per diagnostic and statistical manual of mental disorders. 4th ed (DSM IV) criteria.
2. Age group 20-60 years.
3. Should not have tried any other medication for de-addiction in the past one year.

Exclusion criteria

1. Patients with liver failure
2. Patients with renal failure

This prospective randomised placebo controlled study was carried out at Rajaji Centre for addiction, VHS, Taramani, Chennai (India) for the duration of 8 weeks.

Study procedure

Total 89 chronic alcoholic patients were enrolled and detoxified for 3 weeks. They were randomised to acamprosate or disulfiram or

placebo treatment, after detoxification. They received psychotherapy and group therapy as an adjuvant non-pharmacological therapy. Out of 89 patients, 47 had completed the study. The patients were discharged after a week and then followed as out patients till completion of study. Written informed consent was obtained from each human subject and the procedures followed were in accordance with the ethical standards of the institutional ethics committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

Outcome measures

1. Effect of the drug on serum lipid profile (Total cholesterol, HDL-C, LDL-C, VLDL-C, triglycerides) and lactate dehydrogenase

The patient's serum lipid profile and LDH were measured on the day of admission, at 4 weeks after starting drugs and at 8 weeks after starting drugs, in the laboratory at Department of Pharmacology and Environmental Toxicology, Dr.ALM PGIBMS, Taramani, Chennai.

Statistical analysis

In disulfiram, acamprosate and placebo treated alcoholics - biochemical values of LDH, TC, HDL, LDL, VLDL and TGL were expressed as mean and standard deviation. With in group analysis like baseline versus 4 weeks, baseline versus 8 weeks was calculated by using student's paired t test for each group. Between two groups comparative analysis like disulfiram versus Acamprosate, Disulfiram versus placebo were calculated by using student's independent t test. Mean difference between baseline and 8th week biochemical values were compared between three groups by using one way Analysis of Variance F-Test. Time series graphs were used to show intergroup and intra-group variation.

RESULTS

Prior to participation, all the patients were detoxified for 3 weeks. At baseline, serum lipid

Table 1: Measured LDH at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	150.6 ± 54.6	122 ± 44.12 Δ Δ	94.43 ± 36.02 Δ Δ
Acamprosate (n = 25)	178.2 ± 60.5	131 ± 37.0 Δ Δ	98.4 ± 23.7 Δ Δ
Disulfiram (n = 15)	159 ± 59.5	140.3 ± 51.9 Δ Δ	106.6 ± 45.3 Δ Δ

(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Table 2: Measured total cholesterol at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	238.8 ± 28.1	214.4 ± 23.7 Δ	192.1 ± 23.3
Acamprosate (n = 25)	220.7 ± 37.4	201.3 ± 42.9 Δ Δ	178.9 ± 32.8 Δ Δ
Disulfiram (n = 15)	221.8 ± 41.4	235.5 ± 29.2	□□ 259.6 ± 25.9 Δ Δ

(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Table 3: Measured HDL at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	37.14 ± 6.6	27 ± 4.4 Δ Δ	24.7 ± 5.59 Δ Δ
Acamprosate (n = 25)	39.7 ± 10.9	31.8 ± 8.8 Δ Δ	28.16 ± 7.4 Δ Δ
Disulfiram (n = 15)	35.0 ± 6.8	29.8 ± 7.5 Δ Δ	27.3 ± 6.5 Δ Δ

(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Table 4: Measured LDL at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	158.1 ± 31.2	146.8 ± 22.8	134.7 ± 25.8
Acamprosate (n = 25)	137.8 ± 43.5	135 ± 41.7	+ + 120 ± 31.4 Δ
Disulfiram (n = 15)	141.3 ± 39.8	162.9 ± 30.0 Δ Δ	□□ 185.7 ± 28.3 Δ Δ

