Reduction of Serum Cholesterol and Triglyceride Levels by the Combined Administration of Neomycin and Clofibrate

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SUMMARY
The combined oral administration of neomycin (2 g daily) and clofibrate (2 g daily) reduced significantly serum cholesterol levels in 15 of 16 patients. Most of these patients had type II hypercholesterolemia and clinical evidence of arteriosclerosis. The combined regimen of the two drugs was more effective in reducing cholesterol levels in about one third of the patients than administration of either one of these drugs alone. The average decrease of serum cholesterol in these patients while on the combined regimen was 38% from the control values. Control serum triglyceride levels were normal in most patients, thus the effect of the drugs on triglycerides was moderate. No noteworthy side effects were encountered. It is felt that a trial of treatment by the combined administration of neomycin and clofibrate is justified in patients with type II hypercholesterolemia and arteriosclerosis who are resistant to other forms of treatment or to treatment by a single drug.

Additional Indexing Words:
Hypercholesterolemia Serum lipids Arteriosclerosis

The oral administration of small doses of neomycin sulfate was reported to reduce the concentration of serum cholesterol level in man.1-3 The oral administration of clofibrate has been shown to be very effective in reducing serum triglyceride levels4-8 and moderately effective in reducing serum cholesterol levels5-8 in patients. It is very helpful in the treatment of carbohydrate-induced hyperlipoproteinemias in patients with elevated triglyceride levels, namely in Fredrickson's type IV, and in part types III and V.8 One of the most difficult problems in this field is the management of patients with type II hypercholesterolemia. The multiplicity of the proposed treatments for this condition reflects the magnitude of the difficulties.10 Most of these patients develop clinical manifestations of atherosclerosis early in life, and the long-term prognosis is poor. In the present study the effect of the individual and of the combined administration of neomycin and clofibrate on serum cholesterol and triglyceride levels was investigated in a group of patients, most of whom had type II hypercholesterolemia and clinical evidence of atherosclerosis.

Methods
Sixteen patients, 10 males and six females, were studied. The age range was from 17 to 62 years. Clinical diagnoses are included in table 1. All patients were ambulatory; their respective diseases were under good control, and 11 of the 16 were working at their regular jobs throughout the study. Medications, other than experimental, were kept constant, and other substances known to influence serum lipid levels were not given.
Individual and Combined Effect of Neomycin and Clofibrate on Serum Cholesterol and Triglyceride Levels in 16 Patients (Average ± sd Values and Percentage Decrease)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Type&lt;sup&gt;β&lt;/sup&gt;</th>
<th>Cholesterol Control Average ± sd†</th>
<th>Triglycerides Control Average ± sd†</th>
<th>Cholesterol Neomycin Average ± sd†</th>
<th>Triglycerides Neomycin Average ± sd†</th>
<th>% Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA*</td>
<td>47</td>
<td>F</td>
<td>Coronary artery disease; xanthomatosis</td>
<td>II</td>
<td>536 ± 47†</td>
<td>133 ± 25†</td>
<td>393 ± 18†</td>
<td>143 ± 11†</td>
<td>27%↓</td>
</tr>
<tr>
<td>BA*</td>
<td>18</td>
<td>F</td>
<td>Xanthomatosis</td>
<td>II</td>
<td>418 ± 27</td>
<td>77 ± 20</td>
<td>332 ± 13</td>
<td>75 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>MR*</td>
<td>54</td>
<td>F</td>
<td>Peripheral vascular insufficiency</td>
<td>II</td>
<td>334 ± 22</td>
<td>110 ± 20</td>
<td>226 ± 13</td>
<td>106 ± 15</td>
<td>21%↓</td>
</tr>
<tr>
<td>JS*</td>
<td>38</td>
<td>M</td>
<td>Coronary artery disease</td>
<td>II</td>
<td>427 ± 13</td>
<td>91 ± 14</td>
<td>390 ± 16</td>
<td>72 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>HF</td>
<td>52</td>
<td>M</td>
<td>Coronary artery disease; cerebral vascular accident</td>
<td>II</td>
<td>325 ± 15</td>
<td>139 ± 18</td>
<td>214 ± 11</td>
<td>111 ± 21</td>
<td>9%† NS</td>
</tr>
<tr>
<td>JC</td>
<td>45</td>
<td>M</td>
<td>Cerebral vascular accident</td>
<td>II</td>
<td>324 ± 19</td>
<td>146 ± 25</td>
<td>247 ± 12</td>
<td>145 ± 21</td>
<td>24%† NS</td>
</tr>
<tr>
<td>RK</td>
<td>43</td>
<td>M</td>
<td>Coronary artery disease</td>
<td>II</td>
<td>377 ± 17</td>
<td>125 ± 16</td>
<td>272 ± 26</td>
<td>124 ± 14</td>
<td>28%† NS</td>
</tr>
<tr>
<td>AK</td>
<td>17</td>
<td>M</td>
<td>Coronary artery disease; xanthomatosis</td>
<td>II</td>
<td>716 ± 43</td>
<td>89 ± 21</td>
<td>726 ± 62</td>
<td>88 ± 17</td>
<td>NS NS</td>
</tr>
<tr>
<td>RD</td>
<td>53</td>
<td>F</td>
<td>Coronary artery disease</td>
<td>II</td>
<td>444 ± 18</td>
<td>101 ± 19</td>
<td>326 ± 33</td>
<td>109 ± 32</td>
<td>27% NS</td>
</tr>
<tr>
<td>TB</td>
<td>43</td>
<td>M</td>
<td>Coronary artery disease; xanthomatosis</td>
<td>II</td>
<td>533 ± 49</td>
<td>125 ± 14</td>
<td>460 ± 29</td>
<td>125 ± 12</td>
<td>14% NS</td>
</tr>
<tr>
<td>IL</td>
<td>43</td>
<td>M</td>
<td>Coronary artery disease</td>
<td>II</td>
<td>368 ± 33</td>
<td>127 ± 9</td>
<td>271 ± 33</td>
<td>126 ± 12</td>
<td>26% NS</td>
</tr>
<tr>
<td>AW</td>
<td>43</td>
<td>M</td>
<td>Coronary artery disease; xanthomatosis</td>
<td>III</td>
<td>612 ± 47</td>
<td>274 ± 34</td>
<td>498 ± 36</td>
<td>205 ± 33</td>
<td>19% NS</td>
</tr>
<tr>
<td>SS</td>
<td>62</td>
<td>M</td>
<td>Coronary artery disease; diabetes mellitus</td>
<td>IV</td>
<td>235 ± 19</td>
<td>227 ± 63</td>
<td>165 ± 11</td>
<td>340 ± 78</td>
<td>30% NS</td>
</tr>
<tr>
<td>AF</td>
<td>50</td>
<td>F</td>
<td>No clinical disease</td>
<td>—</td>
<td>258 ± 18</td>
<td>79 ± 14</td>
<td>215 ± 13</td>
<td>60 ± 12</td>
<td>17% NS</td>
</tr>
<tr>
<td>DV</td>
<td>45</td>
<td>M</td>
<td>Coronary artery disease</td>
<td>—</td>
<td>268 ± 18</td>
<td>114 ± 43</td>
<td>174 ± 16</td>
<td>115 ± 24</td>
<td>34% NS</td>
</tr>
<tr>
<td>EG</td>
<td>59</td>
<td>F</td>
<td>No clinical disease</td>
<td>—</td>
<td>240 ± 16</td>
<td>90 ± 17</td>
<td>209 ± 18</td>
<td>83 ± 16</td>
<td>13% NS</td>
</tr>
</tbody>
</table>

