Hypolipidemic Effect of Type Ia Antiarrhythmic Agents in Postinfarction Patients

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Background. Elevated levels of cholesterol and apoprotein B (apo B), the essential carrier protein for low density lipoprotein, are major lipid risk factors for premature coronary disease. Antiarrhythmic agents are frequently prescribed to patients with coronary heart disease and associated cardiac arrhythmias. As part of another study, we retrospectively investigated the effect of antiarrhythmic agents on blood lipids.

Methods and Results. The study population consisted of 1,567 postinfarction patients on whom we prospectively collected serial blood samples for lipid and apoprotein determinations and recorded the concomitant medications the patients were receiving at three follow-up time periods. The lipids, analyzed at a central core laboratory, included total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL C), and apoproteins A-I (apo A-I), A-II (apo A-II), and apo B. The difference in the group mean lipid values for patients receiving and not receiving type Ia antiarrhythmic agents (quinidine, procainamide, and disopyramide) was evaluated by the two-sample t test, and multiple linear regression analyses were performed to adjust for relevant covariates. Patients using type Ia antiarrhythmic agents at the 30-month postinfarction contact (n=76) had 8.6% lower cholesterol (p<0.003), 22.3% lower triglycerides (p<0.0002), 6.2% lower apo A-I (p=0.02), 10.1% lower apo A-II (p<0.001), and 12.7% lower apo B (p<0.0001) levels than patients not on these medications (n=1,491). These lower lipid levels were found after adjustment for age, sex, diabetes, smoking status, concomitant medications, and a variety of clinical factors relating to the severity of the coronary disease process. The HDL C levels were similar in those receiving and not receiving type Ia agents.

Conclusions. Patients on type Ia antiarrhythmic agents had significantly and meaningfully lower cholesterol, triglyceride, apo A-II, and apo B levels than patients not receiving these agents. The mechanism of this hypolipidemic effect is undefined, but the mechanism may be related to an alteration by these agents of ionic membrane currents at the hepatocyte level. (Circulation 1992;85:2039–2044)

Key Words • antiarrhythmic agents • cholesterol • apolipoprotein B

Guidelines developed by the National Cholesterol Education Program's Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults1 identified elevated cholesterol and low density lipoprotein cholesterol (LDL C) concentrations as the major targets for cholesterol-lowering therapy. The importance of cholesterol reduction in patients with overtly manifest coronary artery disease cannot be overstated, because virtually every major epidemiological study performed to date has shown a significant correlation between the level of serum cholesterol at the time of entry and the risk of subsequent coronary disease.2

The results of 22 randomized cholesterol-lowering clinical trials to reduce the risk of coronary heart disease indicate an average reduction of 23% in the risk of nonfatal myocardial infarction and cardiac death in treated compared with control patients.3 In particular, a 10% decrease in the cholesterol level was associated with a reduction of approximately 20% in the incidence of new coronary events.3

Present therapeutic guidelines include the recommendation that cholesterol-lowering drugs should be considered when cholesterol and LDL C levels remain significantly elevated after 6 months of appropriate dietary therapy.1,4 Currently available hypolipidemic agents include bile acid sequestrants (cholestyramine and colestipol), nicotinic acid, probucol, fibric acid derivatives (gemfibrozil and clofibrate), HMG-CoA reductase inhibitors, and ω-3 unsaturated fatty acids found in various fish oil supplements. To date, no other classes of lipid-lowering agents have been approved for clinical use.

Antiarrhythmic agents are frequently prescribed to patients with coronary heart disease and associated cardiac arrhythmias. Presently, antiarrhythmic agents are classified by their presumed mechanism of action at the myocellular level. All type I antiarrhythmic agents are characterized by their blocking effect on fast inward sodium current.5 The presently available type I agents (quinidine, procainamide, disopyramide, lidocaine, tocainide, mexilitine, flecainide, encainide, and the recently released moricizine and propafenone) differ in the way they interfere with the sodium channel (potential- and frequency-dependent block), in their effects on other myocellular ionic channels, and in their binding...
characteristics to cardiac membranes. On the basis of the differences in the electrophysiological and pharmacodynamic properties of the type I agents, they have been subclassified into type Ia (quinidine, procainamide, disopyramide, moricizine), type Ib (lidocaine, tocainide, mexilitine), and type Ic (flecainide, encainide, propafenone) subgroups.

