NALTREXONE EXERTS A FAVOURABLE EFFECT ON PLASMA LIPIDS IN ABSTINENT PATIENTS WITH ALCOHOL DEPENDENCE

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INTRODUCTION

Epidemiological studies show higher general and cardiovascular mortality in abstinent persons and heavy drinkers than in moderate alcohol drinkers (1 to 2 standard drinks/day) (Rimm et al., 1991; Ahlawat and Siwach, 1994; Goldberg et al., 1995). Such a relationship reflects a U-shaped curve, and a possible mechanism of this protective effect of moderate alcohol drinking may be related to the actions of ethanol as well as to other components (e.g. flavonoids) in alcoholic beverages. The antiatherogenic effect of ethanol is exerted via plasma lipids, coagulation, and fibrinolysis (Goldberg et al., 1995). All epidemiological investigations show a positive correlation between alcohol consumption and HDL cholesterol (HDL-C) and the rise in HDL-C levels is the most plausible explanation of the protective effects of drinking alcohol. In some publications, in which HDL subfractions were analysed, an increase in the HDL-3, but seldom in the HDL-2 subfraction (only the HDL-2 fraction is associated with cardiovascular risk; Hafrner et al., 1985) has been reported (Goldberg et al., 1995). The influence of ethanol on total cholesterol (TC) and LDL cholesterol (LDL-C) is dose related. Moderate alcohol drinking decreases LDL-C levels (Kervinen et al., 1991; Langer et al., 1992), but high alcohol consumption leads to an increase in proatherogenic lipoprotein levels (Hojnacki et al., 1992). Moreover, alcohol drinking results in a decrease in lipoprotein (a) levels (Paasikilta et al., 1998). Alcohol drinking is a known causative factor of secondary hypertriglyceridaemia (Ginsberg et al., 1974; Belfrage et al., 1977; Steinberg et al., 1991), but some authors report a lack of alcohol influence on fasting triglyceride (TGL) concentrations or even lower TGL levels in men who drink alcohol (Goldberg et al., 1995). Ethanol consumption also affects postprandial lipid levels (Ginsberg et al., 1974; Hartung et al., 1993; Pownall, 1994). The above ethanol effects on plasma lipids are related to ethanol-induced changes in the activities of enzymes such as: post-heparin plasma lipoprotein lipase (LPL), lecithin-cholesterol acyltransferase (LCAT), and hepatic lipase (Simon and Scheig, 1970; Hojnacki et al., 1992; Nishiwaki et al., 1994; Goldberg et al., 1995). These effects are very complex and may be further modified by diet, liver function (Seidel et al., 1972; Sabesin et al., 1977; Devenyi et al., 1981; Camps et al., 1994), quantity of alcohol drinking (Hojnacki et al., 1992), drinking pattern (binge or regular) and body weight (Hagiage et al., 1992; Hojnacki et al., 1992), exercise, life activity (Hartung et al., 1993), and age and sex (Tollin et al., 1985). In alcohol-dependent males, who often have liver impairment, HDL-C levels after alcohol abuse do not increase (Devenyi et al., 1981) and low TC levels are also observed (Camps et al., 1994).

The effects of ethanol on plasma lipid metabolism and atherosclerosis may also depend on its metabolite, acetaldehyde, which can acetylate the LDL lipoprotein (Steinberg et al., 1989). Such modification of lipoproteins enhances their uptake by macrophages, leading to ‘foam cell’ generation and to atherosclerosis progression (Niemela et al., 1987).

The non-ethanol-related antiatherogenic effect of alcoholic beverages is attributed to flavonoids (epicatechin, quercetin, and resveratrol), notably present in red wine. Flavonoids can act as free radical scavengers (lipid peroxidation prevention;
oxidized LDL lipoproteins are more atherogenic than native lipoproteins), eicosanoid metabolism modulators, and inhibitors of platelet aggregation and inflammation (Goldberg et al., 1995). These effects explain ‘the French paradox’ (less coronary heart disease in various parts of France compared with other industrialized countries, despite a similar level of other atherosclerosis risk factors) (Renaud and De Lorgeril, 1992).

