Effects of Atenolol and Propranolol on Platelet Aggregation in Moderate Essential Hypertension: Randomized Crossover Trial

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Aim
To compare the effects of a selective beta-blocker atenolol and a nonselective beta-blocker propranolol on platelet aggregation.

Methods
Twenty successive outpatients with moderate essential hypertension (6 women and 14 men, mean age ± standard deviation 42.6 ± 8.5 years) were randomized to either propranolol (40 mg three times a day) or atenolol (100 mg once a day) for the first two weeks, followed by a one-day washout period, and then a two-week administration of the alternative drug. Along with standard examinations and tests, circulating platelet aggregates were measured.

Results
There were no significant differences in creatinine, blood glucose, potassium, total cholesterol, hemoglobin, red blood cells (RBC), or platelets in three periods: baseline, atenolol, and propranolol period. Significant and comparable reductions in systolic and diastolic arterial pressure, body weight, heart rate, and HDL-cholesterol were recorded in both patient groups. The LDL-cholesterol concentration increased significantly in propranolol compared with both baseline and atenolol period. Serum triglycerides increased significantly with both medications. The number of circulating platelet aggregates decreased significantly with propranolol (0.99 ± 0.19) in comparison with both atenolol (1.41 ± 0.70; P = 0.004, Wilcoxon matched pairs test) and baseline (1.59 ± 0.94; P = 0.002, Wilcoxon matched pairs test).

Conclusion
Propranolol inhibits platelet aggregation more than atenolol and may have a favorable effect on the management of hypertension especially in patients with increased cardiovascular risk.

Platelet aggregation and arterial hypertension are crucial factors in the development of atherosclerosis (1). Untreated arterial hypertension is the key factor of target organ lesions (2). In addition to lowering arterial pressure, antihypertensive drugs exert an array of other effects, including elevation in glycemia or hypercholesterolemia (2). Some antihypertensive drugs, such as beta-blockers and angiotensin receptor blockers are also known to influence platelet aggregation (3). Whereas there are no definite data on the effect of atenolol on platelet aggregation, metoprolol seems to reduce it (4). For propranolol, contradictory data have been reported, some suggesting that it stimulates and others that it inhibits platelet aggregation (4-6).

The aim of the study was to assess the effect of atenolol, a selective β₁ adrenergic blocker, on platelet aggregation, and to compare it with that of propranolol, a nonselective β₁ and β₂ adrenergic blocker. The study hypothesis was that there was a difference in the action of nonselective propranolol and selective atenolol on platelet aggregation in patients with moderate essential hypertension.
Patients and Methods

Patients

The study was carried out at the Outpatient Hypertension Clinic, Department of Internal Medicine, Split University Hospital, Split, Croatia. Informed, written consent was obtained from all patients prior to entering the study. The Split University Hospital Ethics Committee approved the investigation. Twenty successive previously untreated grade II/III hypertensives were enrolled to the trial. This sample size was determined to ensure 80% power to detect a 10% difference between atenolol and propranolol on platelet aggregation. The variability of this difference, assessed in a pilot study (n = 7) was 15%. Baseline levels of systolic and diastolic arterial pressure were 160-200 mm Hg and 95-119 mm Hg, respectively. All patients had normal laboratory and physical findings, and were classified as essential hypertensives. Persons with secondary arterial hypertension, obstructive arteriopathy, A-V conduction disorders, chronic obstructive bronchitis, or bronchial asthma were not included. Patients suffering from chronic myeloproliferative diseases or heart failure were also excluded, as well as the patients with serum creatinine > 140 μmol/L, blood glucose > 6.5 mmol/L, and heart rate < 60/minute.

Study Design

The participants in this controlled prospective 4-week clinical trial underwent history taking, physical examination, and arterial blood pressure measurements at four time points: baseline, after two weeks, during a one-day washout period, and after four weeks. The measurements included body weight, heart rate, standard electrocardiogram (ECG), and the following laboratory tests: complete blood count, urine, fasting blood glucose, creatinine, potassium, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, platelets, and circulating platelet aggregates. At the initial examination, the patients were randomized to receive either atenolol (100 mg o.d.) or propranolol (40 mg t.i.d.) tablets for two weeks, and then vice versa for two additional weeks after a 24-hour washout period (Fig. 1). The doses of atenolol and propranolol remained unchanged throughout the trial. Upon its completion, the results were classified into the following groups: baseline, first two-week therapy (atenolol or propranolol, period A), one-day washout period, and second two-week therapy (propranolol or atenolol, period B).