As part of the Multicenter Diltiazem Post-Infarction Trial (MDPIT), we prospectively collected serial blood samples for lipid and apoprotein determinations and recorded the concomitant cardiac medications the patients were receiving. We retrospectively evaluated the effect of various cardiac medications on the blood lipids. We unexpectedly found that patients using type Ia antiarrhythmic agents had lower cholesterol, triglycerides, and apoprotein B (apo B) levels than patients not on these medications. These findings are the subject of this report.

Methods

Study Population

The study population consisted of 1,567 survivors of the original cohort of 2,466 postinfarction patients enrolled in the MDPIT on whom lipid and lipoprotein specimens were obtained at study termination. The details of patient recruitment, data acquisition, data management, and follow-up have been previously reported. Patients were randomly assigned to diltiazem or placebo and were followed at periodic intervals throughout the trial. All patients were followed for at least 12 months, to a maximum of 52 months; the average duration of follow-up was 25 months.

Blood Samples for Lipids

Venous blood was collected at enrollment before randomization to diltiazem trial medication (3–15 days after onset of the myocardial infarction), at approximately 6 months after entry into the study (range, 3–12 months), and as part of the closeout procedure at study termination (average, 30 months). An attempt was made to collect blood in the fasting state, but this was not universally accomplished.

The blood from each collected venous sample was allowed to clot at room temperature (30 minutes to 2 hours), and serum was separated by low-speed centrifugation (1,500g for 15 minutes). Sera were initially frozen at -20°C at each participating center and shipped on dry ice to the Miriam Hospital Core Lipid Laboratory in Providence, R.I., where the sera were stored at -70°C until analysis. The baseline and 6-month sera samples were stored for 2–6 months before analysis, whereas the closeout samples were shipped immediately after acquisition to the Core Lipid Laboratory and analyzed promptly (within 2 weeks). Lipid and lipoprotein measurements used lipid standards obtained from the Centers for Disease Control.

Analytic Methods for Serum Lipids

Serum cholesterol and triglyceride concentrations were determined on a Gilford System 3500 Computer Directed Analyzer with the use of enzymatic methods. High density lipoprotein cholesterol (HDL C) values were determined using methods identical to those of the Lipid Research Clinics program with the exception that the isopropanol and zeolite extraction steps are not required with the enzymatic methods.

Apoprotein A-I (apo A-I) and apoprotein A-II (apo A-II) levels were measured by validated double-antibody radioimmunoassay techniques. Apo B levels were determined by both a radioimmunoassay (RIA) and a radial immunodiffusion assay (RID). There was a high degree of correlation between these two methods in normal subjects (114±31 mg/dl versus 119±33 mg/dl, respectively), but the RID was, on average, 23 mg/dl higher than the RIA in subjects with hypertriglyceridemic serum. Apo B levels declined by 20% during 36-week storage at -20°C, with a smaller decline over time with storage at -70°C. Because of the decline in apo B with prolonged storage, apo B levels are reported only for closeout samples in which the serum was analyzed within 2 weeks of collection.

Medication Usage

The cardiac medications that the patients were receiving were identified at baseline, at each follow-up contact, and at closeout by using a prespecified medication dictionary. The medication categories included antiarrhythmic agents, β-blockers, digitalis preparations, diuretic agents, nitrates other than sublingual preparations, and the trial medication (diltiazem or placebo). Each category was subcategorized for specific agents. At closeout, 76 patients were on type Ia antiarrhythmic medication: 41 were on quinidine (mean daily dose, 964 mg); 29 were on procainamide (mean daily dose, 2,578 mg); and six were on disopyramide (mean daily dose, 367 mg). More than 90% of patients on type Ia agents at closeout were receiving these medications for 90 days or longer. Twenty-seven patients were on a variety of other type I antiarrhythmic agents (21 on type Ib and six on type Ic), and these agents had no apparent effect on serum lipids. No patient was on moricizine.

