Dextro-Thyroxine as a Cholesterol-Lowering Agent in Patients with Angina Pectoris

By Roger W. Robinson, M.D., and Raoul J. LeBeau

A THYROID analog has been sought with a potent cholesterol-lowering action and minimal metabolic effects that could be given to patients with coronary heart disease and angina pectoris. Di, tri, and tetraiodothyronine as well as numerous derivatives of these compounds have been studied.1-9 These substances lowered the level of the beta and other low-density lipoproteins but no dissociation of this effect from the concurrent increased metabolism was noted. Of all compounds tested, the p-isomers of thyroxine appeared to exert a disproportionate effect between cholesterol and general metabolic effects.3,6,7,10 This observation led to clinical trials with this agent. Starr and associates11 reported that 16 mg per day of sodium p-thyroxine caused no change in the basal metabolic rate. The serum cholesterol levels were significantly reduced in a group of patients with diabetes mellitus and idiopathic hypercholesteremia. In only one patient was angina increased. Oliver and Boyd12,13 noted good effects on lipids with p-thyroxine, but cautioned about the use of higher doses in patients with angina pectoris. Engleberg,14 Soloff and Winters,15 and Tuna16 observed aggravation of heart disease in patients with coronary heart disease while receiving this drug. Jones and Cohen17 recommended that p-thyroxine be used only in patients free from cardiac symptoms.

In order to observe in as objective a way as possible whether there was a clinical dissociation between the serum lipid and cardiac effects of p-thyroxine, a double-blind study was carried out with patients known to have elevated serum cholesterol levels and angina pectoris.

Materials and Methods

Sixteen ambulatory patients with moderate to severe angina pectoris were selected for study. Patients who had one to five attacks of angina daily, requiring nitroglycerin for relief, were classified as moderate and those with six or more attacks daily as severe. All patients had had a stable pattern of factors that precipitated anginal attacks for at least several months to as long as 8 years. Factors that precipitated attacks were variable in different patients but quite uniform in the individual patient. Unavoidable factors, such as cold weather, sudden emotional tension, increase in physical activity above the usual, were considered and recorded when they applied in an individual case. Patients kept a record of the number of attacks, what initiated the distress, and the number of nitroglycerin pills taken each day. The number of attacks and nitroglycerin tablets were averaged separately for each month. The interrogations were as objective as possible. A decided change in frequency and severity of attacks with distinctly less precipitating cause had to be observed before an aggravation of angina pectoris was recorded. The use of nitroglycerin tablets and frequency of attacks were increased on an average by more than four daily to be classified as aggravation. Attacks that occurred for the first time at rest and especially during sleep were considered to be related to the trial drug. Each patient had a positive Master's double two-step electrocardiogram test,18 which was terminated after 3 minutes or with the onset of angina pectoris. In the control period the test was stopped in five patients because of angina, the remainder were able to complete the 3-minute test. Most had a serum cholesterol above 250 mg per cent. Fourteen patients were clinically euthyroid, confirmed by protein-bound iodine levels and measurement of the Achilles reflex contraction time.19 Two had myxedema.

At least two serum lipid determinations were obtained before treatment on all subjects in the postabsorptive state. These included serum total cholesterol, phospholipids, and ultracentrifugally separated α- and β-lipoprotein cholesterol. After a 3-month control period, the patients were submitted to a double-blind evaluation of 4 mg of p-thyroxine as a lipid-shifting agent, and the effect on the frequency and severity of anginal attacks was recorded. Serum lipids, protein-bound iodine, Achilles reflex, and two-step electrocar-
Diagram tests were repeated once a month. Later a combination of a minimal dose of two cholesterol-lowering agents, 2 mg. of D-thyroxine and 0.25 mg. of stilbestrol daily by mouth, was evaluated with the double-blind technique to see if small doses of both these hormones would lower cholesterol without the undesirable effects of either. Each test period was for 3 months and was preceded and followed by a 3-month placebo period. Patients who received active material or placebo were equally divided between the two in all four seasons of the year to minimize the effect of temperature changes on the incidence of angina. In the third test, 10 patients, who included the seven that reported an increase in frequency of angina pectoris on D-thyroxine, were observed during a single-blind period (the physician but not the patient was aware of a change in medication) on 4 mg. of D-thyroxine with increasing doses of guanethidine to tolerance in a range of 10 to 40 mg. daily in divided doses. The average dose taken was 10 mg. three times daily. It was continued for 5 months, as it required about 2 months to determine the optimal dosage of guanethidine in each patient. The final observation was a single-blind study in the same 10 patients with a combination of 4 mg. of D-thyroxine and 0.25 mg. of reserpine daily. The studies with guanethidine and reserpine were undertaken to minimize if possible the increase in frequency of angina pectoris observed with D-thyroxine in the first and second trial periods.

