Heart failure and the risk of hypoglycemia

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Abstract: In the Recommendations of the European Society of Cardiology and the European Society for the Study of Diabetes 2007 it is emphasized that the use of angiotensin converting enzyme inhibitors (ACE inhibitors) and adrenoblockers (BAB) is the basis for the treatment of chronic heart failure (CHF) in patients with diabetes mellitus (DM). For the first time, doctors' attention is drawn to the fact that the appointment of ACE inhibitors to DM patients receiving hypoglycemic therapy may increase the risk of hypoglycemic conditions. Attention to this side of the action of ACE inhibitors is due to the fact that hypoglycemia is an independent risk factor for cardiovascular mortality. The above Recommendations emphasize the urgent need for careful monitoring of the level of glycemia when prescribing ACE inhibitors to patients with diabetes. This is especially necessary in the initial period of combined cardiac and hypoglycemic therapy. The risk of hypoglycemia depends on many factors and, apparently, varies in different contingents of patients with diabetes. According to available data, patients with CHF have an increased tendency to hypoglycemia due to a decrease in the body's tolerance to a decrease in blood glucose levels. Such functional insufficiency is largely determined by a violation of the processes of gluconeogenesis in the liver and the secretion of glucagon by the pancreas, which are normally included in the body's defense system against a pronounced decrease in blood glucose.

Keywords: diabetes mellitus, chronic heart failure, hypoglycemia, carvedilol

INTRODUCTION

Potential danger of hypoglycemia in patients DM and CHF receiving ACE inhibitors may increase with the addition of BAB to therapy.

Firstly, BAB, suppressing the clinical symptoms of hyperglycemia, complicate its timely diagnosis and, as a consequence, relief. This effect is especially pronounced in non-selective BAB.

Secondly, non-selective BAB, blocking 2-adrenoreceptors, prevent the stimulation of gluconeogenesis and glycogenolysis in the liver, which reduces the flow of glucose from the liver into the bloodstream. In addition, the use of BAB in diabetes is associated with a number of other undesirable shifts in carbohydrate

metabolism. The deterioration of carbohydrate metabolism compensation occurs due to a decrease in insulin secretion and an increase in insulin resistance.

Nevertheless, the use of BAB in patients with diabetes and CHF, as a rule, improves the prognosis of patients, reduces the clinical manifestations of heart failure and improves their quality of life.

One of the drugs recommended for use in patients with diabetes with CHF is carvedilol. Unfortunately, there is practically no adequate information about the effect of carvedilol on the incidence of hypoglycemia in patients with DM with heart failure.

GOAL. The aim of this work was to evaluate the effect of carvedilol on the risk of hypoglycemia in patients with DM Type 2 (SD2) with CHF, receiving ACE.

MATERIALS AND METHODS

The study included 13 patients with DM2 with CHF due to the presence of coronary heart disease. Inclusion criteria there was a left ventricular ejection fraction of less than 45% and the presence of clinical signs of CHF.

The group consisted of 10 men and 3 women, whose age ranged from 51 to 70 years, the average age was 59.8±6.7 years. Arterial hypertension (AH) of 2-3 degrees was observed in 10 patients. In 3 patients, an increase in blood pressure (BP) was associated with the presence of diabetic nephropathy. None of the patients showed signs of renal insufficiency. Among the examined patients, obesity was noted in 10 patients (grade I - 8 people, grade II - 2 people). All patients before inclusion in the study received ACE inhibitors (perindopril - 2 people and enalapril - 11 people) and BAB (atenolol - 9 people, metoprolol - 3 people, bisoprolol - 1 person). Therapy with oral hypoglycemic drugs (PSP) was carried out in 2 patients (sulfonylurea derivatives - in 1 person, biguanides + sulfonylurea derivatives - in 1 person). Seven people were on insulin therapy; combination therapy (PSP + insulin therapy) was received by 4 people. The average level of glycemia when included in the study was - 7.1±2.1 mmol/l, glycosylated hemoglobin (HbA1c) - 8,4±1,4%. Anamnesis of hypoglycemia was observed in 4 patients. None of the patients had a history of severe hypoglycemia, which caused their hospitalization or emergency assistance from third parties.

The study protocol provided for 3 stages of follow-up: the period of the initial examination when switched on; examination after replacement of the outgoing BAB with carvedilol (Talliton, EGIS). The average duration of therapy was 62.0 ± 17.4 days, the average dose of carvedilol was 25± 12.5 mg / day. The final examination was performed after the withdrawal of carvedilol and the return to the initial therapy (the average duration was 56.5 ± 21.8 days).

The following studies were carried out at each stage:

1. Echocardiography by the Simpson method on the "HDI-5000c" device of ATL (USA) using a transthoracic multi-frequency sensor P4-2.