Statistical Analyses

The difference in the group mean values of cholesterol, HDL C, triglycerides, apo A-I, apo A-II, apo B by RIA, and apo B by RID for patients receiving and not receiving type Ia antiarrhythmic agents was evaluated by the two-sample t test. Multiple linear regression analyses (BMDP-2R) were performed on the closeout blood samples to identify baseline demographic, clinical, and closeout therapeutic covariates that influence the serum lipid levels. A separate regression model was developed for the logarithm of each lipid fraction. The log transformation was taken to reduce skewness in the response variables. Relevant covariates were selected by a stepwise procedure ($F \geq 4.0$) from the dichotomized variables listed in Table 1. The covariates used in the selection process involved age, sex, previous myocardial infarction, New York Heart Association class, history of treated hypertension, coronary bypass surgery, diabetes, cigarette smoking, shock, rales, pulmonary congestion by x-ray, creatine kinase level, blood urea nitrogen, blood pressure, anterolateral Q wave, inferior posterior Q wave, non-Q wave, ejection fraction, heart rate, ventricular ectopics, ventricular runs, diltiazem, β-blocker, digitalis, diuretics, and nitrates. Antiarrhythmic medication was then added to the model to evaluate...
The clinical characteristics of the 1,567 patients who had serum lipids obtained at closeout, subdivided by use of type Ia antiarrhythmic medication at study termination, are presented in Table 1. Patients receiving type Ia antiarrhythmic agents were more likely to be male with a history of hypertension and have pulmonary rales during the index myocardial infarction, a reduced radionuclide ejection fraction, and frequent and repetitive ventricular ectopics on the ambulatory ECG than those not on these agents. The weights of the two groups at enrollment and at closeout were similar. Digitalis and diuretics were more frequently used by the patients on antiarrhythmic agents than those not receiving type Ia medications, whereas the reverse was true for β-blockers. Randomized diltiazem therapy had no effect on the closeout blood cholesterol (diltiazem: cholesterol=227±47 mg/dl; placebo: cholesterol=226±47 mg/dl; t=0.39, p=0.70).

The total cholesterol levels at enrollment and at 6 months and 30 months after infarction by antiarrhythmic use at the respective contacts are presented in Table 2. The cholesterol level progressively increased during follow-up, but the cholesterol level was lower (8.7–11%) at each contact for those receiving type Ia antiarrhythmic agents compared with those who were not.

The effects of type Ia antiarrhythmic medication, as well as the effect of quinidine, procainamide, and disopyramide individually on the various lipid fractions at closeout, are presented in Table 3 together with relevant probability values. Patients receiving type Ia medications had 14% lower apo B by both RIA and RID determinations, 14% lower triglycerides, 13% lower apo A-II level, 11% lower total cholesterol, a modest 6% lower apo A-I level than patients not on these medications, and similar HDL C levels to those of
patients not on these medications. Quinidine, procainamide, and disopyramide were associated with similarly lower cholesterol, triglyceride, apo A-II, and apo B levels (Table 3) in those receiving versus those not receiving these medications. Multiple linear regression analyses were performed (Table 4), and the findings indicate that patients on type Ia antiarrhythmic agents had significantly \( p < 0.001 \) lower cholesterol, triglycerides, apo A-II, and apo B levels than patients not on these agents, even after adjustment for age, sex, diabetes, smoking status, concomitant medications, and a variety of clinical factors relating to the severity of the coronary disease process.

**Discussion**

The major finding of this report is that patients receiving type Ia antiarrhythmic agents had significantly \( p < 0.001 \) lower cholesterol, triglycerides, apo A-II, and apo B levels than those not on these agents. There was no significant effect of type Ia antiarrhythmic agents on HDL C, and apo A-I levels were only slightly lower \( (6\% \text{ lower}; p=0.02) \) in those using those not using type Ia agents. The magnitude of the lipid-lowering effect with type Ia antiarrhythmic agents on serum total cholesterol was approximately 9%.

It should be emphasized that in this postinfarction population, patients were not selected for enrollment into the diltiazem study according to any specific inclusion or exclusion criteria for blood lipids. The level of total cholesterol observed in this otherwise unselected postinfarction population was only minimally elevated. For example, the mean total cholesterol for the 1,491 patients not receiving type Ia antiarrhythmic therapy at study closeout was \( 228 \pm 47 \text{ mg/dl} \) -- a value that would be considered "borderline high" \( (200-239 \text{ mg/dl}) \) by the National Cholesterol Education Program.\(^1\)

It should be pointed out that in this and other postinfarction studies,\(^7\) cholesterol levels are lowest during the hospital phase of acute myocardial infarction and then progressively increase during posthospital convalescence. We observed a 9–11\% lower cholesterol level in patients receiving than not receiving type Ia antiarrhythmic agents at three different times after the index infarction (Table 2). This cross-sectional observation is different from the longitudinal reduction in cholesterol from a stable baseline value reported in randomized, double-blind, placebo-controlled clinical trials with standard hypolipidemic agents.\(^8\) For example, in the Lipid Research Clinics Primary Prevention Trial,\(^9\) cholestyramine was associated with a 13\% reduction in cholesterol from baseline. It is interesting that the magnitude of the cholesterol reduction with cholestyramine is similar to the 9–11\% lower cholesterol that we observed in patients using type Ia agents compared with patients not on these medications.