(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Table - 5: Measured VLDL at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	43.4 ± 3.2	41.1 ± 3.2 Δ Δ	38.1 ± 2.7 Δ Δ
Acamprosate (n = 25)	38.7 ± 6.4	+ + 34.4 ± 6.3 Δ Δ	+ + □ □ 29.3 ± 6.4 Δ Δ
Disulfiram (n = 15)	42.8 ± 9.5	44.0 ± 7.7	48.0 ± 6.7 Δ Δ

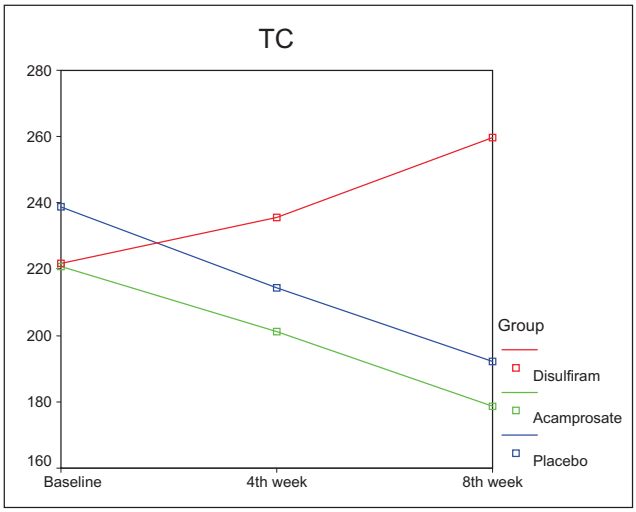
(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, + -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Table - 6: Measured TGL at predefined interval

Group	O Day	4 Weeks	8 Weeks
Control (Placebo) n= 7	218.1 ± 16.4	206.0 ± 16.4 Δ Δ	190.4 ± 13.5 Δ Δ
Acamprosate (n = 25)	193.7 ± 32.1	+ + 170.6 ± 32.2 Δ Δ	+ + □ □ 150.1 ± 32.1 Δ Δ
Disulfiram (n = 15)	213.4 ± 47.5	220.9 ± 38.8	238.7 ± 33.9 Δ Δ

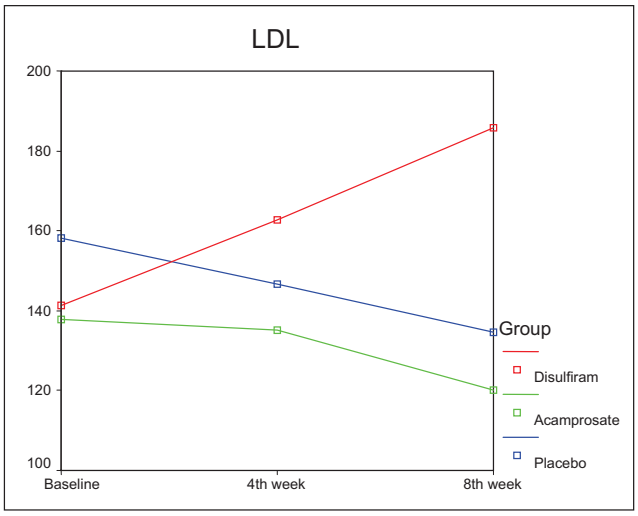
(Δ - O day Vs 4/8th weeks, □ - Control Vs Acamprosate / Disulfiram, + -Acamprosate Vs Disulfiram, Δ - P <0.05, Δ Δ - P <0.01, Δ Δ Δ - P <0.001)

