Hypocholesteremic Effect of Benzmalacene

By Irvine H. Page, M.D., and Roland E. Schneckloth, M.D.

A new substance, Benzmalacene, was tested to determine whether it had hypocholesteremic effect in normotensive, hypertensive and hypercholesteremic patients. It proved effective. But after 4 months' treatment liver function began to deteriorate. It is strongly urged that drugs which interfere with cholesterol synthesis in the body be studied most carefully for long periods before widespread clinical trials to prevent atherosclerosis are attempted.

One approach to the problem of prevention of atherosclerosis is the prevention of hyperlipemia and, more specifically, hypercholesteremia. Diet, nicotinic acid, and \( \beta \)-sitosterol have been most commonly used for this purpose, and with some success, in reducing hyperlipemia. Recently, attempts have been made to suppress the synthesis of cholesterol in the hope that hypercholesteremia would be abolished and yet leave hormonal synthesizes and other metabolic functions of steroids undisturbed. Feeding of delta-4-cholestenone suppressed hepatic cholesterol synthesis and reduced the serum cholesterol level, but caused marked adrenal hypertrophy as well.\(^1\) A number of other agents have been tried with limited success and these have been well reviewed by Kritchevsky\(^2\) and by Curran and Azarnoff.\(^3\)

It has been shown that probenecid inhibits acetate activation of coenzyme A as the latter is involved in glycine conjugation with p-aminobenzoic acid.\(^4\) Recently a compound has been synthesized that is 10 times more active than probenecid in its ability to inhibit renal tubular secretion of penicillin. Correspondingly, it is more active in inhibiting incorporation of acetate and mevalonic acid into the synthesis of cholesterol in vitro.\(^5\)

This substance, Benzmalacene,\(^*\) is a derivative of the monamide of maleic acid, having an aralkyl group on the nitrogen. Its structure (fig. 1) is quite different from probenecid and carinamide though its actions seem similar. It is believed to be well absorbed by the gastrointestinal tract in the form of the sodium salt.

The work of Beyer and his associates\(^1\) made it seem reasonable that Benzmalacene might be useful in reducing hypercholesteremia in man. Plasma cholesterol levels in dogs were sharply reduced by daily doses of 50 to 300 mg./Kg. and the production of hypercholesteremia in rats and chickens was inhibited.\(^5\)

On the basis of these results we have studied Benzmalacene to determine its effects on the serum cholesterol levels in 6 women and 13 men. Of the 19 patients, 10 had severe essential hypertension and 2 presented the syndrome of malignant hypertension: 7 other patients exhibited hypercholesteremia or hyperlipemia. All hypertensive patients were on free diets at home except for moderate salt restriction. Five of the 7 patients with abnormal serum lipid patterns had followed a carefully controlled diet, containing 50 to 80 Gm. of fat as vegetable oil, for periods ranging from 6 to 18 months; the remaining 2 patients (cases 16 and 17) had eaten freely chosen foods.

The dose of Benzmalacene was 250 mg. given by mouth 2 to 4 times daily after meals; the average daily dose was 750 mg.

Results

Administration of Benzmalacene to Hypertensive Patients. All but 2 (cases 8 and 12) of the 12 hypertensive patients showed a fall

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*\([N-(1-methyl-2,3-di-p-chlorophenylpropyl-maleamic acid)], kindly supplied by Dr. Karl Beyer and Dr. E. W. J. De Maar of Merck Sharp and Dohme, West Point, Pa.
in serum cholesterol levels when given Benzomalacene for 1 month (table 1). Three patients (cases 10, 11, and 12) could not tolerate the drug because of gastrointestinal side effects and it was discontinued after 1 month. Serum cholesterol was maintained lower than control levels in all but 2 of the remaining 9 patients in whom administration of the drug was continued for 2 to 4 months.

**Administration of Benzomalacene to Patients with Elevated Serum Cholesterol Levels.** All of the 7 patients with abnormally elevated serum lipid levels had had stable serum cholesterol levels for several months prior to treatment. One patient (case 14) exhibited a profound fall in serum cholesterol when given Benzomalacene; this decrease persisted throughout the treatment period of 4 months (table 2). In addition, a marked rise in the triglyceride fraction, a fall in the total cholesterol to phospholipid ratio, and rise in ratio of free cholesterol to total cholesterol were noted (table 3). Another patient (case 15) had no change in serum cholesterol for 3 months; after 4 months of therapy a sharp drop in serum cholesterol was noted for the first time. Associated with the decrease in serum cholesterol of over 100 mg. were changes in other lipid fractions similar to those noted in case 14.

In 2 patients (cases 13 and 17) serum cholesterol levels showed little change. The remaining 3 patients (cases 16, 18, and 19) continued to maintain serum cholesterol levels lower than control values while taking the drug for 2 to 4 months.