**Results**

**Angina Pectoris**

Seven of the 16 patients while receiving 4 mg. of D-thyroxine daily had a definite increase in frequency and severity of angina pectoris. This was noticeable within 2 to 4 weeks after starting the drug. In two of the patients the attacks were so severe, ranging between 12 and 20 daily, occurring both day and night, that the drug had to be omitted for 2 weeks and it was then restarted at 2 mg. daily. Two patients experienced a moderate increase, and, in three, it was slight. While nine patients did not notice any change in the pattern of attacks of angina on 4 mg. of D-thyroxine daily, seven definitely did. It should be emphasized that all of the patients were ambulatory but had moderate to severe angina before treatment was started.

When a minimal dose of D-thyroxine, 2 mg., was combined with a small dose of 0.25 mg. of stilbestrol daily, complications due to both drugs were observed. Three patients reported a definite increase in frequency and severity of attacks of angina pectoris while receiving 2 mg. of D-thyroxine daily. However, the attacks were not so frequent or severe as with the 4-mg. dose. Surprisingly, three men noticed breast tenderness and one developed a small nodule under one nipple due to the stilbestrol. These changes, due to the estrogen, occurred between the eighth and twelfth weeks of treatment.

In the placebo periods the frequency of attacks of angina returned to pretreatment levels. During both placebo periods, however, one patient of the 16 noticed slight increase in frequency and severity of attacks of angina. In one, it was thought to be due to increased work in cold, winter weather. The other was associated with increased activity during work in the garden in the summer.

Guanethidine, in doses of 10 mg. to as much as 40 mg. daily, in divided doses failed to control the increased frequency of attacks of angina in patients receiving 4 mg. of D-thyroxine. Six of 10 patients still noticed more angina pectoris than in the placebo periods. The guanethidine was given in increasing dosage until weakness or hypotension was noted. Then, the dose was decreased slightly until the patient was free from adverse symptoms. The two patients who had myxedema had the return of clinical symptoms and signs of myxedema while receiving 4 mg. of D-thyroxine plus guanethidine.

Reserpine in a dose of 0.25 mg. daily did not suppress the augmented number of bouts of angina in seven of 10 patients who received it in combination with 4 mg. of D-thyroxine daily.

**Serum Lipids**

On 4 mg. of D-thyroxine daily the mean serum total cholesterol decreased from a control level of 261 to 208 mg. after 3 months of therapy (table 1). This change was statistically significant ($p = <.005$). Phospholipids also decreased from a mean of 235 to 179 mg. ($p = <.001$) so that the resulting C/P ratio was unchanged (fig. 1). The alpha cholesterol declined from 54 mg. to 45.6 mg.
### Table 1

**Summary of the Lipid Effects of D-Thyroxine Alone and in Combination with Stilbestrol**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>D-Thyroxine (4 mg)</th>
<th>Placebo</th>
<th>D-Thyroxine (2 mg)</th>
<th>Stilbestrol (0.25 mg)</th>
<th>Placebo</th>
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<tr>
<td>Months</td>
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<td>1</td>
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<td>3</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cholesterol</td>
<td>261</td>
<td>213</td>
<td>213</td>
<td>208</td>
<td>252</td>
<td>243</td>
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<td>S.E.M.</td>
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<td>7.2</td>
<td>6.8</td>
<td>6.9</td>
<td>12.8</td>
<td>12.3</td>
</tr>
<tr>
<td>N</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>t</td>
<td>3.1</td>
<td>3.1</td>
<td>3.4</td>
<td>0.47</td>
<td>0.97</td>
<td>0.72</td>
</tr>
<tr>
<td>p &lt;</td>
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<td>.005</td>
<td>.005</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Phospholipid</td>
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<td>191</td>
<td>189</td>
<td>179</td>
<td>215</td>
<td>208</td>
</tr>
<tr>
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<td>4.1</td>
<td>5.1</td>
<td>11.8</td>
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<tr>
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<td>32</td>
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<td>32</td>
<td>32</td>
</tr>
<tr>
<td>t</td>
<td>3.7</td>
<td>4.0</td>
<td>4.7</td>
<td>1.25</td>
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<td>1.77</td>
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<tr>
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<td>.001</td>
<td>.001</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>β-Cholesterol</td>
<td>209</td>
<td>164</td>
<td>166</td>
<td>161</td>
<td>201</td>
<td>192</td>
</tr>
<tr>
<td>S.E.M.</td>
<td>12.5</td>
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<td>6.7</td>
<td>12.3</td>
<td>10.9</td>
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<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
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<td>0.91</td>
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<tr>
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<td>.005</td>
<td>.005</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>α-Cholesterol</td>
<td>54.0</td>
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<td>45.6</td>
<td>45.6</td>
<td>50.4</td>
<td>49.7</td>
</tr>
<tr>
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<td>2.9</td>
<td>2.8</td>
<td>2.9</td>
<td>2.9</td>
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<td>N</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>t</td>
<td>2.07</td>
<td>1.75</td>
<td>1.78</td>
<td>0.75</td>
<td>0.89</td>
<td>0.71</td>
</tr>
<tr>
<td>p &lt;</td>
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<td>.05</td>
<td>.05</td>
<td>0.4</td>
<td>0.2</td>
<td>0.2</td>
</tr>
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</table>
(p < .05) but the chief drop was in beta-lipoprotein from 209 to 161 mg. (p < .005). The \( \beta/\alpha \) ratio decreased from 4.1 to 3.7. After placebo therapy was started, there was a prompt recovery in all lipid levels, approaching the control values. Similar lipid changes were observed during three separate treatment periods on this dose of 4 mg. of \( \delta \)-thyroxine daily.

