Serum Cholesterol in Pentolinium-Treated Arterial Hypertension

By Harold H. Orvis, M.D., Irene G. Tamagna, M.D., and John M. Evans, M.D.

Serum lipids were serially determined in 11 patients receiving pentolinium therapy to evaluate changes secondary to blood pressure effects. Substantial reduction in total cholesterol was observed, which in some cases was independent of the hypotensive effect of the drug. Fat absorption, studied in 6 patients, revealed diminished postprandial lipemia in each as compared to placebo determinations. However, few patients showed appreciable weight change during a year of therapy. The evidence suggests that the serum lipid changes secondary to pentolinium administration are due to a qualitative change in fat absorption.

The association of arterial hypertension and an increased incidence of atherosclerosis has been previously noted.1-3 In studies of atherosclerotic patients assays of the serum lipids have been utilized as an indicator of the status of the disease. These measurements usually include serum cholesterol, phospholipid, and total lipid as well as the determination of the distribution of lipid in the lipoprotein complex by ultracentrifugation, zone electrophoresis, or chemical fractionation. According to Page and associates,4 patients with uncomplicated essential hypertension are free of plasma lipid abnormalities. On the other hand, Gofman and associates2 have pointed out that the great majority of patients with sustained hypertension have significantly increased serum levels of Sf 10-20 molecules. More marked derangement of the serum lipids might be predicted in a group of patients with long standing severe hypertension presumably with a greater incidence of atherosclerosis. Were such the case, it would be pertinent to determine if measurable changes in the serum lipids are demonstrable during treatment of the hypertension by the currently available hypotensive agents.

In this study, serum cholesterol was serially determined in a group of 11 middle-aged patients with severe hypertension during treatment with pentolinium and reserpine and during control periods.

The investigation was extended to include a study of fat absorption when it became evident that a substantial drop in serum cholesterol occurred in many of the patients during treatment. In hypertensive patients receiving hydralazine and hexamethonium (Hyphex), Schroeder5 had previously noted a tendency for the serum cholesterol to decrease.

It is the purpose of this paper to report the changes observed in serum lipids incident to pentolinium therapy. Evidence for altered lipid absorption during therapy was obtained in each of the 6 patients so studied. The possible relationship of this finding to the changes in serum lipids during therapy is discussed.

Material and Method

The patients for this investigation were selected from the Hypertension Clinic, The George Washington University Hospital. Criteria for admission to the study included age 55 or under, sustained diastolic pressure of 110 or greater, and unsuccessful prior treatment with reserpine alone or in combination with hydralazine.

Evaluation prior to therapy included a chest film, an electrocardiogram, the phenolsulfonphthalein test, and determination of the blood urea nitrogen. All of the patients had either electrocardiographic or roentgenologic evidence of left ventricular hypertrophy and 9 of the 11 patients had both. Impaired renal function was indicated.

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Dr. Orvis was a Fellow in Cardiovascular Disease, the Washington Heart Association 1955-1956.
PENTOLINIUM-TREATED ARTERIAL HYPERTENSION

TABLE 1.—Summary of Clinical and Laboratory Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pentolinium dosage (mg./day)</th>
<th>Control pressures</th>
<th>Treatment pressures</th>
<th>Serum cholesterol (mg. per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.P.</td>
<td>120</td>
<td>161/128</td>
<td>141/110</td>
<td>354</td>
</tr>
<tr>
<td>F.J.</td>
<td>400</td>
<td>197/122</td>
<td>204/137</td>
<td>272</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W.C.</td>
<td>100</td>
<td>268/148</td>
<td>272/135</td>
<td>274</td>
</tr>
<tr>
<td>C.G.</td>
<td>180</td>
<td>205/125</td>
<td>165/107</td>
<td>388</td>
</tr>
<tr>
<td>L.H.</td>
<td>200</td>
<td>199/113</td>
<td>161/102</td>
<td>292</td>
</tr>
<tr>
<td>G.W.</td>
<td>220</td>
<td>239/151</td>
<td>185/118</td>
<td>344</td>
</tr>
<tr>
<td>E.H.</td>
<td>240</td>
<td>248/107</td>
<td>178/108</td>
<td>292</td>
</tr>
<tr>
<td>M.W.</td>
<td>260</td>
<td>191/133</td>
<td>182/125</td>
<td>403</td>
</tr>
<tr>
<td>D.P.</td>
<td>360</td>
<td>205/127</td>
<td>180/114</td>
<td>282</td>
</tr>
<tr>
<td>M.P.</td>
<td>500</td>
<td>210/125</td>
<td>202/120</td>
<td>262</td>
</tr>
<tr>
<td>L.S.</td>
<td>830</td>
<td>196/133</td>
<td>185/128</td>
<td>221</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td>307.6</td>
</tr>
</tbody>
</table>

