Preparation Erbisol in therapy of insulin-dependent diabetes mellitus.

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The article is devoted to studying the effect of new home preparation Erbisol in patients with insulin-dependent diabetes mellitus. 78 patients who received daily Erbisol in a 2 ml intramuscular dose for 20 days were examined. The control group consisted of 20 patients. The preparation in a complex with hypoglycemic drugs promotes to achieve the compensation of diabetes in the prevalent majority of patients, is conductive to the reduction or elimination of clinical manifestations, has the positive effect on carbohydrate and lipid metabolism, possesses the antioxidant effect and improves a contractile ability of the myocardium. The results obtained are able to recommend it for wide use in complex therapy of patients with diabetes mellitus.

Key words: diabetes mellitus, Erbisol, lipid peroxidation.

Erbisol is biologically active medicinal preparation developed in Scientific Production Centre “ERBIS” under the leadership of A.N.Nikolaenko [1]. This is a solution of hydrolysis products of cellular membrane components of animal embryonic tissue at the stage of the first half of cow pregnancy. The preparation consists of natural protein-free complex of organic compounds of non-hormonal origin with low-molecular weight and includes glycopeptides, peptides, nucleotides and amino acids in its content. The pharmacological properties and activity of Erbisol are determined by its biologically active peptides, in particular by specific glycopeptides, that appear in the role of haptenes directly activating the immune system for the search and elimination of pathological changes in the organs and tissues. This preparation inhibits the processes of lipid peroxidation on the hepatocyte membranes of intoxication animals, increases the activity of the blood glutathion-dependent antioxidant system without changes in the enzyme activity of microsome oxidation and content of cytochrome P-450. There are data about its positive influence on the indices of lipid metabolism. Under condition of experimental gastric ulcer Erbisol has the pronounced regenerative effect [2]. Erbisol was registered by the Ministry of Public Health of the Ukraine in 1994. A number of its Certificate for Registration is N94/136/1 and in 1999 the drug was re-registered (a number of the Certificate for Registration is NP.10.99/01051).

In the clinic of internal diseases Erbisol is used [3,4] for the treatment of patients with viral hepatitis B [5], purulent wounds and trophic ulcers in vascular surgery [6], in therapeutic stomatology [7], and oncology [8].

The studies connected with Erbisol effect in patients with insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) were carried out in the Department of Endocrinology at National Medical University from 1994. The first results demonstrated its significant effect [9]. An antioxidant effect of this preparation was noted in patients with diabetes

mellitus by us [10]. It has been proved that Erbisol has hypolipidemic, cardiotonic and immunomodulating effects [11].

Materials and methods

78 patients with IDDM were examined by us. Diabetes mellitus and severity of its duration were diagnosed by the generally known criteria (V.G.Baranov, 1980; A.S.Yefimov, 1983; M.I.Balabolkin, 1989; N.T.Starkova, 1989). The compensation criteria offered by European Group on Forming Policy in Field of IDDM were used. An age of patients was within the limits of 19-76 years (average 43,28±1,61). The duration of IDDM consisted from 1 month to 37 years (average 11,27±0,99). The severe form of disease was diagnosed in 62 (79,5%) patients. Diabetes mellitus of middle severity was diagnosed in 16 (20,5%) patients. During an original examination the state of compensation was revealed in 60 (76,9%) patients and no ketoacidosis was diagnosed in 29 patients among them. The state of satisfactory compensation was observed in 16 (20,5%) patients with IDDM. Ischemic heart disease (IHD), hypertonic disease (hypertension), chronic cholecystitis, chronic pancreatitis were the most frequent concomitant diseases. IHD was diagnosed in 18 patients with IDDM (23,1%).

All the patients were kept a diet (the table N9) and were received hypoglycemic therapy. In addition the antianginal and hypotensive medicinal drugs were in a case of need prescribed for patients with IHD. Erbisol was prescribed in the 2 ml daily intramuscular dose for 20 days, the total dose consisted of 40 ml preparation. The group of 20 diabetic patients who were received the traditional therapy (dietetics, insulin, angio-hepatoprotectors) was examined for the control.