Figure - 1 : Intergroup difference for total cholesterol measured



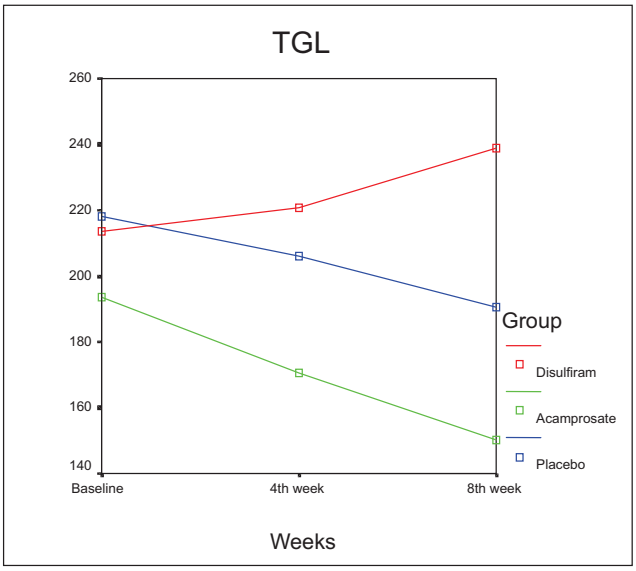
TC= Total Cholesterol

Figure - 2 : Intergroup difference for LDL measured



LDL= Low Density Lipoprotein

Figure - 3 : Intergroup difference for triglyceride measured



TGL= Triglyceride

profile and LDH were measured. Particularly, serum LDH levels were found to be elevated in chronic alcoholics before starting treatment. (Table 1)

In placebo treated group, significant decline in enzymatic activity (P < 0.01) at the end of 4 weeks and 8 weeks was seen, compared to baseline data. Similar results were observed in acamprosate and disulfiram treated group with statistical significance (P < 0.01). In all three

groups there was a significant decline of the enzymatic activity at the end of 8 weeks (P < 0.01) compared to end of 4 weeks.

No significant change observed in intergroup comparison.

Serum total cholesterol (TC) values were found to be raised in all the 3 groups before starting treatment. In placebo treated group, small decrease was seen in total cholesterol at the end of 4th week, when compared with baseline (P <0.05). There was no significant change at the end of 8th weeks. In acamprosate treated group, TC value was significantly decreased at the end of 4th week (P < 0.01) and also at the end of 8th week (P < 0.01). Contradictory, in disulfiram treated group there was a significant increase in TC at the end of 8th week (P < 0.01) compared to the baseline data. (Table 2)

Intergroup variation was significant at the end of 8th week in disulfiram treated group compared to acamprosate treated group and also with placebo treated group. (Figure 1)

Taking serum HDL in account, in placebo treated group, a significant fall was observed at the end of 4th (P<0.01) week and at the end of 8th week (P <0.01) compared to baseline. Similar fashion was observed in disulfiram treated group and Acamprosate treated group. This has eliminated the intergroup variance. (Table 3)

Serum LDL values were above the normal range in all groups before starting treatment. No change at the end of 4th week and 8th week in placebo group was observed compared to baseline. However, in acamprosate treated group there was a mild decrease at the end of 8th week (P < 0.05) compared to baseline and 4th week. In disulfiram treated group increase in LDL values was witnessed at the end of 4th week and 8th week (P < 0.01) compared to baseline. (Table 4)

Disulfiram treated group showed increase in LDL at the end of 8th week (P < 0.01) compared to placebo and acamprosate treated groups, showing intergroup variability. (Figure 2)

Serum VLDL values was decreased at the end of 4th week in placebo treated group and at the end of 8th week (P < 0.01) when compared to baseline and a mild decrease at the end of 8th week (P < 0.05) when compared with 4th week. Same results were observed with Acamprosate treated group. Disulfiram treated group were contrasting with increase in VLDL at the end of 8th week compared to (P < 0.01) 4th week.

VLDL was significantly decreased in Acamprosate group compared to placebo at 8 weeks and disulfiram treated group showed opposite result, with high intergroup variability.