**Side Effects from Benzomalacene.** Of 19 patients, 3 were uncomfortable from mild
TABLE 3.—Changes in Lipid Fractions after Treatment with Benzmalacene for Four Months

<table>
<thead>
<tr>
<th>Case 14</th>
<th>Patient</th>
<th>Case 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>After treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Total cholesterol (mg. %)</td>
<td>560</td>
<td>277</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>228</td>
<td>714</td>
</tr>
<tr>
<td>Total cholesterol/phospholipid</td>
<td>1.34</td>
<td>0.69</td>
</tr>
<tr>
<td>Free cholesterol/total cholesterol</td>
<td>0.25</td>
<td>0.42</td>
</tr>
</tbody>
</table>

TABLE 4.—Liver Function Following Administration of Benzmalacene

<table>
<thead>
<tr>
<th>Patient (case no.)</th>
<th>Duration of treatment (months)</th>
<th>Serum alkaline phosphatase (Bodansky units)</th>
<th>Bromsulfalein (% dye retained 45 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2</td>
<td>1.4</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>1.8</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1.9</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1.8</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>1.1</td>
<td>7</td>
</tr>
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<td>2</td>
<td>4</td>
<td>1.6</td>
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<td>4</td>
<td>3.7</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2.2</td>
<td>14</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>2.3</td>
<td>20</td>
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<tr>
<td>15</td>
<td>4</td>
<td>1.9</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>1.7</td>
<td>2</td>
</tr>
</tbody>
</table>

nausea, epigastric discomfort, and diarrhea; symptoms were often relieved by reduction of the daily dose of Benzmalacene from 1.0 Gm. to 0.5 Gm. Five patients were so disabled by gastrointestinal symptoms that administration of the drug was discontinued after 1 to 2 months. Symptoms when present usually persisted throughout the treatment period. Five of the hypertensive patients had weight loss of 11 to 15 lbs. during therapy; all of the 7 hypercholesteremic patients maintained a constant weight while taking the drug.

Liver function was measured at the end of the treatment period (2 to 4 months) in 12 patients (table 4). Serum alkaline phosphatase was within normal limits in all. Abnormal retention of bromsulfalein dye (more than 5 per cent after 45 minutes) was noted in 8 of 12 patients and was usually greater in those patients with the longer treatment period.

**DISCUSSION**

The problem of the desirability of lowering blood cholesterol by preventing its synthesis is a highly complex one. The multiplicity of derivatives of cholesterol necessary for the proper functioning of the body is now appreciated. Whether the level of cholesterol itself can be lowered without concurrently seriously disturbing the functional levels of its derivatives remains to be determined.

Clearly Benzmalacene can lower blood cholesterol levels for long periods without marked changes in body weight but liver function as measured by dye retention slowly but progressively becomes disturbed. While slow in onset, the liver dysfunction could become serious, therefore after a maximum of 4 months the drug was discontinued. We were unable in this period of time to detect other cognate changes in the patients.

Gastric burning, pain, nausea, and diarrhea occurred in some patients requiring discontinuance of the drug; in others, these symptoms were hardly noticeable.

In 2 patients the serum lipid pattern was studied by Dr. Helen Brown. It was shown that approximately 5 months after beginning the drug the total cholesterol had fallen significantly but concurrently the triglycerides had risen, along with the ratio of free to total cholesterol. But the ratio of total cholesterol to phosphatide fell sharply. These changes were profound. Without further studies we can no more than guess their significance. For our current purpose, the change underscores the capacity of drugs such as...
Benzmalacene to alter the lipid economy of the body for better or for worse.

We believe that drugs such as this one should be carefully studied in animals for long periods and in a few select patients before they are used in the hopes of preventing atherosclerosis.

Summary

Benzmalacene [N-(1-methyl-2,3-di-p-chlorophenylpropyl-maleamic acid)] effectively lowers blood cholesterol levels in most hypertensive patients but with some weight loss. Cholesterol was lowered in some hypercholesteremic patients but not in all and this occurred without weight loss. In 2 hypercholesteremic patients a sharp rise in triglycerides occurred while the cholesterol : phospholipid ratio fell and the free : total cholesterol ratio rose. Liver function as measured by bromsulfalein after 4 months' treatment had deteriorated in 8 of the 12 patients studied. Nausea, epigastric discomfort, and diarrhea were on occasion sufficiently discomfiting to require discontinuing the drug. Drugs that interfere with cholesterol synthesis should be studied with great care for long periods before their widespread use in an attempt to prevent atherosclerosis.

Summario in Interlingua

Benzmalacena reduce efficacemente le nivellos sanguinees de cholesterol in le majoritate del patientes hypertensive, sed illo effec-
tua un leve perdita de peso. Le nivellos de cholesterol eseva reduceite in alieun patientes con hypercholesterolemia, sed non in omnes, e isto occurreva sin perdita de peso. In 2 patientes con hypercholesterolemia um marcate augmento de trigyleeridos occurreva, durante que le proportion de cholesterol a phospholipido descendeva e le proportion de cholesterol libre a cholesterol total montava. Le function hepatic, mesurate per bromosulfaleina post 4 menses de tractamento, se monstrava deteriorante in 8 ex 12 patientes studiate. Nausea, disconforto epigastric, e diarrhea eseva a vices suffisemente discomfite pro require le interruption del delipar retro. Drogas que disrumpe le synthese de cholesterol deberea esser studiate caulis-simemente e durante prolongate periodos de tempore ante que illos es usate extensamente como agentes in le prevention de atherosclerosis.

References

5. —: Personal communication.
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