Blood plasma cholesterol (CH) and high density lipoproteins cholesterol (HDLC) were determined by the Ilk' method. The index of atherogenicity (Ia) was expressed by a formula:

$$Ia = (CH\ total - HDLC) / HDLC$$

TBK-active products (that additionally to malondialdehyde (MDA) consisted of the low-molecular compounds) were determined by the following method [12] and the activity of processes in lipid peroxidation (LPO) was evaluated by their content. Glycosylated hemoglobin was determined by the method of Standefer et al. [13]. Fructosamine – by the method of Koberstein et al. [14]. Echocardiography was realized by polycardioanalizer PKA-4-01 in M-regimen. Longitudinal rheography was carried out in the symmetrical sites of the lower extremities. Data obtained were statistically analysed on computer Pentium-166 MMX using Student's t test.

Results

The preparation Erbisol exerts a considerable clinical effect in complex therapy of diabetes mellitus. None of patients had any side effect of the preparation. The improvement in general self-feeling, the increase in capacity for work, the improvement of mental and emotional conditions were noted in patients after the treatment. The disappearance of weakness, the normalization of sleep and the appearance of cheerfulness were registered in our patients. These changes

were maintained for 2-3 months. After the Erbisol treatment course the decrease and disappearance of pain in the lower extremities and crural spasms were observed in patients. It was noted the improvement of cutaneous sensitivity in the lower extremities, the disappearance of rigor and numbness of the feet, the fingers of the lower extremities and the appearance of agreeable feeling of warm in feet and crura. Besides the stable decrease in the frequency of painful syndrome in heart region, the intensity and duration of pain and the requirement in antianginal agents were decreased in patients with IHD. The improvement of intestine peristalsis, the normalization of stools, the disappearance of meteorism were observed in patients. There was an acceleration in healing of foot wounds and ulcers. Before the Erbisol treatment ketoacidosis was diagnosed in 29 patients and after the Erbisol inclusion in complex therapy ketoacidosis was liquidated 2-3 days early comparing to control group. During two months of observation ketoacidosis was not even registered in patients with its predisposition in the past.

After the Erbisol treatment fasting and after meals glycemia had been decreased against a background for the same mean daily dose of insulin usage in patients. These changes remained stable for two months of our observation. In addition a significantly decrease in the level of glycosylated hemoglobin and fructosamine was noted in a corresponding period (Table 1). In patients with the Erbisol treatment a tendency to the decrease in middle daily dose of insulin from 46,9±1,73 U/day to 43,77±1,69 U/day after treatment (6,67% decrease in a dose), 13,07% decrease (up to 40,77±2,38 U/day ($P<0,05$)) in 1 month after treatment and (up to 39,15±2,67 U/day ($P<0,01$)) in 2 months after treatment was shown that was in accordance with 16,52% decrease comparing to an initial dose. The decrease in daily requirement of insulin up to 18 units was registered in some patients. An improvement of the carbohydrate metabolism indices was accompanied with the increase in insulin dose.

The normalization both carbohydrate as well as lipid metabolism serve as a criterion for compensation of diabetes mellitus. A timely correction of metabolism is able to prevent or slow down
the development of diabetic complications. Plasma cholesterol was decreased but HDLC was increased in our patients. The index of atherogenicity was decreased in 20 days of Erbisol treatment.

A significant differences between the indices of atherogenicity in the control group of diabetic patients who received traditional treatment and the group of patient treated with Erbisol ($P<0,01$) were observed (Table 2).

The group of patients with newly diagnosed IDDM (n=10) was examined by us too. A decrease in the number of active T-lymphocytes, in the unbalance of T-helper and T-suppressor subpopulations, in the inversion index of T-h/T-s ratio, an increase in a number of O- lymphocytes, a decrease in the functional activity of T-lymphocytes, a decrease in the level of IgA were observed before the treatment in patients. Following the 20 day course of Erbisol treatment a relative number of immunocompetent cells was increased and their functional activity was normalized, the unbalance between T-h and T-s was abolished, the level of low-differentiated O- lymphocytes was decreased. No significant changes were noted in the level of immunoglobulins.

Table 1.

