Effects of bisoprolol on lipoprotein cholesterol subfractions and apolipoproteins in patients with hypertension

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Effects of Bisoprolol on Lipoprotein Cholesterol Subfractions and Apolipoproteins in Patients with Hypertension

H. Drexel, H. R. Schmid, F. Follath, F. W. Amann

Non-selective beta-blockers tend to increase triglycerides and low-density lipoprotein (LDL) cholesterol while decreasing the atheroprotective high-density lipoprotein (HDL) cholesterol, particularly the HDL₂ cholesterol subfraction. The aim of this study was to investigate whether the highly beta₁-selective beta-blocker bisoprolol shares with non-selective beta-blockers these effects on blood lipids in patients treated for mild or moderate essential hypertension. In particular, HDL cholesterol and its subfractions HDL₂ cholesterol and HDL₃ cholesterol as well as apolipoproteins A1 and B were investigated. In a multicentre outpatient trial, 86 hypertensive patients received bisoprolol for eight weeks. Diastolic blood pressure was reduced from a baseline of 102 ± 7 mmHg (mean ± SD) to 87 ± 8 mmHg after 8 weeks of therapy with bisoprolol. Systolic blood pressure decreased from 159 ± 17 mmHg to 139 ± 14 mmHg. Blood pressure was normalized in 69% of patients with 5 mg bisoprolol once daily and, after increasing the dosage to 10 mg bisoprolol once daily in non-responders, in 80% of patients. Treatment with bisoprolol decreased triglycerides by 4.8% and LDL cholesterol by 1.7%, whereas HDL cholesterol increased by 5.2%, which was attributable to an increase by 9.2% of HDL₂ cholesterol and by 3.0% of HDL₃ cholesterol, respectively. None of these single changes were significant at the p < 0.05 level. Surprisingly, however, all lipid effects were in the favourable direction and opposite to the changes usually observed with non-selective beta-blockers. In a mathematical model derived from angiographic studies, the improvement of lipid risk factors brought about by bisoprolol equalled that of a decrease in age by 3.5 years. We thus conclude that effective antihypertensive doses of bisoprolol do not exert the typical dyslipidaemic effects of beta-blockers but rather tend to induce small but favourable changes in plasma triglycerides, LDL and HDL cholesterol, and especially in the atheroprotective HDL₂ cholesterol subfraction. J Clin Basic Cardiol 2001; 4: 57–60.

Key words: bisoprolol, beta-blocker, blood lipids, LDL cholesterol, HDL cholesterol, HDL subfractions, apolipoproteins
Methods

Patients
The study was conducted by general practitioners in Switzerland as a multi-centre outpatient study. After informed written consent had been obtained, patients with mild to moderate essential hypertension were enrolled into the study if they fulfilled two criteria: (a) mean sedentary diastolic blood pressure at > 2 blood pressure readings of > 90 mmHg, and (b) no severe organ damage due to longstanding hypertension. Criteria for excluding patients were: contraindications for beta-blockers, renal or hepatic dysfunction, history of stroke or myocardial infarction within the preceding 6 months, pregnancy and lactation. Concomitant use of other drugs that could affect the serum lipids was avoided during the study; in particular no diuretics or drugs affecting lipid metabolism were used. Also, no other antihypertensive drugs were allowed during the trial. If a patient had already taken antihypertensives before the study, the drugs were discontinued 4 weeks prior to the onset of the protocol.

Prior to the onset of treatment, a lipid profile was obtained, which included measurements of the plasma concentrations of triglycerides, cholesterol, HDL cholesterol, LDL and HDL3 cholesterol subfractions, LDL cholesterol, and apo A1 and apo B. Serum creatinine and serum potassium were also measured before and after treatment, and sedentary blood pressure and heart rate were recorded.

Biochemical methods
Lipid and lipoprotein measurements were performed as previously described [11]. In short, after an overnight fast and complete abstinence from ethanol for 12 hours, venous blood was drawn without the use of a tourniquet in a sitting position. Plasma was frozen immediately after centrifugation and stored at –20 °C. The frozen samples were collected from all participating physicians by a courier within 5 days and transported in a container at –20 °C to the analysing center. Only non-haemolytic plasma samples were further processed; patients whose plasma samples were haemolytic were excluded from the analysis.