Average fall in responders (%):

Number of patients responding: 15 4

* Patients with type II hypercholesterolemia in whom the combined regimen resulted in further decrease in serum cholesterol concentrations.
† Average ± standard deviation in mg%; % fall is % of control value.
‡ P < 0.001.
§ P < 0.01.
** P < 0.05.

The diet was uncontrolled, but the patients were instructed to adhere to their customary diets. Patients with type II or type III hyperlipoproteinemia were on a low fat, low cholesterol diet and the patient with type IV hyperlipoproteinemia was on a low carbohydrate, diabetic diet. The patients were seen weekly; they were weighed, and physical examinations, blood counts, tests of urine, blood urea nitrogen, blood sugar, serum bilirubin, serum transaminases, cephalin flocculation, thymol turbidity, and stool cultures for pathogens were carried out periodically. Patients with evidence of kidney or liver disease were not accepted into the group.
Weekly blood specimens were obtained after a 12-hour overnight fast. Total serum cholesterol concentrations were determined by the method of Abell and associates. Serum triglyceride levels were measured by the method of Van Handel and Zilversmit. Serum lipoprotein electrophoresis was carried out by the method of Fredrickson and Lees. Control serum lipid levels, prior to the administration of the drugs, were observed for a period of 8 to 30 weeks (period I). The average length of the control period was 20.1 weeks. Of the 16 patients, 11 were classified as having type II hypercholesterolemia, one as type III, and one as type IV. Three patients had no classifiable abnormality of serum lipids (table 1). Neomycin sulfate was given orally at the daily dose level of 2 g for periods varying from 6 to 43 weeks (period II). The average length was 14.9 weeks. The combined administration of neomycin (2 g daily) and clofibrate (2 g daily) was maintained for 6 to 18 weeks (average, 10.3 weeks) (period III). Finally clofibrate (2 g daily) was given alone (period IV) for 6 to 17 weeks (average, 10.3 weeks). Usually, the experimental periods followed each other in the order described above. In some patients, however, the order of the experi-
Results

The results of the study are summarized in table 1. During the administration of neomycin (period II), total serum cholesterol levels were reduced in 15 of the 16 subjects studied. The average fall of cholesterol was 24% as compared to control values. Serum triglyceride levels were decreased significantly in four of the 16 patients. During the combined administration of neomycin and clofibrate (period III), serum cholesterol levels were reduced in 15 of 16 patients. The average fall from control values was 29%. Serum triglyceride levels fell in six of 16 patients during period III, by an average of 25% from control values. During the administration of clofibrate alone (period IV), serum cholesterol levels decreased from control levels in 12 of the 16 patients by an average of 17%, and the level of serum triglycerides was reduced in six by 26%.