Total abstinence by alcohol-dependent patients after alcohol withdrawal prevents them from benefiting from the effect of moderate alcohol drinking. First of all, the above-mentioned changes in plasma lipid concentrations do not occur: HDL-C levels fall and total and LDL cholesterol as well as lipoprotein(a) concentrations rise (Lamisse et al., 1994; Goldberg et al., 1995). There is much epidemiological and experimental evidence that such disturbances in plasma lipid concentration could increase the global risk of cardiovascular events (Steinberg et al., 1991; Pyörälä et al., 1994; Paassilta et al., 1998). The positive relation between frequency of coronary heart disease (CHD) and TC, LDL-C (Castelli et al., 1983; Freedman et al., 1994; Pyörälä et al., 1994; Wood et al., 1998) and TGL concentrations (Patsch et al., 1992; Hodis and Mack, 1998) is well known as is the negative relation between the risk of CHD incidence and HDL levels (Gordon and Rifkind, 1989; Gordon et al., 1989), particularly the HDL-2 subfraction (Haffner et al., 1985). The strong relationship between plasma lipid levels and mortality was also evident from the simultaneous decrease of TC concentration (by 20–30%) and decrease of general and cardiovascular mortality observed in investigations in which lipid-lowering drugs were given in primary (decreased CHD risk by 19–31%) and secondary (decreased CHD risk by 29–34%) prevention (Law et al., 1994; Scandinavian Simvastatin Survival Study Group, 4S, 1994; Gould et al., 1995; Shepherd et al., 1995). These results, in relation to general mortality, were challenged in publications in which authors reported lower TC levels in the course of neoplasms (International Collaborative Group, 1982) and no effect on general mortality after cholesterol-lowering therapy (Muldoon et al., 1990; Muldoon and Manuck, 1994). It seems that, in neoplastic diseases, the decrease in TC levels is secondary to the disease course. Moreover the 4S study showed improvement not only in cardiovascular (42%) but also in general (30%) mortality following 6 years of lipid-lowering therapy (Scandinavian Simvastatin Survival Study Group, 1994). Furthermore, it was suggested that low TC levels lead to disturbances of serotonin metabolism that may result in an increase in psychiatric disorders and suicides (Brown, 1996). Why, then, do the Japanese, who have one of the lowest mean TC concentrations, commit suicide less frequently than eastern European counterparts? In spite of this anomaly, it seems important in the pharmacotherapy of alcohol dependence to prevent, not only drinking relapse, but also accompanying plasma lipid disturbances during abstinence. Currently, in alcohol-dependence therapy, the most frequently used drugs are disulfiram, acamprosate, and naltrexone, the latter being an opioid receptor antagonist. These drugs, like other drugs that do not belong to typical lipid-affecting agents (e.g. β-blockers, diuretics, glucocorticoids, oestrogens, progestins, anabolic steroids, and 13-cis-retinoid acid), can exert an effect on plasma lipid levels. Anticonvulsant drugs (carbamazepine, phenytoin) (Luoma, 1988; Isojarvi et al., 1993; Calandre et al., 1998) and disulfiram (Noussainen and Ryhanen, 1984; Ogishima et al., 1987) can exert a hyperlipaemic effect and during therapy with these drugs TC, LDL-C, and HDL-C levels increase. Anticonvulsant drugs cause induction of microsomal enzymes and disulfiram blocks the conversion of cholesterol to bile acids via inhibition of the Δ5-hydroxylase of 25-hydroxycholesterol. Other drugs can also act as modulators of enzymes involved in lipid metabolism or can change hormonal function, especially the pituitary–adrenal and pituitary–thyroid axes. To our knowledge only Best et al. (1996) have reported that naltrexone can decrease total cholesterol levels in abstinent men.

On the basis of the above reports we suggest that, in alcohol-dependent males during an abstinence period, proatherogenic changes in plasma lipid concentrations occur and that some drugs can intensify this and that others can exert a favourable effect. The aim of this study was to determine the influence of naltrexone, carbamazepine, lithium carbonate, and placebo on plasma lipid level changes in alcohol-dependent males during withdrawal therapy.