* Average of all blood pressures obtained in 3-month period prior to therapy.
† Average of all blood pressures (standing) during therapy.
‡ Average of 2 or more determinations.

in all patients by reduced 15-minute excretion of phenolsulfonphthalein, but in none was there elevation of the blood urea nitrogen.

Each of the patients received reserpine, in doses of 0.25 to 0.75 mg. daily, beginning at least 1 month before administration of pentolinium (Ansolysen).* Upon initiation of the latter medication, patients were seen weekly or biweekly until the desired pressure response was obtained. When symptoms of postural hypotension appeared, standing blood pressures were recorded in the clinic every half hour for 3 hours after the midday dose. This procedure was usually satisfactory in establishing the maximum hypotensive effect of the drug. Severe constipation occurred in 6 patients for which 15 mg. of prostigmine bromide or 5 mg. of pilocarpine nitrate was administered daily throughout the study. Patients' diets were not altered and none had been on a low-fat diet. Only 1 subject (E.H.) lost weight during the year of therapy and in this patient there was a complicating illness.

Congestive heart failure was severe (requiring diuretic therapy) in 1 patient (L.S.). Significant fluid retention was not encountered in the other patients, so that we were able to maintain a constant therapeutic regimen during the investigation.

One year after initiation of therapy 6 patients with the least cardiorenal involvement were given a lactose placebo for 6 weeks in place of the pentolinium. Reserpine, parasympathomimetic drugs, and all other medications were continued. Thus, it was thought that any alteration in serum lipids could be ascribed to withdrawal of the pentolinium.

Blood samples were obtained in the fasting state at the onset of the study and at intervals thereafter. During the placebo period, fasting specimens were obtained biweekly. Serum cholesterol determinations were done in the hospital laboratory by the method of Bloor.6 An oral fat-tolerance test was done just prior to and in the third week of the placebo period. The oral fat-tolerance method utilizes changes in serum turbidity after a standard fat meal as a measurement of post-prandial lipemia. The test was performed by the method of Waldow and associates.7

RESULTS

Pentolinium dosage and average control and treatment blood pressures are presented in table 1. It may be seen that a substantial reduction in average blood pressure was achieved in 6 of the 11 patients. Five of these 6 were in the group given the placebo and in each the blood pressure rose to approximate the pretreatment level.

The serum cholesterol for each individual in relation to the periods of study is given in table 1. It is apparent that the control cholesterol exceeded 250 mg. per cent in 10 of the 11 patients, and, that several patients exhibited a marked drop, the reduction being

*Kindly supplied by Wyeth Laboratories.
most evident in patients with the higher initial cholesterol levels. The average decrease in serum cholesterol was 57.8 mg. per cent, with a range of 24 to 211 mg. per cent. In one subject (D.P.) the cholesterol was higher and in another subject (W.C.) it was unchanged after therapy. It may be pertinent that the latter subject received a relatively small dose of pentolinium.

These findings were further borne out by the results obtained during placebo administration in 6 subjects. Here, it was observed that the cholesterol rose in 5 of the 6. The average level for this group increased from 254.8 to 295.8 mg. per cent. The range of the increase was from 30 to 79 mg. per cent with an average of 48.9 mg. per cent.