2. Assessment of diastolic myocardial dysfunction in the pulse-wave mode of Doppler echocardiographic examination, taking into account the National Recommendations of the IOC and OSS for diagnosis and treatment HSN (second revision, 2002).The measurement was carried out peak of early diastolic filling of the left ventricle (E), peak of late atrial diastolic filling of the left ventricle (A), calculation of their E/A ratio. The peak ratios E/A>1 were taken as normal values.

3. Control of HELL. Blood pressure was measured by the auscultative Korotkov method in accordance with the recommendations of the American Heart Association ((American Heart Association, 1981) and WHO (1993). In obese individuals with a shoulder circumference of more than 32 cm, a wide cuff was used to measure pressure sphygmomanometer company "Omron Healthcare, Inc." (USA).

4. Continuous glucose monitoring by the system CGMS Gold, Medtronic MiniMed USA. The principle of operation of the sensor is based on an electrochemical reaction with glucose contained in the interstitial fluid of the patient. The enzyme glucose oxidase is used to transform glucose on the sensor surface into electronic signals. The sensor continuously sends these signals via a cable to the monitor. The monitor records the average signal every 5 minutes, creating 288 records in 24 hours. All data is stored in the monitor's memory. The study was conducted for three days. As a result of monitoring, the following indicators were calculated: the average level of fasting glycemia; the average level of glycemia 2 hours after food; the number of episodes of glycemic reduction below the physiological level (< 4.5 mmol / l); the total duration of episodes of glycemic reduction <4.5 mmol / l per minute; the number of severe hypoglycemic episodes (glycemia < 2.5 mmol/ l).

5. Determination of the HbA1c level. Determination of HbA1c in capillary blood by cation chromatography was carried out on the DiaStat device of the company "Bio-Rad" (Germany).

Statistical data processing was carried out using the SPSS 12 application software package. The data are presented as mean ± standard deviations (M±SD). The differences were considered significant at $p<0.05$.

RESULTS

At the first, second and third examinations, there were no statistically significant differences in the levels of systolic and diastolic blood pressure (Table 1).

The average indicators of glycemia on an empty stomach and 2 hours after meals in patients with DM2 with CHF before, during and after treatment with carvedilol did not change ($p > 0.05$). At all stages of the survey, no reliable dynamics of HbA1c was recorded (Table 2).

Table 1.

Comparative characteristics of the blood pressure level in the examined patients with DM before, during and after treatment with carvedilol

Indicator	Initially	On the background of therapy	After cancellations
SAP, mmHg	134,6±8,0	134,5±8,5	135,6±5,0
DAP, mmHg	86,5±4,7	84,1±3,8	83,1±4,6

Table 2.

Indicators of carbohydrate metabolism in patients before, during and after treatment with carvedilol

Indicator	Initially	On the background of therapy	After cancellations
Fasting glycemia, mmol/l	7,1±2,1	8,3±1,2	8,6±2,3
Glycemia 2 hours after meals,mmol/l	9,3±2,4	10,2±2,8	10,1±2,4

The average indicators of glycemia on an empty stomach and 2 hours after meals in patients with DM2 with CHF before, during and after treatment with carvedilol did not change ($p > 0.05$). At all stages of the examination, no reliable dynamics of HbA1c was recorded (Table 2). The data obtained indicate that the change in the type of BAB was not accompanied by a significant change in the indicators of compensation of carbohydrate metabolism in patients SD with CHF.

Replacement of the initial BAB with carvedilol was accompanied by a statistically significant decrease in the average number of episodes of glycemic decrease < 4.5 mmol / l (initially - 2.1±1.9 episodes / person; against the background of carvedilol intake - 0.2± 0.4 episodes / person, $p < 0.05$). After the withdrawal of carvedilol, there was an increase in cases of hypoglycemia (0.8±0.9 episodes /person, $p < 0.05$).

Before the appointment of carvedilol, the total time of glycemia < 4.5 mmol/l was 80.6±105.4 min. Against the background of carvedilol therapy, there was a significant decrease in the total duration of such episodes to 0.9 ± 2.0 minutes. When returning to the initial therapy, a statistically significant increase in the duration of these periods to 31.3 ± 51.4 minutes was recorded.

Episodes of severe hypoglycemia (< 2.5 mmol / L) were observed before taking carvedilol (1.2± 1.6 episodes / person) and after its withdrawal (0.5± 0.8 episodes / person). No cases of severe hypoglycemia have been reported against the background of carvedilol therapy.