Arterial blood pressure was measured with a mercury sphygmomanometer in three positions at three time points, recording the mean of the last two of three measurements. Diastolic pressure was determined at the Korotkoff phase V level. Circulating platelet aggregates (CPA) were determined by the method described by Wu and Hoak, and modified by Grotemeyer (7-9). The test is based on the effect of ethylenediaminetetra-acetate (EDTA) and formalin on platelet aggregates formed in vivo or during blood sampling. These aggregates were fixed in formalin and precipitated along with red blood cells (RBC) by blood centrifugation. Platelet count in an EDTA and formalin anticoagulated blood sample is inversely proportional to the amount of platelet aggregates in the sample. In a sample with EDTA only the CPAs are dissolved. The result is expressed as a ratio of platelet counts in EDTA blood sample and in EDTA plus formalin sample, as follows: circulating platelet aggregates (CPA) = red blood cells (EDTA + formalin) × platelets (EDTA)/ red blood cells (EDTA) × platelets (EDTA + formalin). According to our laboratory standards, a CPA ratio of < 1.05, 1.05-1.2, or > 1.2 indicates normal, borderline, or increased value, respectively.
Statistical Analysis

Data were recorded in individual test lists and the results were presented in tables and graphics. Comparison of the baseline values at the beginning and after the washout period between the groups were tested by student t-test and Mann-Whitney U test. Comparisons of the baseline values between the groups were tested by student t-test for repeated measures and Wilcoxon matched pairs test. The results were collated according the interventions and compared by repeated measures ANOVA and Dunn test for normal distribution variables or by Friedman analysis of variance and Wilcoxon matched pairs test (10). The level of significance was set at P<0.05.

Results

Twenty successive patients with moderate essential hypertension were included in this prospective study. There were 6 women and 14 men, with the mean age (± standard deviation) of 42.6±8.5 years (range 28-57).

Table 1 shows the means of all variables measured at baseline and after the one-day washout period in two groups of 10 patients, each receiving either propranolol or atenolol as the first drug. As there were no significant differences between groups, the obtained results were collated in three groups according to interventions in order to make data processing as simple and reliable as possible (Table 2). There were no significant differences between the three points of measurement in the values of body weight, creatinine, blood glucose, potassium, total cholesterol, hemoglobin, RBCs, and platelets (P>0.05). However, there was a significant decrease from baseline values in systolic and diastolic pressure in sitting and supine positions, and in the heart rate following the administration of either beta-blocker (P<0.001). HDL-cholesterol concentration decreased significantly from baseline with the administration of either beta-blocker (P=0.03). LDL-cholesterol concentration increased significantly from the baseline with the administration of either beta-blocker (P=0.02) but not with the administration of atenolol (P=0.056). Triglycerides showed a significant increase from baseline (P=0.03), with no significant difference between atenolol and propranolol.

The baseline CPA values showed a nonsignificant decrease (P=0.056) after atenolol,