Changes in indices of carbohydrate metabolism in patients with IDDM after Erbisol treatment

Indices	Group of patients	Before treatment	After treatment	In 1 month after treatment	In 2 months after treatment
Fasting glycemia, μmol/l	Erbisol (n=78)	12,13±0,47	7,48±0,27**	8,35±0,48*	8,16±0,29**
	Control (n=20)	12,18±1,06	9,94±1,06	11,14±1,20	11,38±1,03
Glycemia after meals, μmol/l	Erbisol (n=78)	12,49±0,53	7,91±0,29**	9,63±0,42**	9,39±0,42**
	Control (n=20)	13,93±1,96	10,97±1,26	11,60±1,82	12,35±1,92
Fructosamine, μmol/l	Erbisol (n=78)	4,29±0,39	3,31±0, 31*	2,47±0,27**	2,89±0,35**
	Control (n=20)	4,66±0,47	4,18±0,47	4,10±0,38	4,20±0,65
Glycosilated hemoglobin, %	Erbisol (n=78)	9,64±0,56	8,79±0,68*	7,46±0,50**	6,10±0,29**
	Control (n=20)	9,49±0,72	8,79±0,69	8,79±0,69	7,74±0,81

Note: * - significance according to indices before treatment $P<0,05$

**- significance according to indices before treatment $P<0,01$

Table 2.

Changes in indices of lipid metabolism in patients with IDDM after Erbisol treatment

Indices	Group of patients	Before treatment	After treatment
Plasma cholesterol, μmol/l	Erbisol (n=78)	5,99±0,23	4,94±0,20**
	Control (n=20)	6,23±0,44	6,03±0,14
HDLC, μmol/l	Erbisol (n=78)	2,27±0,18	4,38±0,32**
	Control (n=20)	2,82±0,26	3,15±0,69
Index of atherogenicity, cU	Erbisol (n=78)	4,00±0,93	0,78±0,19**
	Control (n=20)	2,91±0,90	2,16±0,50

Note: * *- significance according to indices before treatment P<0,01

The activation of lipid peroxidation (LPO) processes plays an important role in the development of diabetes mellitus and its complications [15, 16]. The accumulation of peroxidation products correlated with the manifestation of diabetic microangiopathies. No the significant changes in LPO activity were demonstrated against a background of the compensation of carbohydrate metabolism.

Before treatment the level of plasma MDA consisted of 2,64±0,22 μmol/l, on the 10th day of Erbisol treatment the MDA level decreased up to 1,88±0,22 μmol/l (P<0,05), in 20 days of treatment course the MDA level was in accordance with 1,83±0,15 μmol/l (P<0,01), but in 1 and 2 months after treatment the level of plasma MDA had not the significant differences from the initial level in patients with insulin-dependent diabetes mellitus.

The decrease in the MDA level of HDL from 1,84±0,7 μmol/l before treatment up to 1,75±0,18 μmol/l on the 10^{th} day of Erbisol treatment course was insignificant (P>0,1) and its level was decreased up to 1,38±0,07 μmol/l (P<0,05) in 20 day treatment, this index was in accordance with 1,29±0,08 μmol/l (P<0,01) in a month after finishing the treatment course, and 1,69±0,23 μmol/l (P>0,1) – in 2 months.

The MDA of LDL and VLDL levels differed significantly from the level of this index before treatment (28,89±1,88 μmol/l) within all the control periods of time: on the 10^{th} day of treatment - 16,14±2,06 μmol/l (P<0,01), in 20 days of Erbisol treatment course - 18,51±1,53 μmol/l (P<0,01), in a month - 19,46±1,81 μmol/l (P<0,01), in 2 months - 16,16±1,48 μmol/l (P<0,01).

During two months a decrease in the level of MDA of erythrocytes was observed in 20 days of Erbisol therapy. The MDA level of erythrocytes was equivalent to 11,43±0,65 μmol/l before treatment and 9,09±0,59 μmol/l (P<0,01) on the 10^{th} day of treatment course and it was decreased up to 6,18±0,36 μmol/l (P<0,01) after treatment. In a month the level of erythrocyte MDA consisted of 7,24±0,45 μmol/l (P<0,01), in 2 months - 7,49±0,58 μmol/l (P<0,01).

Analysing the dynamics of echocardiographic indices the improvement of contractive ability for the myocardium was shown after treatment in patients with IDDM. A fraction of blood output was increased from 50,95±1,36% to 56,70±1,37% (P<0,01), a volume of the left ventricle into the systole was decreased from 58,04±3,05 cm^3 to 50,07±2,43 cm^3 P<0,05). No changes in a volume of the left ventricle into diastole were revealed (P>0,1). After the Erbisol treatment an increase in the stroke volume from 60,71±1,99 cm^3 to 67,60±1,89 cm^3 (P<0,05) and cardiac output from 4,39±0,14 l/min to 5,37±0,21 l/min (P<0,01) were revealed. The rate of circulatory contractility of the myocardial fibers was increased from 0,97±0,03 s^{-1} to 1,18±0,05 s^{-1} (P<0,01). The time of the left ventricle wall contractility was reduced from 273,04±6,16 ms to 265,73±6,14 ms but these changes were statistically insignificant (P>0,1). No changes in a mass of the myocardium of the left ventricle was noted: before and after treatment this index was 122,95±4,95 g and 116,45±2,20 g (P>0,1), respectively.

