Comparative Characteristic of the use of Glucose-Containing Drugs in A Complex and Separate with Diabetes Mellitus Associated with Chronic Renal Pathology

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Abstract: This article presents the results of a prospective study in which the experience of using the sulfanilamide line combination with dapagliflozin was applied. It is known that drugs that lower glucose levels are used separately, but in special cases and in a complex manner. Combined use is much more effective in many clinical trials around the world. In our study we tried to compare the effectiveness of the use of glucose lowering drugs in combination and separately.

Key words: Gliquidone, diabetic nephropathy, diabetes mellitus.

Introduction. Type 2 diabetes mellitus (type 2D) is a severe progressive chronic disease that is an independent risk factor for heart failure (HV) and cardiovascular complications. Glurenorm (gliquidone) is a second-generation oral hypoglycemic agent from the sulfonylurea group. This drug was synthesized and first used in clinical practice for the treatment of insulin-independent diabetes mellitus (type II diabetes) more than 20 years ago. Unlike other drugs, glurenorm has a short-term effect, which makes it easy and quick to correct hyperglycemia without fear of developing prolonged hypoglycemia [4,6,8]. In addition, glurenorm is the only sugar-reducing drug that is practically not excreted by the kidneys [1,2,3,7] and, therefore, should be safe when used in patients with kidney disease. The latter property is extremely important for patients with diabetes mellitus, since 40-45% of them develop a severe complication - diabetic nephropathy (DN) [5,9]. The purpose of the study. The task of our work was to study the effect of glurenorm in combination with dapagliflozin on the functional state of the kidneys in patients with type II diabetes mellitus with varying degrees of severity of DN, as well as to study its effect on the function of the vascular endothelium, since it is the vessels of the microcirculatory bed that are the main target in the development of late complications of diabetes mellitus.

Materials and methods of research. 61 patients with insulin independent diabetes mellitus aged 36 years to 71 years with a duration of the disease from 1 year to 35 years were examined. Patients with
urinary tract infection, urolithiasis or anamnestic indications of kidney disease of a different origin (not associated with diabetes) were excluded from the study. The control group was 30 healthy volunteers who were excluded from kidney disease, arterial hypertension and hereditary burden of diabetes. Of the 31 patients who underwent a full course of examination, 8 were only on diet therapy and served as a comparison group, the remaining 23 people had previously received drug therapy with sulfonylureas of the glibenclamide (maninil), glipizide (minidiab) or glyclazide (diabeton, predian) and for the purposes of the study were transferred to monotherapy with glurenorm at a dose of 30 mg (1 tablet) to 120 mg (4 tablets) per day in two doses.

Patients treated with glurenorm in combination with dapagliflozin were divided into 2 groups: 1st group (10 people) - without laboratory signs of kidney damage (absence of proteinuria, swelling syndrome, arterial hypertension), 2nd group (13 people) - with the presence of DN (severe proteinuria, arterial hypertension; in 6 patients - moderate degree of chronic renal failure – GRF, serum creatinine up to 200 μmol / l).

Results and their discussion. Effect of gluenorm in combination with dapagliflozin on the quality of metabolic control. Patients of the control group who received only diet therapy, before the start of the study, were in a state of compensation for carbohydrate metabolism (the level of HbAc averaged 8.5% with a norm of up to 8%). After 6 months of observation, these patients were still in a state of compensation or subcompensation for carbohydrate metabolism (HbAc 8.8%), which did not require the appointment of oral sugar-reducing drugs. In patients of the 1st group (previously received oral sacchar-lowering drugs that did not have kidney damage), the initial state of metabolic control was regarded as satisfactory (the level of HbAc on average in the group was 9.8%). After replacing therapy in these patients with glurenorm and introducing stricter diet control after 6 months, the level of HbAc, reflecting the degree of metabolic control, decreased to 8.8%. In patients of the 2nd group, who had a pronounced lesion of the glomerular apparatus of the kidneys, the transfer to glurenorm therapy in combination with dapagliflozin was accompanied by stabilization of carbohydrate metabolism and a significant decrease in the level of HbAc - from 11 to 9.8% after 6 months of observation (p<0.05). The effect of gluenorm in combination with dapagliflozin on the functional state of the kidneys. In patients of the control group receiving diet therapy, after 6 months of observation, there was a twofold increase in albuminuria (from 48±29 to 99±33 mg / day), unreliable due to large fluctuations in individual values of albuminuria. Glomerular filtration rate (GFR) in this group of patients tended to decrease (from 114 ±8 to 100 ± 7 ml / min / 1.73 m2). In patients receiving glurenorm in combination with dapagliflozin, there was a tendency to decrease microalbuminuria in the 1st group and proteinuria in the 2nd. GFR in the treatment process practically did not change, and in patients who had severe kidney damage, treatment with glurenorm in combination with dapagliflozin was accompanied even by a certain increase in GFR.