DISCUSSION

The results of the study were quite unexpected for us. It could be assumed that the effect of carvedilol on the level of glycemia due to the additional 1- blocking effect will either decrease or will not differ significantly from that of selective women. However, the replacement of selective women with carvedilol was

accompanied by a significant decrease in the frequency of occurrence and a decrease in the duration of episodes of hypoglycemia. Moreover, when using carvedilol, severe forms of hypoglycemic conditions that occurred before taking it completely disappeared. For the first time, the data of our study were reported at the Russian Congress of Cardiologists in September 2006. A year later, data were published comparing the effects of carvedilol and metoprolol on hypoglycemia in patients with DM2 treated with ACE inhibitors and/or angiotensin II B receptor antagonists (ARA). These results were obtained as part of the largest controlled clinical trial "Glycemic control in diabetes mellitus comparison of carvedilol and metoprolol in patients with arterial hypertension" (The Glycemic Effect inDiabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives - GEMINI). The study compared the metabolic effect of adding the above-mentioned BAB to the treatment of patients with DM2 and hypertension receiving ACE/ARA. The study included 1210 patients, of whom 726 received metoprolol after randomization (average dose 104.7 mg / day), and 424 - carvedilol (average dose 15.6 mg / day).

The GEMINI study lasted 5 months. The first results were published back in 2004. The addition of metoprolol and carvedilol reduced systolic and diastolic pressure to the same extent. However, the metabolic effects of the addition of these BAB were different. Thus, when taking carvedilol, in contrast to metoprolol, a significantly more stable level of HbA1c was observed (0.02% on carvedilol, $p = 0.65$; 0.15% on metoprolol, $p < 0.001$). There was also a significant decrease in insulin resistance (carvedilol resistance decreased by 9.1%, $p = 0.004$; on metoprolol - by 2%, $p = 0.48$). In addition, there was a significantly more pronounced decrease in microalbuminuria (on carvedilol - by 14%, $p < 0.01$; on metoprolol by 2.5%) and a significantly slower appearance of new cases of microalbuminuria (40% less when taking carvedilol compared with metoprolol; $p = 0.04$).

In addition, a special questionnaire was used to assess the severity of clinical symptoms in DM, reflecting the mental state, neurological, cardiovascular and ophthalmological complications, as well as manifestations of hyper- and hypoglycemia. This particular piece of research was published in 2007.

According to the GEMINI questionnaire, the addition of carvedilol to the therapy of patients with DM2 led to a significant decrease in the frequency of symptoms of hypoglycemia ($p = 0.02$). When metoprolol was added, no significant shifts in the frequency of hypoglycemia symptoms were detected. At the same time, when using self-monitoring data on the level of glycemia, no significant differences in the frequency of hypoglycemia were obtained. Thus, asymptomatic hypoglycemia was observed in 11.6% of patients taking carvedilol and in 10.3% taking metoprolol ($p = 0.46$). Objectively confirmed symptoms of hypoglycemia on the background of

carvedilol administration, 8.4% of patients were observed, and on the background of metoprolol - in 8.8% (p = 0.81).

Despite the fact that the authors of the GEMINI study emphasize the imperfection of the methodology for assessing episodes of hypoglycemia, it is obvious that carvedilol is at least no more dangerous in relation to hypoglycemia than metoprolol. This is fundamentally important, since non-selective drugs are traditionally considered as drugs that worsen the prognosis in patients with diabetes.

The conclusions of our study do not contradict the GEMINI data. Of course, carvedilol turned out to be safer in the studied aspect than metoprolol. The difference in the formulation of conclusions most likely follows from the difference in the methods used to assess hypoglycemia.

Carvedilol differs from other BAB in a number of additional properties that are likely to have clinical significance. It has an α1-adrenoblocking effect, is characterized by high lipophilicity, prevents the development of tolerance to nitrates and exhibits pronounced antioxidant activity.According to the degree of lipophilicity, it surpasses all lipophilic substances: acebutolol, betaxolol, bisoprolol, metoprolol, timolol. It has been proven that lipophilic BAB, able to more easily penetrate the blood-brain barrier, increase the activity of N. vagus, which reduces the likelihood of ventricular fibrillation and the risk of sudden death.

There are several mechanisms of "hypoglycemic" safety of carvedilol. Glucose delivery to the brain centers increases due to an increase in cerebral blood flow under its influence. In addition, the compensatory reaction of the central nervous system to a decrease in blood glucose levels increases, as well as the secretion of glucagon in response to hypoglycemic stimulation of blood flow.

CONCLUSION

In conclusion, I would like to remind you that only carvedilol significantly improves the prognosis of patients with CHF in combination with DM. Neither bisoprolol nor metoprolol CR/XL have a significant effect on the course of CHF in patients with DM. At the same time, such patients account for up to 20-30% of all CHF patients. It is difficult to get rid of the idea that the above-described "hypoglycemic" safety of carvedilol plays one of the leading roles.

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