In patients with IDDM and IHD only a volume of the left ventricle into the systole was changed after treatment: from 72,70±4,04 cm^3 to 60,92±4,34 cm^3 ($P<0,1$); fraction of output was increased from 49,40±1,76% to 59,17±2,85% $P<0,05$). A tendency to the increase in the stroke volume from 68,65±5,10 cm^3 to 81,90±5,40 cm^3 ($P<0,1$) was outlined. No change in other indices of echocardiogram (a volume of the left ventricle into the systole, rate of circulatory contractility of myocardial fibers, cardiac output, time of contractility in posterior wall of the left ventricle, myocardial mass) was revealed in patients with IDDM and IHD.

Erbisol effect was studied in 102 children aged from 4 to 15 years: the duration of insulin-dependent diabetes mellitus was noted more than 3 years in 39 children, newly diagnosed diabetes mellitus - in 58 children, impaired glucose tolerance – in 5 children. A scheme for the preparation administration was an analogous with the scheme for group of adult patients. After treatment a positive dynamics of clinical symptoms, an improvement in psycho-emotional sphere, a significant improvement in indices of lipid and carbohydrate metabolism (the level of glycosylated hemoglobin was reduced) against a background of a decrease in a daily insulin dose from 1,1 U/kg to 0,4 U/kg/body mass were observed in all the children. Ketoacidosis was liquidated in 2-3 days of treatment. The disease compensation was achieved 5±0,5 days early than against a background of traditional therapy and it was more stable and prolonged. The normalization of the immune status of organism was also observed. The remission was shown in 30% cases with newly diagnosed diabetes mellitus and only in 12% of control group (Fig.1). There was the remission of disease in 18 children with newly diagnosed diabetes from 3 to 12 months. After the remission period the daily requirement in insulin was smaller comparing to control group during 24 months (Fig.2).

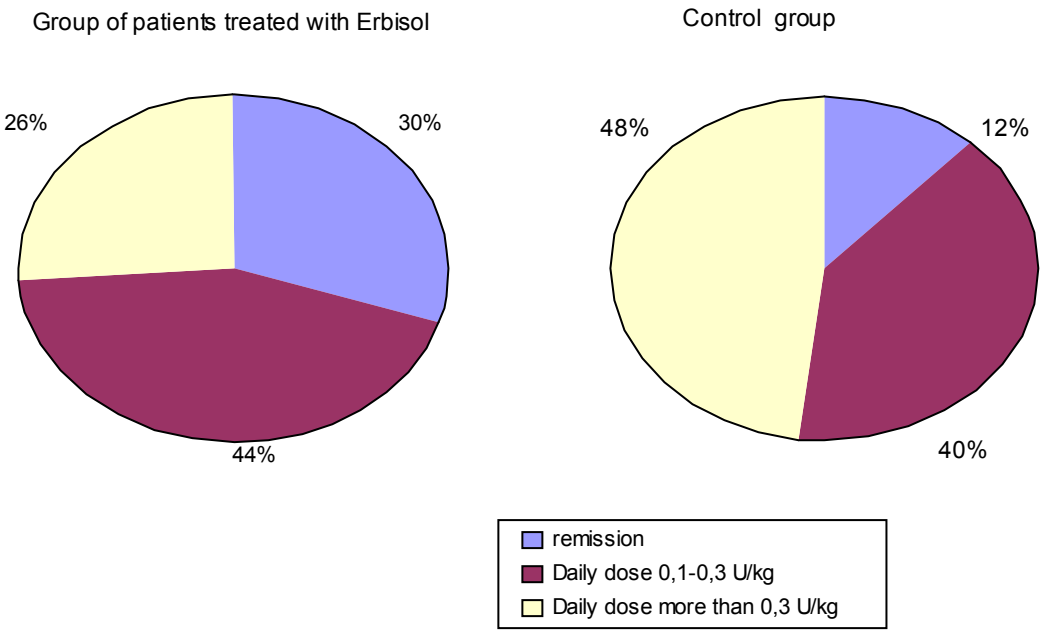

Fig.1. Remission in newly diagnosed diabetes mellitus.