LDL, the major cholesterol-carrying particle in serum, has a lipid core and a single surface apoprotein, apo B-100.\(^{10,11}\) An elevated level of LDL C is a major risk factor for the premature development of coronary atherosclerotic disease, and there is considerable interest in lowering LDL C by diet and medication. LDL C is usually computed by the Friedewald formula\(^{21} \) from directly measured total cholesterol, HDL C, and triglyceride values. The accuracy of this computation assumes a fasting blood sample and a fixed ratio of triglyceride to cholesterol in the triglyceride-rich lipoprotein moieties.

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**Table 3. Effect of Type Ia Antiarrhythmic Medication on Various Lipid Fractions at Closeout**

<table>
<thead>
<tr>
<th>Lipid fraction</th>
<th>Type Ia antiarrhythmic agents (n=1,491)</th>
<th>Specific type Ia antiarrhythmic agents (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>228±47</td>
<td>201±39‡</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>38±11</td>
<td>36±9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>228±150</td>
<td>212±247</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>116±26</td>
<td>108±24</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>28±8</td>
<td>24±5$</td>
</tr>
<tr>
<td>Apo B (RIA)</td>
<td>121±29</td>
<td>105±26†</td>
</tr>
<tr>
<td>Apo B (RID)</td>
<td>121±29</td>
<td>103±23‡</td>
</tr>
</tbody>
</table>

Figures are mean±SD serum lipid concentrations in mg/dl. Probability values relate to comparison between the indicated value and the value in the 1,491 patients on no type Ia antiarrhythmic agents.

HDL, high density lipoprotein; Apo, apoprotein; RIA, radioimmunoassay; RID, radial immunodiffusion assay.

\*p<0.01; ‡p<0.001; \$p<0.0001.

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**Table 4. Magnitude and Significance of Lipid Reductions by Type Ia Antiarrhythmic Agents on Closeout Blood Sample After Adjustment for Relevant Clinical Variables**

<table>
<thead>
<tr>
<th>Model</th>
<th>Lipid fraction</th>
<th>Reduction (%) by type Ia agents</th>
<th>95% Confidence limits</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cholesterol</td>
<td>8.6</td>
<td>4.0, 13.0</td>
<td>3.64</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>2</td>
<td>Triglycerides</td>
<td>22.3</td>
<td>11.4, 31.9</td>
<td>3.75</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>3</td>
<td>HDL C</td>
<td>-1.4$</td>
<td>-8.1, -4.9</td>
<td>0.42</td>
<td>0.67</td>
</tr>
<tr>
<td>4</td>
<td>Apo A-I</td>
<td>6.2</td>
<td>0.9, 11.2</td>
<td>2.29</td>
<td>0.02</td>
</tr>
<tr>
<td>5</td>
<td>Apo A-II</td>
<td>10.1</td>
<td>3.9, 15.9</td>
<td>3.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>Apo B (RIA)</td>
<td>12.7</td>
<td>7.1, 18.1</td>
<td>4.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>Apo B (RID)</td>
<td>14.8</td>
<td>9.4, 19.9</td>
<td>5.09</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stepwise multiple linear regression analyses were performed to adjust for relevant covariates. For each lipid fraction, a regression model was developed in which all dichotomized variables from Table 1 that had an influence \( (F^2\geq4.0) \) on the lipid fraction were included in the model. Type Ia antiarrhythmic agents were then stepped into the covariate model to determine the independent effect that type I agents had on the specified lipid fraction. See "Methods" for further details.

HDL C, high density lipoprotein cholesterol; Apo, apoprotein; RIA, radioimmunoassay; RID, radial immunodiffusion assay.

*Indicates elevation in HDL C.
We calculated the LDL C concentrations but did not report the findings in the “Results” section because all blood samples were not drawn in the fasting state and because of potential inaccuracies in the Friedewald assumptions. Despite these reservations, the calculated LDL C level was significantly ($p=0.003$) lower among those receiving type Ia antiarrhythmic agents (LDL C = 127 ± 47 mg/dl) than those not on these medications (LDL C = 145 ± 45 mg/dl) at closeout. This computed 12% lower LDL C level is internally consistent with the independently measured 13% lower apo B level.