Cholesterol and triglycerides were measured enzymatically using the cholesterol CHOD-PAP method and the triglyceride GPO-PAP method, respectively. HDL cholesterol, HDL2 cholesterol and HDL3 cholesterol were determined using a stepwise precipitation procedure with dextran sulfate [19, 20]. The results obtained by this stepwise HDL cholesterol precipitation procedure are easily comparable to those obtained by HDL cholesterol subfraction analysis using rate zonal ultracentrifugation [10]. Plasma concentrations of apo A1 and B were determined by turbidimetric immunoprecipitation assays (Uni Kit T, Roche) on a Cobas Mira. These methods have been shown to give excellent agreement with nephelometric assays [21]. LDL cholesterol was calculated [22].

Treatment
Bisoprolol was administered once daily as a 5 mg tablet in the morning at an initial dose of 5 mg/day. If blood pressure was not lowered to values ≤ 155/90 mmHg within two weeks, the dosage of bisoprolol was increased to 10 mg/once daily in the morning. Treatment was continued for a total of eight weeks. During the study the patients were regularly interviewed for the presence of subjective symptoms or adverse reactions. At the end of the study blood pressure and heart rate were recorded and measurements of lipid parameters, serum creatinine and serum potassium were repeated.

Lipid formula
The amount of atherosclerosis in the coronary tree can be quantitated as the extent of coronary atherosclerosis (ie the number of lesions with ≥ 50% narrowing). The quantitative interrelation of risk factor levels (eg age, lipids, etc.) with the extent of disease can be determined as recently reported [12]. Then the effects of the various lipids and of age on the disease extent are compared. The amount of a given lipid, that increases disease extent by the same amount as an age increase of one year, can be standardized as an age-equivalent of 1 year. The age equivalents of 1 year are: an increase by 0.092 mmol/l of LDL cholesterol, by 0.101 mmol/l of triglycerides, as well as a decrease by 0.020 mmol/l of HDL2 cholesterol and by 0.046 mmol/l of HDL3 cholesterol, respectively. In the present study the changes of the various lipids observed after 8 weeks of bisoprolol treatment were entered into the formula to obtain the total age equivalent of the lipid effects brought about by bisoprolol.

Statistical analysis
Values before and after 8 weeks of therapy were compared using a t-test for paired data with a level of significance set at p < 0.05.

Results
A total of 86 patients (46 men, 40 women) were included into the analysis. Clinical characteristics of patients are summarized in Table 1. Effects of treatment on serum potassium, creatinine, and blood pressure are given in Table 2.

Lipid effects
Levels of blood lipids obtained before and at the end of the study are summarized in Table 3 and Figure 1. There was no

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Bisoprol and Plasma Lipids

Table 1. Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Means ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>169 ± 8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>76 ± 13</td>
</tr>
<tr>
<td>Body mass index (kg x m⁻²)</td>
<td>26.5 ± 3.6</td>
</tr>
</tbody>
</table>

Table 2. Effects of 8 weeks of treatment with bisoprol on serum potassium, creatinine, blood pressure and heart rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.5 ± 1.8</td>
<td>4.3 ± 0.5</td>
<td>–0.2 ± 0.5</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>86 ± 17</td>
<td>85 ± 17</td>
<td>–1 ± 1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>159 ± 17</td>
<td>139 ± 8*</td>
<td>–20 ± 8*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>102 ± 7</td>
<td>87 ± 8*</td>
<td>–15 ± 8*</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>76 ± 9</td>
<td>67 ± 9*</td>
<td>–9 ± 9*</td>
</tr>
</tbody>
</table>

* statistically significant differences

Table 3. Effect of 8 weeks of treatment with 5–10 mg bisoprol daily on lipid parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean before treatment</th>
<th>Mean after 8 weeks of treatment</th>
<th>Mean of intraindividual differences*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.83</td>
<td>1.74</td>
<td>–0.087</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.71</td>
<td>5.68</td>
<td>–0.025</td>
</tr>
<tr>
<td>LDL-C-cholesterol (mmol/l)</td>
<td>3.71</td>
<td>3.66</td>
<td>–0.064</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.20</td>
<td>1.26</td>
<td>+0.062</td>
</tr>
<tr>
<td>HDL2 cholesterol (mmol/l)</td>
<td>0.26</td>
<td>0.28</td>
<td>+0.024</td>
</tr>
<tr>
<td>HDL3 cholesterol (mmol/l)</td>
<td>1.12</td>
<td>1.15</td>
<td>+0.034</td>
</tr>
<tr>
<td>apo A1 (g/l)</td>
<td>1.55</td>
<td>1.55</td>
<td>+0.000</td>
</tr>
<tr>
<td>apo B (g/l)</td>
<td>1.21</td>
<td>1.22</td>
<td>+0.013</td>
</tr>
</tbody>
</table>