Figure 1 shows the effect of the drugs in patient B.A.

The fall in serum cholesterol due to the administration of neomycin was augmented by the addition of clofibrate to the regimen in five of the 16 patients. After the addition of clofibrate to the administration of neomycin, serum cholesterol levels decreased by an additional 18% in those five subjects, so that the total fall was 29% as compared to control periods. Serum triglyceride levels were further decreased in four of 16 patients by an average of 24% during the combined administration of the drugs. When the data during period III (neomycin and clofibrate) were compared to period IV (clofibrate), serum cholesterol levels increased by an average of 22% in 14 of 16 patients from the lower plateau, after the administration of neomycin was discontinued. Serum triglyceride levels increased in only three of 16 subjects when periods III and IV were compared.

No significant side effects were noted during the administration of the drugs. Six of the 16 patients developed mild diarrhea and abdominal cramps during the first week of neomycin administration. The administration of the drug was continued, and the symptoms subsided by the end of the second week in each patient. The weight of the patients remained within 2 lb variation, and physical examinations and the monitoring laboratory tests remained unchanged during the study.

Discussion

The reduction of serum cholesterol concentrations during the administration of neomycin in the present study is comparable with results previously reported from this and from other laboratories. It should be pointed out that the drug is highly effective in patients with type II hypercholesterolemia, as the present results indicate. Marked reduction
of serum triglycerides was reported during the administration of large daily doses of neomycin (12 g/day) from one laboratory.13 However, daily oral doses of 2 g by another group of investigators resulted in inconsistent variations of serum glycerides.14 In the present study serum triglyceride levels were reduced in 25% of the 16 patients studied during the administration of neomycin. It must be emphasized that 14 of our 16 patients had normal triglyceride levels (below 150 mg%) during control periods. Of the two subjects with high initial levels, serum triglycerides were reduced in one.

When clofibrate was added to the administration of neomycin, the level of total serum cholesterol was further reduced in five of the 16 patients. Four of these subjects had type II hypercholesterolemia, and the fall of serum cholesterol levels during the combined administration of the drugs was rather impressive. Control levels of cholesterol were reduced from 334 to 197, 427 to 306, 536 to 299 and 418 to 256 mg%, respectively, in the four patients. In these patients the reduction in serum cholesterol levels was significantly enhanced by the combined therapy, as compared to the individual effect of either of the two drugs (table 1). Since the total number of patients with type II disease was 11 in this study, the data suggest that a combined regimen of neomycin and clofibrate was more effective in about one third of these patients than the administration of either of these drugs alone. The percentage seems large enough to warrant a trial in type II hypercholesterolemia in an effort to lower serum cholesterol levels, especially in patients who are resistant or respond poorly to other forms of treatment or to treatment by a single drug. It should be pointed out though that the number of patients in the present study was comparatively small and continued studies will be necessary to further confirm this point.

The effect of the administration of clofibrate on serum cholesterol and triglyceride levels in this study is in general agreement with data published in the literature.4-8 It should be noted that when the administration of neomycin was discontinued and clofibrate was given alone, serum cholesterol levels increased significantly in 14 of the 16 patients studied.

The exact mechanisms by which neomycin or clofibrate reduces serum lipid levels are unknown. One of the working theories in this laboratory is that neomycin reduces serum cholesterol levels through its action upon the intestinal bacterial flora. This theory was discussed in detail in previous publications.1-3 Discussion on the possible lipid-lowering mechanisms of clofibrate was included in several papers published.4-8

The theoretical justification of lowering serum cholesterol is the assumption that the amount of cholesterol in the body will be reduced, including cholesterol deposited in atheromas, although specific information on this point is scarce. It has been shown that reduction of serum cholesterol by neomycin coincides with significant reduction in the size of cholesterol pools in the body.15 There are no similar studies for clofibrate at present.

No major side effects were encountered during the administration of the drugs either singly or in combination. The occurrence of toxicity from parenterally administrated neomycin has been discussed in many reports. However, the daily oral administration of small doses of the drug was well tolerated in our patients and in those of other investigators when the patients were free of renal insufficiency.1-3,15,14 Previous studies from this laboratory showed that the uninterrupted daily oral administration of 0.5 to 2 g of neomycin for as long as 3 years, for cholesterol-lowering purposes was easily feasible and well tolerated by the patients without noteworthy side effects.9 Surprisingly few side effects have been reported from administration of clofibrate. In recent reports the possibility of musculoskeletal abnormalities was described during administration of clofibrate.16 Properly chosen and monitored patients can receive these drugs to lower serum lipid levels with no serious side effects. It is thus felt that in patients with type II hypercholesterolemia and clinical evidence of
arteriosclerosis a trial of combined administration of neomycin and clofibrate is warranted.

References

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