The second treatment schedule with 2 mg. of \( \delta \)-thyroxine plus 0.25 mg. of stilbestrol resulted in slight lowering of the cholesterol values. The main change was seen in the estrogen effect of this small dose of stilbestrol, increasing the phospholipid and \( \alpha \)-lipoprotein with resultant lowering of C/P and \( \beta/\alpha \) ratios (fig. 1)\( (p < .005) \). Again in the placebo period, the lipids reverted to pretreatment levels.

**Protein-Bound Iodine and Achilles Reflex Tests**

Serum protein-bound iodine increased from a mean control value of 6.4 to 12.2 meq. per cent after 3 months of 4 mg. of \( \delta \)-thyroxine.

This test was used as a check to verify that the patients had taken the medication. During the control period, it returned to 6.1 meq. per cent. With 2 mg. of \( \delta \)-thyroxine the mean protein-bound iodine increased to 9.3 meq. per cent. Achilles reflex contraction times were shortened an average of 30 milliseconds during the 3 months on 4 mg. of \( \delta \)-thyroxine.

**Clinical Observations**

On the 4-mg. dose of \( \delta \)-thyroxine pulse rates were unchanged in six and slightly increased in 10. The blood pressure of these patients was not significantly altered. Body weight was stationary in four, increased slightly in four, and diminished slightly in six. The two myxedema patients lost 10 and 11 pounds, respectively, on 4 mg. daily for 3 months. No deterioration in the appearance of the electrocardiogram following the two-step test was observed in these patients.* However, the test had to be stopped prior to the elapse of the 3 minutes of exercise in 10 patients because of angina, while they were receiving 4 mg. of \( \delta \)-thyroxine daily.

**Discussion**

In the present series of cases the aggravation of attacks of angina pectoris was more marked than has been previously reported.11-17 Many of the patients recorded in the literature had hypercholesteremia without angina pectoris prior to starting the drug. The low incidence of angina in this type of patient was understandable.

The trial with minimal amounts of \( \delta \)-thyroxine and stilbestrol was initiated with the hope of obtaining cholesterol lowering with little or no side effects of either drug. It was postulated that \( \delta \)-thyroxine might increase the turnover or possibly lower the miscible pool of cholesterol while estrogen shifted a portion of the cholesterol from the low-density to the high-density lipoproteins. Significant lipid effects did indeed occur, but not without mild but definite complications due to both drugs.

*To be classified as aggravation of the two-step tests a further 1-mm. depression of the ST segments in leads I or II, or a 2-mm. depression in leads V₆ or V₇ had to be recorded as compared to the control test.
This combination, although not ideal, was the best compromise between lipid and clinical effects observed in these four trial periods. It may be that combinations of one or more agents that affect cholesterol by different metabolic pathways will be useful in the future.

Theoretically, guanethidine and, to a lesser degree, reserpine cause a peripheral catechol depletion. This effect might decrease the synergistic action between the catecholamines and thyroxine and thus minimize the increase in work of the myocardium observed with D-thyroxine. Unfortunately, this theoretical advantage was not observed in the separate clinical trials with these two agents.

Conclusions
In a double-blind study, seven of 16 patients with moderate to severe angina noticed a definite increase in frequency and severity of attacks of angina pectoris while receiving 4 mg. of D-thyroxine daily.

Significant lowering of total cholesterol, phospholipid, and β-lipoprotein was observed with 4 mg. of D-thyroxine.

A combination of 2 mg. of D-thyroxine and 0.25 mg. of stilbestrol daily, although not ideal, was the most satisfactory compromise between lipid and clinical effects in the present study.

Guanethidine did not prevent the increase in frequency of attacks of angina pectoris noticed by patients receiving D-thyroxine. Reserpine also failed in this respect.

Acknowledgment
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References
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