### Table 1. Clinical and laboratory characteristics of patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline before propranolol</th>
<th>Propranolol washout</th>
<th>Baseline before atenolol</th>
<th>Atenolol washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine RR (systolic, mm Hg)</td>
<td>175±17.4</td>
<td>173.5±14.6</td>
<td>173.0±13.6</td>
<td>172.5±17.9</td>
</tr>
<tr>
<td>Supine RR (diastolic, mm Hg)</td>
<td>103.8±7.8</td>
<td>102.6±6.9</td>
<td>103.1±8.9</td>
<td>102.3±7.6</td>
</tr>
<tr>
<td>Sitting RR (systolic, mm Hg)</td>
<td>185.2±11.9</td>
<td>183.8±11.9</td>
<td>184.0±13.0</td>
<td>184.2±17.0</td>
</tr>
<tr>
<td>Sitting RR (diastolic, mm Hg)</td>
<td>104.1±6.7</td>
<td>102.5±7.9</td>
<td>102.2±7.9</td>
<td>101.2±4.8</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>93.4±5.7</td>
<td>93.2±6.1</td>
<td>94.8±6.5</td>
<td>95.0±6.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>84.8±20.3</td>
<td>84.5±18.5</td>
<td>84.9±17.5</td>
<td>83.8±19.0</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>89.4±18.3</td>
<td>90.0±15.9</td>
<td>88.5±16.0</td>
<td>90.5±13.4</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>6.30±1.60</td>
<td>6.0±1.10</td>
<td>6.10±1.26</td>
<td>5.90±1.40</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.20±0.25</td>
<td>4.1±0.22</td>
<td>4.2±0.25</td>
<td>4.2±0.22</td>
</tr>
<tr>
<td>Cholesterolamb (mmol/L)</td>
<td>6.0±1.10</td>
<td>6.1±1.10</td>
<td>5.8±1.20</td>
<td>6.1±0.92</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.20±0.21</td>
<td>1.14±0.23</td>
<td>1.15±0.25</td>
<td>1.15±0.22</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>4.10±1.12</td>
<td>3.94±1.02</td>
<td>3.93±1.15</td>
<td>3.91±1.17</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.15±1.22</td>
<td>2.35±1.25</td>
<td>2.33±1.13</td>
<td>2.29±1.15</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>142.2±10.2</td>
<td>141.4±10.5</td>
<td>142.0±10.2</td>
<td>142.0±10.2</td>
</tr>
<tr>
<td>RBC (×10¹²/L)</td>
<td>4.76±0.55</td>
<td>4.75±0.53</td>
<td>4.77±0.63</td>
<td>4.72±0.46</td>
</tr>
<tr>
<td>Platelets (×10¹²/L)</td>
<td>224.8±27.3</td>
<td>223.4±27.8</td>
<td>222.9±29.0</td>
<td>222.5±27.9</td>
</tr>
<tr>
<td>Circulating platelet aggregates (CPA)</td>
<td>1.85±0.98</td>
<td>1.80±0.97</td>
<td>1.58±0.99</td>
<td>1.56±0.91</td>
</tr>
</tbody>
</table>

*Ten patients per group. Data are expressed as mean±standard deviation.
whereas significantly lower values were recorded after propranolol administration ($P=0.002$). Significantly lower CPAs compared with atenolol administration were also observed after propranolol ($P=0.004$). As illustrated in Figure 2, CPA values in baseline period and after atenolol administration were slightly elevated (>1.2), and lowered after propranolol (<1.05).

**Discussion**

As antihypertensive agents show comparable antihypertensive but variable metabolic effects, it has been postulated that they act differently on atherogenesis as well (11-13). Our data suggested that propranolol induced stronger inhibition of platelet aggregation than atenolol, i.e., that atenolol sustained the increased platelet aggregability in hypertensive patients (6).

The decrease in HDL-cholesterol and increase in LDL-cholesterol concentrations registered in this study confirm the unfavorable effects of beta-blockers on lipid metabolism (17,18). Some authors found no appreciable change in total cholesterol, HDL-cholesterol, and LDL-cholesterol after the administration of atenolol (14,15) in contrast to other reports of an increase in total cholesterol and LDL-cholesterol in propranolol treated hypertensives (19). Although the impact of serum triglycerides on the cardiovascular risk has not yet been defined, the present study showed both beta-blockers to be associated with a significant triglyceride increase. Whereas some authors found no changes, others reported significantly elevated concentrations of triglycerides in atenolol, as well as in propranolol treated hypertensives (4,14,20). There are reports that both selective and nonselective beta-blockers increase the levels of serum cholesterol and triglycerides (21). A large meta-analysis of the effects of different antihypertensives on the lipid status in 65,000 hypertensive subjects showed that all beta-blockers increased the level of triglycerides (22). Consistent with the literature data, the present study also showed that propranolol, to a greater extent, and atenolol, to a lesser extent, increased triglycerides and LDL-cholesterol, and both decreased HDL-cholesterol, with no major variation in the level of total cholesterol.