PATIENTS AND METHODS

The investigation was done within the framework of a double-blind study of 160 alcohol-dependent male patients, diagnosed according to ICD-10 criteria (World Health Organization, 1992), hospitalized in the Addiction Treatment Unit, Department of Psychiatry of The Ludwik Rydygier Medical University in Bydgoszcz (Poland) between 1993 and 1996. The mean age of the patients (± SD) was 39 ± 7 years, mean duration of alcohol dependence 13 ± 6 years, mean score for the Michigan Alcoholism Screening Test (MAST) was 42 ± 13 and mean score for the Short Alcohol Dependence Data (SADD) was 25 ± 7. Prior to admission to hospital, the patients drank an average of 693 ± 595 standard drinks (1 drink = 1 oz. of pure ethanol) for 90 days. All patients smoked both before and during the study.

The therapy was carried out in two phases. In the initial 4 weeks after admission, patients received mainly psychotherapy and, after this period, they were randomized to pharmacotherapy with either naltrexone (50 mg/day, 40 men), carbamazepine (600–800 mg/day, 40 men), lithium carbonate (500–1000 mg/day, 39 men) or placebo (41 men), administered between weeks 4 and 20 of the study. In the period between weeks 4 and 8, pharmacological treatment was given in the Addiction Treatment Unit and for the following 12 weeks, therapy was on an out-patient basis. All patients received similar hypolipemic diets, according to the European Atherosclerosis Society (1992) recommendations (see also Pyörälä et al., 1994). Energy consumption was on average 2000 kcal/day, but in patients with a body mass index (BMI) above 25 kg/m² a reduced diet (20 kcal/kg body mass) was recommended. The daily calories consumed consisted of one-third in cereal products, one-quarter in vegetables, one-fifth in fruit, 15% in milk products and the remainder in meat, fish or legumes. In this way, daily cholesterol consumption was lower than 300 mg and daily fat-energy consumption was lower than 30% (saturated fatty acids below 10% energy, monounsaturated fatty acids 10–15% energy and polyunsaturated fatty acids 7–10% energy). In patients with a BMI above 25 kg/m²...
and in those with hypertriglyceridaemia (TGL > 200 mg/dl), no sugar consumption was recommended. During the study period, patients did not take any other drugs.

Blood samples for biochemical determinations were taken after 14 h of fasting, at the beginning of the study and every 2 weeks for 20 weeks. Included in the analysis were results obtained from 116 patients (31 from the naltrexone, 24 from the carbamazepine, 31 from the lithium carbonate, and 30 from the placebo groups), who maintained abstinence throughout the study and had normal results for glucose tolerance, kidney, and thyroid function tests (TSH level < 0.25 mU/l and > 5.0 mU/l). Biochemical markers of alcohol abuse [activities of \( \gamma \)-glutamyltranspeptidase (GTP), aspartate aminotransferase (GOT), alanine transferase (ALT)] and concentrations of the following lipids, TC, HDL-C, LDL-C (for patients with TGL levels below 400 mg/dl calculated using the Friedewald pattern), and TGL were estimated. Determinations were made using routine clinical laboratory methods.

All subjects gave their informed consent to participate in this study, which was approved by the Local Ethics Committee of the Ludwik Rydygier Medical University in Bydgoszcz. The investigation was in compliance with the Declaration of Helsinki for medical research.

Regularity of drug taking was estimated every 2 weeks using drug capsules marked with riboflavin and randomly checking for the characteristic yellow colour of urine. In all patients, the result of checking was positive in all eight evaluations.

Statistical significance was determined using, respectively, paired and unpaired Student’s \( t \)-test, \( \chi^2 \)-test and two-factorial ANOVA with two repetitions, and the NIR post-hoc test using STATISTICA PL 5.0 statistical software.

**RESULTS**

No clinical (Table 1) and biochemical (Table 2) differences were found at the start of the study between patients treated with naltrexone, carbamazepine, lithium carbonate or placebo.

In Table 3, the results of the biochemical determinations before and after 16 weeks of pharmacotherapy are shown for the number of patients in each group who completed treatment.

After 16 weeks of pharmacotherapy, a significant decrease of alcohol misuse markers was observed in naltrexone- and lithium carbonate-treated patients (both GTP and ALT activities) and in the placebo group (GTP activity only). In patients treated with carbamazepine, a significant increase of GTP activity was found.

Using ANOVA, a significant effect of applied therapy on TC changes during the pharmacotherapy period was found \( [F(3,91) = 5.84; P < 0.01] \). The significance of pharmacotherapy influence on LDL-C level changes was borderline.