The mechanism of the hypolipidemic effect of type Ia antiarrhythmic agents is uncertain. Apo B is the essential carrier protein for LDL. The lower apo B, triglyceride, and LDL C levels in patients using versus patients not using type Ia antiarrhythmic agents may be due to type Ia agent inhibition of hepatocyte apo B synthesis, reduction of triglyceride-rich very low density lipoprotein (VLDL) secretion by liver parenchymal cells (apo B-100) is an important component of VLDL, a major precursor of LDL, enhancement of LDL clearance by its receptor, or combinations of these mechanisms. It is known that VLDL secretion is inhibited by agents that alter hepatic transmembrane ionic gradients. Type Ia antiarrhythmic agents exert their cardiac electrophysiological effect primarily through reduction in sodium conductance across the myocellular membrane. These agents surely affect other cells in the body, as well. It is interesting to speculate that type Ia agents may inhibit hepatic VLDL secretion by pharmacologically altering the flux of ions across hepatocellular membranes. A sustained reduction in VLDL secretion could produce secondary reductions in the levels of apo B, triglycerides, and LDL C. It is interesting that the approved hypolipidemic agent probucol and type Ia antiarrhythmic agents have similar electrophysiological effects on heart muscle, i.e., QT prolongation. It may be that type Ia agents lower lipid levels by the same mechanism as probucol does, i.e., through similar effects on hepatocellular ionic currents.

Type Ia agents also lowered the concentration of apo A-II but had no apparent effect on HDL C concentration (Table 3). We do not have an adequate explanation for this disparity. However, it should be noted that HDL has considerable particle heterogeneity, and some subfractions of HDL exist without apo A-II.

A hypolipidemic effect was not observed in the 21 patients on type Ib antiarrhythmic agents at closeout (cholesterol: Ib no = 227 ± 47 mg/dl; Ib yes = 221 ± 49 mg/dl; $t=0.56, p=0.58$). The reason for the differential hypolipidemic effects between type Ia and type Ib agents is unclear, but it might relate to the different membrane-binding characteristics of these two groups of agents.

The current observations must be interpreted with some reservation in view of the known limitations associated with a retrospective study. A major concern is that patients selected for therapy with type Ia antiarrhythmic agents might have had lower cholesterol levels as a result of confounding factors such as diet, the severity of the cardiac disease, and the effects of concomitant medication. In an attempt to control for this, we carried out multiple linear regression analyses adjusting for a large number of measured clinical variables. Even after adjustment, the cholesterol, triglyceride, apo A-II, and apo B levels were significantly ($p<0.001$) lower in those using type Ia agents than in those not on these medications. In this observational study, the nonrandomness of how patients were selected for antiarrhythmic therapy may have introduced unsuspected bias. We cannot adjust for covariates that were not measured. For example, we did not have information on which patients were in a fasting state when the blood samples were drawn. It is possible that there was some imbalance in the distribution of fasting and nonfasting specimens between those using and not using type Ia agents that could bias the results. It should be noted that at closeout (30 months after infarction) the average weight of patients receiving type Ia antiarrhythmic agents was similar to those not on these agents—a finding that rules against a major disparity in diet, caloric intake, and cardiac cachexia between the two groups.

The blood samples were collected prospectively as part of the original study protocol. The lipid determinations were obtained at baseline, at 6 months, and 30 months after infarction, with consistently lower lipid levels in patients using type Ia agents at all three time periods. All specimens were analyzed in blinded fashion at a core lipid research laboratory that had no preexisting knowledge of any clinical or laboratory information during the conduct of the trial that could have in any way biased the results of the current analysis.

In summary, this study shows that patients on type Ia antiarrhythmic medications had significantly lower cholesterol, triglyceride, apo A-II, and apo B levels than patients not on these medications. These lipid-lowering effects were independent of age, sex, body weight, diabetes, smoking status, concomitant medications, and a variety of measured covariates relating to the severity of the coronary disease process. These data suggest that type Ia antiarrhythmic agents may represent a new class of hypolipidemic agents. The mechanism of these effects is undefined. Additional investigation will be necessary to further clarify the potential role of such pharmacological agents in cholesterol-lowering therapy.

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