The oral fat-tolerance test revealed that the serum turbidity was higher 3 hours after fat ingestion during the placebo period in all 6 patients in comparison with the pentolinium period (table 2). The average optical density at 3 hours was 0.1613 on pentolinium as compared with 0.2405 on placebo. The range of the increase was from 0.0210 to 0.5360 with an average of 0.0792.

**Discussion**

Coincident with pentolinium administration there was a substantial drop in serum cholesterol in 9 of 11 patients. Schroeder has reported similar changes in serum cholesterol with the administration of hydralazine and hexamethonium. It is possible that the responsible common factor is the ganglonionic-blocking agent. The changes in cholesterol were seen in 3 of our patients in the absence of any lowering of blood pressure. This would seem to indicate that the drop in cholesterol is not due primarily to the decline in arterial blood pressure. Such an inference is further supported by our failure to demonstrate the hypocholesteremic effect in patients rendered hypotensive by reserpine alone or in a patient relieved of hypertension by surgery for coarctation of the aorta.

It is suggested that the observed lipid changes may be due in part to altered lipid absorption, since postprandial lipemia after fat tolerance testing was invariably lower during pentolinium therapy in the 6 patients so studied. The change in lipid absorption would seem to be in the direction of a qualitative alteration rather than reduced absorption, since only 1 of the 11 subjects lost weight during treatment. An additional factor may be the decrease in intestinal motility accompanying ganglonionic-blockade therapy. It has been repeatedly shown that the hydrolysis of triglycerides in the small intestine is incomplete during the usual absorptive period. Increased transit time of food in the small intestine might allow more complete fat digestion prior to absorption. While this could be the mechanism by which pentolinium lowers postprandial lipemia, altered intestinal motility does not readily explain the hypocholesteremic effect. Further study is indicated to clarify this point.

**Summary**

Fasting serum cholesterol was determined in 11 patients with severe arterial hypertension before and at intervals during treatment.
with pentolinium. In 9 of the 11 patients there was a decrease in cholesterol averaging 57.8 mg. per cent for the group, after therapy. These findings were further substantiated in 6 of these patients in that serum cholesterol levels rose during a period of placebo treatment. The lipid changes observed appeared to be independent of the hypotensive effect of pentolinium.

An oral fat-tolerance test revealed lower postprandial lipemia in 6 subjects during pentolinium as compared to placebo treatment. This finding was interpreted as evidence for altered lipid absorption or digestion incident to pentolinium therapy. It is suggested that the alteration is qualitative in nature, since body weight remained stable over a year of treatment in most of the patients.

**Addendum**

Since the completion of this paper, a similar fall of serum cholesterol has been observed in patients treated with mecamylamine or chlorisondamine; the decrease averaged 26 per cent of control values in a group of 10 patients. It was again noted that the greater effect was in patients with higher initial cholesterol values.

**Summario in interlingua**

Le cholesterol del sero eseva determinate in stato jejun in 11 patientes con sever hypertension arterial ante e periodicamente durante le tractamento con pentolinium. In 9 del 11 patientes, un reduction de cholesterol eseva notate post le tractamento, amontante a un valor medie pro le gruppo integre de 57,8 pro cento. Iste constatation eseva corroborate additionalmente in tanto que le nivellus del cholesterol sereal montava in 6 del mesme patientes durante un periodo de tractamento a medication fictitie. Le alterationes lipidic observate eseva apparentemente independente del effecto hypotensive de pentolinium.

Un test de tolerantia de grassia oral revelava plus basse nivellus postprandial de lipemia in 6 subjectos durante tractamento a pentolinium que durante tractamento a medication fictitie. Iste constatation eseva interpretate como prova de un alterate absorption o digestion de lipid in association con le therapia a pentolinium. Es exprimite le opinion que le alteration es de character qualitative, proque le pesos corporee remaneva stabile in le majoritate del patientes in le curso de un anno de therapia.

**References**

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