**β-Adrenoreceptor-blocking agents and lipid metabolism**

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**Summary**

1. Chlorothiazide twice a day plus atenolol, metoprolol, pindolol and propranolol in single daily doses administered to patients with essential hypertension achieved effective control of blood pressure.

2. Each β-adrenoreceptor-blocking drug was associated with small, but significant, increases in plasma triglyceride concentrations and suppression of fasting immuno-reactive glucagon concentrations.

**Key words:** β-adrenoreceptor antagonists, atenolol, glucagon, metoprolol, pindolol, propranolol, triglycerides.

**Introduction**

In essential hypertension effective blood pressure control may be achieved with various β-adrenoreceptor-blocking drugs. Most reported studies have used two, three or four doses of these drugs each day. This study reports experience with once daily treatment. The drugs were chosen because they exhibited varying degrees of β₁-selectivity, partial agonist activity and different metabolism so that the contribution of these factors to the blood pressure response could be assessed.

**Methods**

Eighteen patients (13 female, 5 male) with essential hypertension, aged 16–60 years (mean 45, sd 12.6) were studied. All had moderate hypertension (W.H.O. Grade I or II) and normal renal function. They had been previously shown to respond favourably to β-adrenoreceptor-blocking drugs.

Each patient took chlorothiazide, 500 mg twice a day, throughout the study. In the open phase of the study good blood pressure control was achieved in each patient using divided (t.d.s.) doses of pindolol and propranolol. The total daily amount of drug required for each patient was recorded. Checks for compliance with medication instructions were made during this period. In the later, double-blind, study the total amount of pindolol (15–30 mg) or propranolol (160–240 mg) was given as a single dose each morning. Fixed doses of atenolol (100 mg) and metoprolol (100 mg) were used. A double-blind randomized block design was used for atenolol, pindolol and propranolol so that each 4 week treatment period was preceded and followed by 2 weeks of thiazide treatment alone. At the end of this study 17 of the patients entered a single-blind comparison of chlorothiazide with and without metoprolol. Each patient was seen at two weekly intervals for the measurement of blood pressure and heart rate. These measurements and the collection of blood samples were made 24 h after the last dose of the β-adrenoreceptor-blocking drug. On the occasions when samples for lipids, glucose and glucagon were to be taken the patients were requested to fast overnight and to refrain from smoking and alcohol. All patients were aware of the value of weight reduction, but no specific dietary modifications were introduced during the study. The plasma triglyceride concentrations were measured by a Boehringer enzymatic method and ‘pancreatic’ glucagon was measured by a radioimmunoassay (Alford, Bloom & Nabarro, 1977).

**Results**

There were significant decreases in both lying and standing blood pressure with each β-adrenoreceptor-blocking agent. The falls in the resting supine blood pressure when compared with the
Triglycerides
Cholesterol (mmol/l)
Blood glucose (mmol/l)
Fasting insulin (munits/l)
Fasting glucagon (pg/ml)

<table>
<thead>
<tr>
<th>Normal range</th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Metoprolol</th>
<th>Pindolol</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.17-2.00</td>
<td>1.35±0.11</td>
<td>2.19±0.44</td>
<td>1.79±0.22</td>
<td>1.73±0.19</td>
<td>1.85±0.28</td>
</tr>
<tr>
<td>2.6-6.9</td>
<td>5.5±0.21</td>
<td>5.6±0.33</td>
<td>5.6±0.22</td>
<td>5.8±0.28</td>
<td>5.7±0.27</td>
</tr>
<tr>
<td>3.6-5.3</td>
<td>4.3±0.21</td>
<td>4.1±0.16</td>
<td>4.1±0.15</td>
<td>4.0±0.11</td>
<td>4.1±0.15</td>
</tr>
<tr>
<td>5-25</td>
<td>12.2±0.86</td>
<td>12.5±1.65</td>
<td>13.3±1.38</td>
<td>11.8±0.89</td>
<td>12.4±1.21</td>
</tr>
<tr>
<td>62±10</td>
<td>24±4</td>
<td>31±5</td>
<td>28±4</td>
<td>29±5</td>
<td></td>
</tr>
</tbody>
</table>

precending 'placebo' therapy were (systolic/diastolic mmHg) atenolol 20/16 (P < 0.001), metoprolol 11/12 (P < 0.05), pindolol 14/6 (P < 0.05), propranolol 19/12 (P < 0.001). The reductions in pulse rate taken with the patients standing (beats/min) were atenolol 19, metoprolol 23, pindolol 8, propranolol 18, these all differed significantly from the 'placebo' period (P < 0.001 for each) and the smaller fall with pindolol also differed from the responses with the other three drugs (P < 0.001).

The values for fasting lipids, blood glucose, insulin and glucagon are shown in Table 1. There were elevations in the fasting triglyceride concentrations with all β-adrenoreceptor-blocking agent therapy phases when compared with chlorothiazide plus placebo. Although the increases were significant for all drugs (P < 0.05 for each), there were no significant differences between the drugs.

The fasting immunoreactive glucagon was suppressed with each β-adrenoreceptor-blocking agent, in many instances to the limit of sensitivity of the assay employed (17 pg/ml of plasma). There were no significant changes in insulin or blood glucose concentrations with the different treatments.

Discussion

Previous studies involving patients with mild hypertension have demonstrated a rise in triglyceride concentrations with thiazide diuretics alone (Ames & Hill, 1976). Also, increases in triglycerides, but not cholesterol have been reported in patients given metoprolol either for the first time or in place of another β-adrenoreceptor-blocking drug (Waal-Manning, 1976). Changes in lipoprotein composition during chronic administration of propranolol have also been reported (Tanaka, Sakaguchi, Oshige, Niimura & Kaneshisa, 1976).

The variations in triglyceride concentrations which were observed in this study may be the result of dietary or alcohol excess, but the blood glucose and insulin concentrations would suggest that the patients had fasted as requested. It seems likely, therefore, that the changes are related to the drug treatment. In the present study all patients received a constant amount of chlorothiazide throughout all phases so that the observed changes in triglyceride concentrations cannot be directly related to this treatment. The rises in plasma triglycerides which occurred in association with each of the β-adrenoreceptor-blocking drugs may be a direct effect of these drugs, or they may result from an interaction between the β-adrenoreceptor-blocking drugs and chlorothiazide.

The clinical significance of such a drug-induced rise in triglyceride concentrations remains to be assessed. However, in view of the association between high lipid concentrations and atherosclerosis it may constitute an added risk. Such an effect could mask or reduce the benefits of blood pressure reduction in mild hypertension.

References