**Table 1. Clinical characteristics of the patient groups at the start of the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naltrexone (n = 40)</th>
<th>CMZ (n = 40)</th>
<th>Lithium (n = 39)</th>
<th>Placebo (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37 ± 8</td>
<td>36 ± 6</td>
<td>39 ± 7</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Duration of alcohol dependence (years)</td>
<td>14 ± 8</td>
<td>11 ± 5</td>
<td>13 ± 6</td>
<td>14 ± 6</td>
</tr>
<tr>
<td>Age of onset of dependence (years)</td>
<td>24 ± 5</td>
<td>25 ± 6</td>
<td>26 ± 6</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>No. of drinks for 90 days before the start of the study</td>
<td>696 ± 742</td>
<td>640 ± 464</td>
<td>723 ± 580</td>
<td>636 ± 463</td>
</tr>
<tr>
<td>No. of drinking days over 90 days before study</td>
<td>43 ± 25</td>
<td>48 ± 24</td>
<td>42 ± 25</td>
<td>51 ± 30</td>
</tr>
<tr>
<td>MAST (score)</td>
<td>45 ± 13</td>
<td>41 ± 12</td>
<td>43 ± 14</td>
<td>41 ± 13</td>
</tr>
<tr>
<td>SADD (score)</td>
<td>27 ± 7</td>
<td>25 ± 8</td>
<td>26 ± 9</td>
<td>25 ± 6</td>
</tr>
<tr>
<td>Alcohol dependence among first-degree relatives</td>
<td>(52%)</td>
<td>(54%)</td>
<td>(45%)</td>
<td>(43%)</td>
</tr>
<tr>
<td>Delirium tremens in anamnesis</td>
<td>(39%)</td>
<td>(21%)</td>
<td>(23%)</td>
<td>(20%)</td>
</tr>
<tr>
<td>Decrease in alcohol tolerance</td>
<td>(32%)</td>
<td>(42%)</td>
<td>(39%)</td>
<td>(37%)</td>
</tr>
</tbody>
</table>

Data are means ± SD or %. No significant differences between groups were found. CMZ, carbamazepine; MAST, Michigan Alcoholism Screening Test; SADD, Short Alcohol Dependence Data.

**Table 2. Biochemical data in the patient groups at the start of the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naltrexone (n = 40)</th>
<th>CMZ (n = 40)</th>
<th>Lithium (n = 39)</th>
<th>Placebo (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mg/dl)</td>
<td>14.9 ± 1.2</td>
<td>14.9 ± 1.4</td>
<td>14.7 ± 1.5</td>
<td>15.0 ± 1.1</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>95.6 ± 4.3</td>
<td>95.6 ± 4.1</td>
<td>96.5 ± 4.9</td>
<td>96.2 ± 4.7</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>4.2 ± 0.5</td>
<td>4.3 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>0.7 ± 0.4</td>
<td>0.7 ± 0.4</td>
<td>0.8 ± 0.5</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>GTP (U/l)</td>
<td>67 ± 68</td>
<td>88 ± 104</td>
<td>85 ± 99</td>
<td>82 ± 83</td>
</tr>
<tr>
<td>GOT (U/l)</td>
<td>32 ± 24</td>
<td>35 ± 43</td>
<td>50 ± 81</td>
<td>41 ± 40</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>31 ± 23</td>
<td>28 ± 21</td>
<td>40 ± 39</td>
<td>38 ± 36</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>218 ± 45</td>
<td>220 ± 46</td>
<td>222 ± 43</td>
<td>221 ± 46</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>55 ± 15</td>
<td>60 ± 23</td>
<td>57 ± 20</td>
<td>54 ± 17</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>4.3 ± 1.6</td>
<td>3.9 ± 1.2</td>
<td>4.3 ± 1.3</td>
<td>4.5 ± 1.6</td>
</tr>
<tr>
<td>TGL (mg/dl)</td>
<td>136 ± 46</td>
<td>130 ± 39</td>
<td>132 ± 40</td>
<td>144 ± 46</td>
</tr>
</tbody>
</table>