* all single differences were non-significant
adverse effect on plasma triglycerides or cholesterol, LDL cholesterol, VLDL+IDL+LDL range or in the HDL range. Bisoprolol
proved even superior to traditional beta1-selective blockers
in that it had not only no adverse influence on lipid metabo-
lim, but rather induced a favourable trend in triglycerides,
LDL cholesterol, HDL cholesterol, and in its two
subfractions, HDL2 and HDL3 cholesterol. Quantitative data
derived from our angiographic lipid formula indicate that the
grand total of lipid effects brought about by bisoprolol de-
creased the risk for coronary atherosclerosis by the same
amount as a decrease in age by 3.5 years. It should, however,
be kept in mind that this “gain” of 3.5 years refers to an
amount of angiographic extent of coronary atherosclerosis
and does not mean automatically that clinical morbidity or
mortality are postponed by 3.5 years.

These data agree well with and extend the findings of pre-
vious studies that found that bisoprolol did not adversely in-
fluence total cholesterol, HDL cholesterol, or LDL choles-
terol [16–18]. Frithz and Weiner reported that bisoprolol had
no undesirable effects on total cholesterol, HDL cholesterol,
LDL cholesterol and triglycerides in 42 patients studied over
10 months [16]. Fogari et al. reported from a study with a
follow-up of three years that bisoprolol did not adversely af-
fect HDL cholesterol or triglycerides, while propranolol
and atenolol both deteriorated these lipid parameters [17].

The mechanisms by which beta-blockers usually lower
LDL cholesterol levels and increase plasma triglycerides is
not firmly established. One explanation is that beta-blockade
leaves naturally occurring alpha-adrenergic stimulation un-
opposed. Predominant alpha stimulation decreases the activ-
ity of lipoprotein lipase, the key enzyme of triglyceride hy-
drolisis, whereas the enzyme would be activated by stimula-
tion of beta2 receptors [23, 24]. Low lipoprotein lipase activity
in turn leads to an accumulation of plasma triglycerides
and concomitant decrease of HDL cholesterol, specifically
HDL2 cholesterol as was observed for beta-blockers [15].
In one trial, propranolol reduced HDL2 cholesterol by 38 %
and also reduced apo A1 [25]. Thus, the lipid changes typically
seen with non-selective beta-blockers can be readily ex-
plained by the catecholamine-induced alpha-receptor medi-
ated inhibition of lipoprotein lipase activity [23].

While the adverse changes of lipid metabolism are very
pronounced with non-selective beta-blockers, they have also
been observed with beta2-selective blockers. Indeed, beta1-
selective agents like metoprolol (that does not block beta2-receptors) or celiprolol (that
has a mild beta2-stimulating action) would not negatively in-
der any significant changes of serum creatinine or
serum potassium levels after 8 weeks of bisoprolol treatment.

**Discussion**

The data of the present study demonstrate that bisoprolol,
administered at a daily dose of 5 to 10 mg, sufficiently control-
ed hypertension in about 80 % of patients. At this dosage,
bisoprolol had no adverse effects on total plasma cholesterol
or triglycerides, LDL cholesterol, HDL cholesterol, HDL2
cholesterol, HDL3 cholesterol, or on apo A1 or apo B. That
plasma levels of apo A1 and B remained constant, indicates
that there was no change in the number of particles in the
VLDL+IDL+LDL range or in the HDL range. Bisoprolol
Our study also demonstrated a potent antihypertensive effect and high safety of bisoprolol in patients with moderate to mild hypertension. About 69% of the patients were sufficiently treated by 5 mg of bisoprolol daily. Increasing the dosage to 10 mg bisoprolol daily resulted in an overall response rate of about 80%. No serious adverse events were reported. Minor side-effects were reported by 14% of the patients, but drop-out rate was only around 2%.

In conclusion, thus, bisoprolol is an effective antihypertensive drug that is well tolerated by most patients. There is a slight beneficial influence of bisoprolol on the lipid fractions measured. Hence bisoprolol appears rather to decrease than to increase the lipid-mediated risk for developing or accelerating coronary atherosclerosis.

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References