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Beta-blockers have been shown to worsen insulin resistance and deteriorate lipoprotein metabolism in hypertensive patients. However, beta-1 selective beta-blockers seem to offer some advantage over non-selective ones and the degree of beta-1 selectivity is of importance. Thirty patients with primary hypertension were treated with the highly beta-1 selective beta-blocker bisoprolol for three months. There was a highly significant reduction of the blood pressure but no changes in fasting plasma-glucose or plasma-insulin levels were observed. J Clin Basic Cardiol 2001; 4: 229–230.

Key words: bisoprolol, hypertension, plasma-insulin, blood-glucose

In patients with essential hypertension, glucose intolerance and/or hyperinsulinaemia are common findings. The concept that insulin resistance is associated with essential hypertension is well established. Insulin resistance is said to be present when the ability of insulin to stimulate the uptake and disposal of glucose by muscle is impaired.

It is well known that various antihypertensive drugs in common use may worsen insulin resistance and deteriorate glucose and lipid metabolism [1].

Among the most widely used antihypertensive agents are beta-adrenergic antagonists, beta-blockers. These drugs are known to impair glucose metabolism and prolonged beta-blockade may be diabetogenic. There are, however, differences between the various beta-blockers in this aspect. Beta-1-selective beta-blockers, such as atenolol and metoprolol, seem to between the various beta-blockers in this aspect. Beta-1-selective beta-blockers, such as atenolol and metoprolol, seem to offer some advantages compared to non-selective ones like propranolol and timolol [2]. It has been assumed, that the degree of beta-1 selectivity is of importance in that context. For that reason, a study of the effects of the highly selective beta-1 blocker bisoprolol on glucose metabolism and insulin levels should be of interest.

Methods

Patients

Thirty patients with untreated essential hypertension, 19 men and 11 women (mean age 49 years), were included in the study. Criterion for hypertension was a diastolic blood pressure (DBP) of > 95 mmHg in the supine position, measured on three different occasions with a mercury sphygmomanometer (13 cm cuff) after a ten minutes’ rest. None of the patients had any other disease and in particular no one suffered from diabetes mellitus. Routine clinical and laboratory examinations were carried out to rule out any secondary cause of hypertension.

Design and measurements

Treatment started with 5 mg bisoprolol given once daily in the morning. The dose was increased to 10 mg after one month if a DBP of < 90 mmHg had not been reached. No further increase of the dose was done, as it is well-known that most of the effect is obtained with 10 mg bisoprolol or less.

As the aim of the study was to investigate the effect of bisoprolol alone, no further drugs were added even if the blood pressure was not normalised. Oral glucose tolerance test (OGTT) was performed before the treatment started and after three months according to the standard routine of the laboratory, i.e., 75 g glucose given in 300 ml water. Blood-glucose levels and plasma-insulin (p-insulin) concentrations were determined at 0 h and 2 h. Glucose was determined by the Cobas Mira SRM 909 analyzer and insulin by radioimmunoassay (RIA-gnost).

Insulin sum, i.e., basal fasting p-insulin and p-insulin after 2 h OGTT was used as an estimate of insulinemia as described by Modan et al. [3]. Body mass index (BMI) was calculated at the start and at the end of the study. Statistical evaluation was performed using Student’s t-test for paired differences.

Results

All patients completed the study. There was a highly statistically significant reduction of the systolic as well as the diastolic blood pressure (Tab. 1). Twelve patients were on the higher dose of bisoprolol, i.e. 10 mg. There were no changes of the fasting blood-glucose levels and after 2 h OGTT at the end of the study compared to the initial values. Further, there was no change of the corresponding p-insulin sums. The BMI was unchanged (Tab. 2).

| Table 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP, mmHg) at start and after 3 months (n = 30). |
|-----------------|-----------------|-------------------|----------------|-------------------|
| SBP             | Start           | 174.4 ± 12.7      | 103.3 ± 3.6     |
| DBP             |                 | 154.7 ± 11.2      | 92.1 ± 5.91     |
| Difference      |                 | < 0.01            | < 0.01          |
| p-value         |                 |                   |                 |
| Table 2. BMI, blood-glucose and plasma-insulin levels during glucose challenge and after 3 months’ treatment with bisoprolol (n = 30). |
|-----------------|-----------------|-------------------|----------------|-------------------|
| BMI             | B-g 0 h         | 2.9               | P-i 0 h         | P-i 2 h           |
|                 |                 |                   |                 |                   |
| Start           | 26.1            | 5.3               | 6.7             | 0.17              |
|                 |                 |                   | 0.59            | 0.76              |
| Month 3         | 26.2            | 5.3               | 6.8             | 0.18              |
|                 |                 |                   | 0.61            | 0.79              |
| Difference      | n. s.           | n. s.             | n. s.           | n. s.             |
| p-value         |                 |                   |                 |                   |
| BMI             | Blood Mass Index, B-g = blood-glucose (mmol/l), P-i = plasma-insulin (mmol/l) |

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Discussion

The study was performed along normal clinical routine within an out-patients department. Therefore, no placebo or control groups are available. However, it can be concluded that there was no influence of clinical importance upon the \( p \)-insulin levels as reflected by the insulin sum during three months' treatment with bisoprolol.

The ideal experimental setting had of course been using the hyperinsulinaemic-euglycaemic clamp-technique, directly measuring glucose uptake in peripheral tissue, but that was not possible.

However, the \( p \)-insulin sum in response to glucose challenge is an important factor determining glucose tolerance. A decreased sensitivity to insulin is reflected in an increase of \( p \)-insulin levels and glucose concentrations after glucose challenge. It is well known that hypertensive patients, untreated or even well-controlled ones, display a significant hyperinsulinaemic state compared to normotensive individuals. The values for \( p \)-insulin before and after OGTT in the present study are in accordance with this observation and the figures are fairly comparable with those found in another Swedish population [4].

As mentioned before, treatment with beta-blockers may worsen carbohydrate metabolism and may even precipitate an overt diabetes mellitus in non-diabetic patients [1]. Current literature suggests that especially non-selective beta-blockers may influence the carbohydrate metabolism in an unfavourable way. However, both propranolol (non-selective beta-blocker) and metoprolol (selective beta-blocker) were found to reduce insulin sensitivity and decrease glucose tolerance in a comparative study [2].

For sure, the present study was not designed to explore insulin resistance and glucose metabolism with sophisticated techniques. However, these results confirm the results elicited in healthy volunteers measured by the euglycaemic clamp-technique in a 4-week study with the ACE-inhibitor lisinopril or bisoprolol. Neither drug did exhibit any influence on insulin sensitivity [5]. Nevertheless, the results from this study in a normal clinical setting are encouraging and may indicate that a high degree of beta-1 selectivity, higher than that of metoprolol [6], is favourable from the metabolic point of view in the treatment of non-diabetic patients with primary hypertension.

In this context it is also of interest that bisoprolol in anti-hypertensive doses does not exert the typical dyslipidaemic effects of beta-blockers. On the contrary, small but favourable changes have been demonstrated recently in plasma triglycerides, LDL, and HDL cholesterol [7].

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References