Concerning TGL level, in placebo treated group, there was a significant decrease at the end of 4th week (P < 0.01) and at the end of 8th week (P < 0.01) compared to baseline. Same pattern of results were repeated in Acamprosate treated group with statistical significance (P < 0.01). In disulfiram treated group, a significant increase (P < 0.01) in TGL was observed at the end of 8th week. (Table 6)

In intergroup comparison, TGL level was decreased in Acamprosate treated group compared to disulfiram (P < 0.01). Compared with placebo treated group, acamprosate group showed more decrease in TGL at the end of 8th week (P < 0.01). (Figure 3)

DISCUSSION

Presented prospective clinical study was aimed to evaluate the effects of acamprosate and disulfiram on lipid profile and LDH. Overall 47 patients were evaluated at baseline for serum LDH levels, revealed elevation of enzymatic activity. This increase levels showed that there might be myocardial muscle damage. Damaged muscle part has led to production of pyruvate and lactate-toxic compounds. This might be due

to acetaldehyde[18] (toxic metabolite of alcohol) or due to lipid peroxidation[17]. Chronic alcoholism can cause cardio-myopathy with symptoms ranging from unexplained arrhythmia in the presence of left ventricular impairment to heart failure with dilatation of all four heart chambers and hypo-contractibility of heart muscles. In all the three groups (acamprosate, disulfiram, placebo) serum LDL levels decreased to normal level at the end of 8th weeks when compared with baseline showing beneficiary effects of abstinence therapy. Disulfiram and acamprosate might reduce LDL level, but the same was seen in placebo group, showing alcohol withdrawal as the probable mechanism than drug action only.

Though moderate intake of alcohol can cause beneficial effect by increasing apolipoprotein AI and AII levels, decreasing serum lipoprotein (a), preventing oxidation of LDL and decreasing cholesterol ester transfer protein[14,15,16], chronic alcoholism usually develop triglyceridemia and Pancreatitis. Serum cholesterol values decreased at the end of 8th weeks in both placebo and acamprosate treated groups when compared with baseline. But in disulfiram treated group, the levels increased further at the end of 8th weeks when compared with baseline. Since disulfiram was metabolized to carbon disulfide and this could increase the serum cholesterol values[8, 9], or it might be due to fourfold increase in activity of hepatic HMG-CoA reductase. HDL levels decreased in all three groups over the period of 8 weeks compared to the baseline, revealing no effects on HDL. There was no intergroup significance.

Low density lipoprotein (LDL) becomes atherogenic when they are modified by oxidation, a required step for LDL uptake by macrophages. This leads to foam cell formation in arterial lesion. In acamprosate treated group, LDL was slightly decreased at the end of 8th weeks when compared to baseline. But in disulfiram treated group LDL values were increased at the end of 8th weeks.

The metabolism of ethanol enhances the level of NADH[19] in the liver, which in turn stimulates the synthesis of fatty acid and their incorporation in to triglycerides. So, ethanol is known to produce hyper-triglyceridemia. Both in placebo and acamprosate treated groups, TGL and VLDL values decreased at the end of 8th weeks when compared to baseline. But acamprosate was better than placebo in this aspect. This demonstrates therapeutic add on effects of acamprosate in chronic alcoholics. In disulfiram treated group both TGL and VLDL values were increased at the end of 8th weeks, revealing warning signals in use of disulfiram for alcoholics with lipemia or atherosclerosis.

In above manner, acamprosate is a well-disposed than disulfiram on plasma lipid lowering effects in abstinent patients with alcohol dependence. Indirectly, acamprosate showed protective mechanism in reducing cardio-vascular complications.

In conclusion, conceiving chronic alcoholism as a potential vascular hazard, abstinence pharmacotherapy with add on vascular protective mechanism is highly accepted. Atherosclerotic disease by increase in serum cholesterol and triglyceride values is common. Hence, it is preferable to prescribe drug with lipid lowering effects. Conventional disulfiram has been observed to increase the LDL, Triglyceride and serum cholesterol in chronic alcoholics. Physicians should be cautious in prescribing disulfiram in chronic alcoholics, since it can be detrimental to cardiovascular system by inducing atherosclerosis.

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