The imbalance between prostacyclin (a potent aggregation inhibitor) and thromboxane (a potent aggregation stimulant) may lead to platelet adhesion and aggregation, one of the crucial points in the generation of microthrombi and in the overall process of atherogenesis (23,24). Frishman et al (26) seem to have been the first to observe that beta-blockers influence platelet activation in coronary patients. This observation has prompted a number of studies not only in patients with ischemic heart disease but also in healthy volunteers and hypertensive subjects (25,26).

Total platelet count did not change significantly during our study. This phenomenon deserves a brief comment. Platelets’ function is not affected by the number but by the quality of plate-
Platelets, e.g. membrane and granule content. So, platelet adhesion and aggregation, except when the platelet values are extremely high, is not influenced by their number (27).

In this study, significantly lower CPA values were observed after propranolol than after atenolol therapy. These results indicate a favorable effect of the nonselective beta-blocker propranolol on platelet adhesion, ie the potential antithrombotic effect of this agent, in contrast to the selective beta-blocker (25). Some authors found that propranolol, both in usual and in high doses, reduced the synthesis of thromboxane, thus decreasing platelet aggregation (28,29), whereas others, observing an increase in platelet aggregation, believed that $\beta_2$ receptor blockade with platelet cAMP decline is responsible for this (4). Reduced platelet aggregation observed in coronary patients treated with propranolol increased after drug discontinuation (5). Similar antithrombotic effects were also reported in treated hypertensives (19). According to other studies, atenolol facilitates arachidonic acid release, thus facilitating platelet aggregation, whereas propranolol has the opposite effect (29). Winter et al (4,6) reported that metoprolol inhibited platelet aggregation, in contrast to an increase induced by propranolol. Our results show that propranolol inhibits platelet aggregation, as reported in the majority of other studies (5,25,28,29,32). Such contradictory results may be due to different propranolol dosage and different methods used to assess platelet aggregation. We measured spontaneous aggregation, whereas other authors assessed induced aggregation (4,7-9).

In the thrombotic process, beta-blockers may change not only platelet aggregation but the levels of serum fibrinogen as well. In one study atenolol did not change, and propranolol decreased the fibrinogen serum levels (14). Other authors found that atenolol increases serum fibrinogen (32). Propranolol’s negative impact on platelet aggregation appears to be partly due to the blockade of platelet $\beta_2$ receptors (4). Platelets possess $\alpha_2$ receptors, the stimulation of which leads to aggregation, and $\beta_2$ receptors the activation of which leads to inhibition of aggregation (4,29). In contrast to selective beta-blockers (e.g. atenolol), the nonselective agents (e.g. propranolol) that inhibit both $\beta_1$ and $\beta_2$ receptors impair platelet aggregation (4,29,31). Some authors have found that beta-blockers (alprenolol and propranolol) in small doses potentiate and in high doses inhibit platelet aggregation. It seems that this phenomenon could depend on the dosage and selectivity of a particular drug (32,33). Others consider that favorable effects of beta-blockers (carvedilol, propranolol) on platelet aggregation depend primarily on their interaction with membrane phospholipids, ion channels, or various enzymatic processes at the cellular membrane level, rather than on alpha or beta blockade (34). Differential effects of the selective beta-blocker atenolol and the nonselective propranolol on platelet aggregation, observed in this study, derive probably not only from their beta-blocking features but from different effects on cAMP or cellular calcium concentration, from their solubility, or from contrasting effects on platelet phospholipase A2 as well (32,35).

In this respect, propranolol has superior antithrombotic effect in comparison with alprenolol, metoprolol, and atenolol (35).

In a recent meta-analysis, the antihypertensive activity of atenolol was not superior to placebo and inferior to other antihypertensive agents in terms of cardiovascular morbidity and mortality (36). The authors explain this finding with atenolol’s low lipophilicity, minimal central effects, poor regression of left ventricular hypertrophy, and marginal improvement in endothelial dysfunction (36). Sustained increase in platelet aggregability, confirmed in the present study, could offer an additional explanation of the phenomenon.

In conclusion, propranolol, in contrast to atenolol, inhibits platelet aggregation. This feature should be considered, along with the impact on lipid status, on glucose tolerance, and possibly on the fibrinogen levels in choosing the most appropriate antihypertensive agent, especially in patients with increased cardiovascular risk.

References

36. Received: November 8, 2004
Accepted: February 9, 2005

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