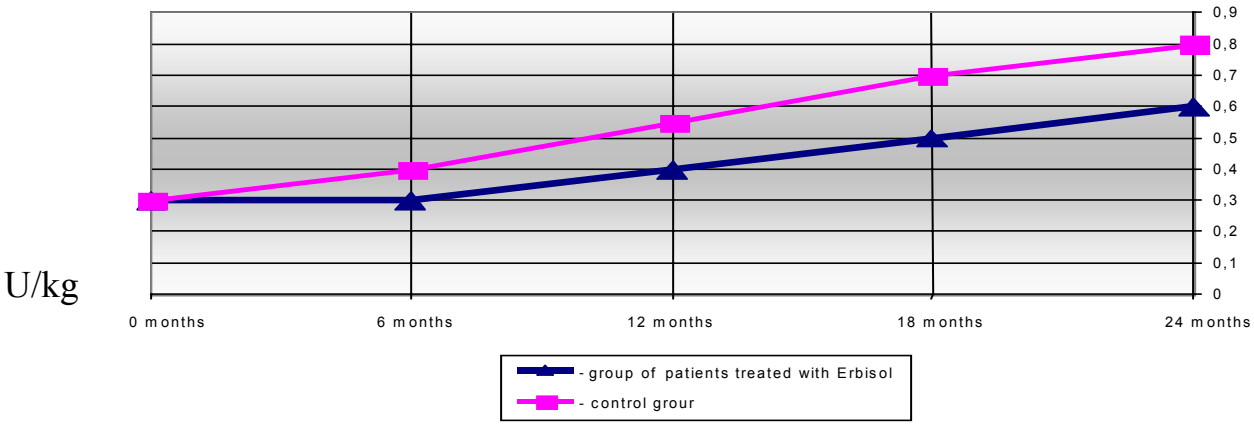

Fig. 2. Daily requirement in insulin after Erbisol treatment.

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Conclusion

Preparation Erbisol has antioxidant properties. Antioxidant effect of Erbisol is mediated by the presence of cell membrane components containing sulphhydril groups.

Under the influence of Erbisol treatment the inhibition of lipid peroxidation processes in both plasma as well as membrane structures took place. MDA is necessary to consider as the most objective criterion for estimating the state of peroxidation processes. MDA content in plasma, LDL, HDL and VLDL, erythrocytes was significantly decreased after Erbisol treatment course. A decrease in the content of peroxidation products specifically in MDA prevents the progress of diabetic angiopathies. The indices of MDA in plasma, LDL, HDL and VLDL, erythrocytes were changed more pronounced in 20 day after the treatment course. The decreased MDA content was maintained for 2 months of observation in erythrocyte membranes, fractions of LDL and VLDL.

Antioxidant properties of preparation, its normalizing effects mediated by peroxidation inhibition on carbohydrate and lipid metabolism had positive effect on cardiovascular system. A decrease in the content of POL (MDA) end-products contributes to the reduction of the circulatory endothelium-dependent regulation, enzymic activity of mitochondria membranes, cardiac microsomes, prevents the development of perivascular fibrosis, changes in nervous fibers and contractile system of the myocardium. This influence is more expressed in patient without IHD, and may be explained by not metabolic changes but coronarogenic disorders of the myocardium that took place in patients with diabetes mellitus and IHD.

Thus, taking into account the marked, antioxidative, hypolipidemic and cardiotonic effects Erbisol can be recommended for usage in complex therapy of patients with IDDM in all the aged groups and with different severity and duration of disease, with the phenomenon of diabetic angiopathy, diabetic cardiopathy for achievement of the stable compensation in carbohydrate and lipid metabolism, relaxation of POL processes, for a positive influence on the cardiovascular system, a decrease in an expression of manifestations of cardiovascular complications. Erbisol has more pronounced cardiotonic effect in patients with noncoronarogenic myocardial disorders. An advisable Erbisol prescription is 2 ml daily intramuscular dose, the mean course of treatment - 20 days, 2-3 courses is recommended for a year. The preparation can also be used as a prophylactic agent.