Data are means ± SD. No significant differences between groups were found. CMZ, carbamazepine; MCV, mean corpuscular volume; GTP, \( \gamma \)-glutamyltranspeptidase; GOT, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; HDL-C, HDL-cholesterol; LDL-C, LDL cholesterol; TGL, triglycerides.
Results of studies have shown that, in alcoholics after a 1–4-week abstinence period, proatherogenic changes in plasma lipid levels occurred, involving most often decreased HDL-C levels and increased LDL-C levels (Goldberg et al., 1995). However, in all available reports, the observation time was no longer than 4 weeks of alcohol abstinence. In our study, after 4 weeks of abstinence (the psychotherapy phase), we observed a significant increase in TC and LDL-C levels and in the TC/HDL-C ratio value and a decrease in HDL-C levels (Tables 2 and 3). During the following 16 weeks of abstinence (the pharmacotherapy phase), the majority of plasma lipid fractions in the placebo group did not change and only the HDL-C levels rose (Table 3). However, in the naltrexone-treated group, significant decreases in TC (10%) and TGL (31%) concentrations were observed. After 16 weeks of pharmacotherapy in the naltrexone-treated group, TC and LDL-C levels were also lower than in the carbamazepine- and lithium carbonate-treated groups, and TGL levels were lower in the naltrexone than in the other groups. The decrease in the alcohol misuse markers in the studied patients may indicate that they maintained alcohol abstinence during the treatment period.

Results of many investigations and of coronary heart disease (CHD) preventive programmes underline the importance of control for smoking, hypertension, diabetes, obesity etc. as well as lipid atherosclerosis risk factors. There is evidence that a decrease in fasting plasma lipid concentrations, such as that observed in our naltrexone patients, can decrease the risk of coronary events in the general population (Pyörälä et al., 1994; Goldberg et al., 1995; Criqui, 1998; Hodis and Mack, 1998). Results of the 4S study (Scandinavian Simvastatin Survival Study Group, 1994) showed that a decrease in TC levels of 24% led to a decrease in general risk of death by 30%, in cardiac death risk by 42%, and in severe cardiac event risk by 34%. This suggests that a decrease of TC levels by 10% (such as in our naltrexone group) can decrease the coronary event risk by 18%. The results of meta-analysis of many clinical trials also showed that CHD risk decreased directly in

### DISCUSSION

Results of studies have shown that, in alcoholics after a 1–4-week abstinence period, proatherogenic changes in plasma lipid levels occurred, involving most often decreased HDL-C levels and increased LDL-C levels (Goldberg et al., 1995). However, in all available reports, the observation time was no longer than 4 weeks of alcohol abstinence. In our study, after 4 weeks of abstinence (the psychotherapy phase), we observed a significant increase in TC and LDL-C levels and in the TC/HDL-C ratio value and a decrease in HDL-C levels (Tables 2 and 3). During the following 16 weeks of abstinence (the pharmacotherapy phase), the majority of plasma lipid fractions in the placebo group did not change and only the HDL-C levels rose (Table 3). However, in the naltrexone-treated group, significant decreases in TC (10%) and TGL (31%) concentrations were observed. After 16 weeks of pharmacotherapy in the naltrexone-treated group, TC and LDL-C levels were also lower than in the carbamazepine- and lithium carbonate-treated groups, and TGL levels were lower in the naltrexone than in the other groups. The decrease in the alcohol misuse markers in the studied patients may indicate that they maintained alcohol abstinence during the treatment period.

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proportion to the percentage decrease in TC levels (Gould et al., 1995) and duration of TC level reduction (Law et al., 1994). These latter authors showed that a decrease in TC levels of 23 mg/dl (as in our naltrexone group, see Table 3) led to a decrease in coronary events risk of 7% during the first 2 years and by 25% when the lipid-lowering therapy period was longer than 5 years.

As is the case with total cholesterol, fasting TGL levels are a well-recognized risk factor for cardiovascular events and death (Pyörälä et al., 1994; Criqui, 1998; Hodis and Mack, 1998; Wood et al., 1998). Moreover, in patients with higher fasting TGL concentrations, a higher level of postprandial lipaemia was found (Hartung et al., 1993). The elevation of the late phase of postprandial lipaemia is considered to be a greater risk factor for coronary artery disease than plasma HDL-C levels (Patsch et al., 1992). The latter is recognized as a main antiatherogenic factor responsible for the lipid-mediated protective effect of moderate alcohol consumption (Casleli et al., 1983; Gordon and Rifkind, 1989; Kervinen et al., 1991; Camps et al., 1994; Freedman et al., 1994; Goldberg et al., 1995). As a 31% reduction of TGL levels was observed in our naltrexone patients, a preventive effect of naltrexone on atherosclerosis may be suggested.