In a detailed study of the functional state of the glomerular apparatus of the kidneys, we found that in patients who do not have diabetic kidney damage or have only the initial stage of DN (microalbuminuria), GFR against the background of treatment with glurenorm in combination with dapagliflozin practically did not change, and the excretion of albumin in the urine tended to decrease. At the same time, in patients with severe DN (even at the stage of initial GFR), treatment with glurenorm in combination with dapagliflozin for 6 months was accompanied not only by a decrease in proteinuria, but also by a significant increase in GFR. Both of these effects (decreased proteinuria and increased GFR) indicate an improvement in the functional state of the kidneys. There is no doubt that both of these effects were directly or indirectly related to treatment with glurenorm in combination with dapagliflozin, since in patients of the control group who received only diet therapy, for 6 months of observation, the opposite trend was noted - an increase in albuminuria and some (unreliable) decrease in GFR. It remained unclear how (through what mechanisms) glurenorm in combination with dapagliflozin has a positive effect on the kidneys. The direct effect of the drug on the kidneys seems to
be excluded, since the drug is not excreted by the kidneys and, therefore, does not come into direct contact with the renal structures. Improving the compensation of carbohydrate metabolism against the background of treatment with combined drugs and a stricter diet could undoubtedly contribute to a decrease in albuminuria. However, a decrease in albuminuria in patients with the initial stage of nephropathy is observed, as a rule, after a longer than 6 months, the period of maintaining compensation or subcompensation of diabetes mellitus, and in patients with severe kidney damage (especially at the stage of GRF), compensation for diabetes mellitus does not give an antiproteinuric effect at all.

We suggested that a fairly rapid (within 3-6 months) positive effect of glucrenorm in combination with dapagliflozin on the functional state of the kidneys may be mediated by its systemic effect associated with the effect on the vascular wall and parietal blood components (platelets) during circulation. In recent years, it has become known that the endothelial lining of blood vessels is a powerful endocrine organ that produces various factors, including those regulating vascular tone. These factors include vasoconstrictor ET-1 and vasodilator PG12. In platelets, another vasoactive factor that causes vasoconstriction is synthesized - THA2. All these factors, regulating the tone of blood vessels (in particular, renal), are able to modulate renal hemodynamics (increase or decrease GFR). In addition, TXA2 can also have a direct effect on the permeability of the renal filter, increasing albuminuria.

Reducing the content of THA2 under the influence of treatment with glucrenorm can give a beneficial effect, eliminating the risk of developing severe vascular complications in type II diabetes. First, given the fact that THA2 is a powerful stimulant of platelet aggregation and thrombosis, a decrease in its content in the blood during treatment with glucrenorm can give a pronounced antithrombotic effect and improve blood rheology. Secondly, a decrease in the concentration of TCA2 can explain the decrease in systemic blood pressure observed with prolonged use of glucrenorm in combination with dapagliflozin in patients with diabetes mellitus with arterial hypertension. Thus, a detailed study of renal function and the state of the vascular endothelium in patients with type II diabetes mellitus showed that the use of glucrenorm in combination with dapagliflozin in the presence of severe renal pathology is not only safe, but also has a beneficial effect on intrarigene hemodynamics, and also gives an antiproteinuric effect.

Findings.

1. Therapy with glucrenorm in combination with dapagliflozin in therapeutic doses does not give a nephrotoxic effect, but on the contrary, preserves and supports the filtration function of the kidneys, including in patients with the initial stage of CRF (with serum creatinine content up to 200 μmol / l).

2. Therapy with glucrenorm in combination with dapagliflozin for 3 and 6 months causes a significant decrease in the production of vasoconstrictor factor - TXA, which probably provides an improvement in intrarenal hemodynamics and gives an antiproteinuric effect in patients with severe DN.

References


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