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E-Book

Diabetes 2 Types for Fellow an Edition _ Part 4

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"The life plus a cat is a surprising combination, I swear to you!"

"Rajner Maria Rilke"

"We cannot solve a problem, using the same mentality which we have created them"

-A. Einstein

Competent treatment a diabetes of 2 type at Children and Adults - psychosomatic and an infectious disease (4 part).

Clinical a BOOK (clinical cases are approved in the practice).

Sulfanilurea preparations represent the basic group of the medicines applied to treatment of a diabetes of type 2.

These preparations concern to Secretogens insulin, and the basic them hypoglicemic action is connected with stimulation of formation and liberation of insulin from pancreas islets. Last years the mechanism of action of preparations Sulfanilurea on stimulation of secretion of insulin by pancreas b-cages is completely deciphered. These preparations contact the corresponding receptors localized on membranes of b-cages, change activity K-atfazy, promote closing calium's channels (K-ATF-DEPENDENT channels) and increase of the relation of levels ATF/ADF in cytoplasm that leads depolarization membranes. It in turn promotes opening voltage-dependent Ca2 +-channels, to increase of level of cytocindery calcium and stimulation Ca2 +-dependent exocytoz's secretor granules in which result there is a contents liberation secretor granules in an intercellular liquid and blood. Last stage of secretion of insulin is under the control calcium/kalmodulin-dependent proteinkinazy-2. Thus, a target of action of preparations Sulfanilurea are ATF-SENSITIVE caluim's channels, which consist of a receptor to Sulfanilurea (fiber with molecular weight 140-kDa (SUR)) and specific fiber - (KIR6.2).

However all preparations derivative Sulfanilurea 2 generations have certain lacks greater or smaller degree of expressiveness which do not allow to achieve proof indemnification of a diabetes and normalisation of indicators of a carbohydrate exchange in all cases, both throughout long time, and throughout days.

The last is connected by that peak of action of any preparation Sulfanilurea and increase postadsorbcion hyperglicemia's do not coincide on time. It leads, on the one hand, to insufficient decrease in level of glucose in blood for a long time, and with another - to development hypoglicemia's to various degree of expressiveness in the next hours after food intake, especially in case of its insufficient quantity or the food intake admission. Episodes hypoglicemia's meet at patients of advanced age as a result of infringement of the scheme of application hypoglicemic preparations at the expense of memory impairment is more often. For example, at 2-3-briefyly reception Glibenclamid's patients often forget, whether they accepted a preparation in the morning. To compensate possible absence of reception of a preparation before a breakfast, the patient accepts a double dose that leads to development hypoglicemia's at night before a supper.

Studying of molecular mechanisms of action Sulfanilurea preparations has allowed to obtain the data which throwing light on processes of interaction of various stimulators of secretion of insulin and have shown, that Secretogenes insulin, despite the identical definitive effect shown in strengthening of secretion and liberation of insulin from b-cages, carry out this action through involving in corresponding process of various albuminous and alarm molecules.

ATF-SENSITIVE calium's channels are the primary structures co-operating with various Secretogenes of insulin.

Opening and closing ATF-SENSITIVE calium's channels, and, hence, iniciation secretions of insulin and its inhibition is provided aggregation ATF with various subunits calium's channels. Linkage ATF with carboxiterminal domain KIR6.2 stabilises dissociation

SUR1 and KIR6.2, caused Glibenclamid's and promotes closing calium's channels. Aggregation ATF with NBF-1 and Mg2 + ADF with NBF-2 on SUR1 causes opening calium's channels.

In spite of the fact that Glibenclamid's and Glimepirid render stimulation influence on secretion of insulin by means of closing ATF-SENSITIVE calium's channels, the mechanism of this influence has certain differences. It is established, that at Glimepirid constants of speed of association in 2, 2-3 times, and speeds dissociation at 8-10 time above, than at Glibenclamid's. These data testify that affinity Glimepirid's to a receptor Sulfanilurea in 2-3 times more low, than at Glibenclamid's. Besides it, Glibenclamid, aggregation with polypeptid's a receptor, having molecular weight 140 kDa, whereas Glimepirid with polypeptid's the same receptor, but having molecular weight 65 kDa which is designated as SURX.

The carried out additional researches have shown, that Glibenclamid's, besides the core aggregation with polypeptid's 140 kDa, also specifically aggregation with fibers with molecular weight 40 and 65 kDa, that has allowed to come out with the assumption that Glibenclamid also can aggregation with fiber SURX though affinity to such aggregation at it much more low, than at Glimepirid's All listed allows to consider, that fibers-targets of a receptor to Sulfanilurea for Glibenclamid's and Glimepirid's are various: for Glibenclamid's - SUR1, for Glimepirid's - SURX. Both fibers co-operate with each other and supervise through KIR6.2 opening and closing calium's channels, and, hence, processes of synthesis and insulin liberation in a pancreas b-cage.