The hypolipidaemic effect of naltrexone (10% TC levels reduction and 30% reduction in TGL concentrations) was weaker than that usually obtained when typical lipid-lowering drugs are used, but was comparable to the diet effect. Among the most often prescribed lipid-lowering agents, the statins decrease TC levels by 20–30%, LDL-C levels by 20–50%, TGL levels by 10–40%, and increase HDL-C levels by 5–15% (Jones, 1998; Schrott, 1998), whereas fibrates decrease TC levels by 20–25%, LDL-C levels by 25%, TGL levels by 30–50%, and increase HDL-C levels by 10–30% (Farnier et al., 1994), and nicotinic acid reduces TC levels by up to 30% and TGL concentrations by 20–60%, bile acid sequestrants decrease LDL-C levels by 15–30% and increase TGL levels by 5–15% (Betteridge and Morrell, 1998).

The naltrexone effect on plasma lipids was reported previously in an animal model (Bryant et al., 1988a,b). In rats during stress caused by immobilization, naltrexone prevented the stress-induced increase in TC (Bryant et al., 1988b). LDL-C, VLDL cholesterol (VLDL-C) and a decrease in HDL-C levels (Bryant et al., 1988a). Because naltrexone is an opioid receptor antagonist, the results of these studies may suggest a role for opioids in the pathogenesis of stress-induced hyperlipoproteinaemia. This is also supported by the results of investigations in which increases in TC, LDL-C, VLDL-C, TGL and a decrease of HDL-C levels were found after long-term therapy with opioid receptor agonists, such as morphine (Bryant et al., 1987, 1998b) or L-α-noracetylmethadol (NorLAAM) (Borzelleca et al., 1995). Our results corroborate these previous studies. Plasma lipid concentrations in our placebo group remained high for the 16-week period of abstinence. However, a significant decrease of TC and TGL levels in our naltrexone group may suggest a hypolipidaemic effect of this opioid receptor antagonist. This hypolipidaemic effect of naltrexone requires further confirmation, because of our study limitations. First, the abstinence period before the start of the study differed among the patients. Second, the drugs investigated were not given immediately after the end of the alcohol misuse period (i.e. at or immediately after detoxification), but following 4 weeks of psychotherapy. The results of other reports have shown that after this period, plasma lipid levels return to values similar to those in the general population (Goldberg et al., 1995) and, because of this, no hyperlipidaemic effect of abstinence was observed in the placebo group. Third, drugs used in our study were given in the morning, whereas the most frequently used lipid-lowering agents, the statins and long-acting fibrates, should be given in the evening. Perhaps the hypo- and hyperlipidaemic effects of the drugs studied would have been greater if the drugs were given in the evening, i.e. at the time of greatest cholesterol synthesis. Fourth, when patients were discharged from our clinic, dietary control was difficult to ascertain.

The hyperlipidaemic drug effect, observed in the carbamazepine-treated group, namely the increases in TC, LDL-C and, HDL-C levels was probably due to the inductive effect of the drug on microsomal enzymes and has also been observed in previous studies (Luoma, 1988; Isojarvi et al., 1993; Calandre et al., 1998). This explanation is confirmed by the simultaneous increase in GTP activity observed in this group.

In conclusion, the present results show that naltrexone exerts a mild hypolipidaemic effect which may have favourable consequences for atherosclerosis prevention in alcohol-dependent male patients after alcohol withdrawal. If such an effect is confirmed, naltrexone should be the preferred drug for pharmacotherapy of alcohol dependence. Carbamazepine, lithium carbonate, and disulfiram should be used with caution, as they should not be given to patients with hyperlipidaemia, due to their unfavourable effect on lipids, which may increase the cardiovascular risk. Further studies of drugs’ effect on plasma lipids are clearly needed to determine the safety of pharmacotherapy in alcohol-dependent patients.

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