From time of application of preparations Sulfanilurea for treatment deabetes type 2 discussions about out pancreatic (peripheral) action of preparations Sulfanilurea do not stop.

In laboratory, guided G.Muller, researches are for many years carried out in this direction. Studying *in vitro* and *in vivo* influence Glimepirid's, Glipizid's, Glibenclamid's and Gliclazid's on the maximum decrease in level of glucose of blood and the minimum increase in secretion of insulin during 36 hours after reception of the listed preparations, has been established, that Glimepirid in a dose of 90 mkg/kg caused the maximum decrease in the maintenance of glucose in blood at the minimum secretion of insulin; Glipizid in a dose of 180 mkg/kg possessed the lowest hypoglicemic activity and caused the maximum increase in secretion of insulin; Glibenclamid in a dose of 90 mkg/kg and Gliclazid in a dose of 1, 8 mg/kg occupied intermediate position between two extreme indicators. Curves of dynamics of concentration of insulin and glucose in blood at application of the specified preparations Sulfanilurea were practically identical. However at factor definition (average increase in level of insulin in plasma to average decrease in the maintenance of glucose in blood) these indicators have appeared unequal (Glimepirid - 0, 03; Gliclazid - 0, 07; Glipizid - 0, 11 and Glibenclamid - 0,16). This distinction was a consequence of lower secretion of insulin: at Glimepirid's an insulin average level in plasma of 0, 6 mked/ml, at Gliclazid - 1, 3; at Glipizid's - 1, 6 and Glibenclamid'- 3, 3 mked/ml (G.Muller, 2000). The least stimulating influence Glimepirid's on insulin secretion provides smaller risk of development hypoglicemia's.

Results of these researches show, that preparations Sulfanilurea have to some extent expressivenesses peripheral effect, but this effect is more expressed at Glimepirid's. Peripheral action Glimepirid is caused by activation of translocation GLUT-4 (to a lesser degree GLUT -2) and increase in synthesis of fat and glicogen's in fatty and muscular fabrics accordingly. In a plasmatic membrane adipocities under influence Glimepirid's quantity GLUT -4 in 3-3, 5 times, and insulin - in 7-8 times above. Besides, Glimepirid causes dephosphorylation GLUT - 4, that is obligate a condition of stimulation of key enzymes lipogenez's (glycerine-3-fosfatatsiltransferaza) and glicogeneza's (glycogen-sintetaza). Glimepirid, as well as Glibenclamid's, raises activity factor glycogen-sintetaza's to 45-50% from the maximum effect of insulin. Simultaneously activity glycerine-3-fosfatatsiltransferazy increases to 35-40% from the maximum influence of insulin. Glimepirid oppresses activity proteinkinaza's A and lipoliz by means of activation tsamf-specific fosfodiesteraza's.

GLUT - Glucose transporters

GLUT-1 (GLUT-1, the glucosic conveyor type 1) - unidirectional fiber-carrier of glucose. At the person it is coded by a gene - SLC2A1. GLUT-1 promotes facilitated to glucose carrying over through a plasmatic membrane cages mammal.

Widespread in fetal fabrics. At adults the maximum expression is observed in eritrocytes and also in cages endotelium's barrier fabrics, such as hemato-encephalic a barrier.

Glucosic conveyors in eritrocytes (GLUT-1) - integrated membranes fibers, having 12 waterproof segments, each of which as it is considered, is a spiral crossing a membrane. Detailed structure GLUT-1 while is unknown, but one of perspective models assumes, that a little located the friend near to the friend to spirals form transmembranes with hydrophyl the rests which can contact glucose on a course of its movement on the channel.

GLUT-1 Is responsible for mastering basal the glucose, necessary for maintenance of process of breath of all cages. Levels of expression GLUT-1 in cellular membranes increase at reduction of level of glucose, and on the contrary.

GLUT1 Also is the important receptor participating in mastering of Vitamin C, especially at mammals who do not make it. At the mammals making vitamin C, instead of GLUT-1 it is frequent expressed GLUT-4.

GLUT1 Contains 12 alpha spirals crossing a membrane, each of which consists from 20 aminoadids the rests. The analysis shows, that spirals are amphipilic, on the one hand polar, with another - waterproof. Six of these alpha spirals communicate together in a membrane, in the centre creating the channel through which there can pass glucose. Outside of the channel waterproof regions, near to tails of fat acids of a membrane are located.

Mutations of gene SLC2A1 are responsible for deficiency GLUT-1 also known as illness De Vivo, rare autosom -prepotent disease. This disease is characterised by low concentration of glucose in a spinal liquid (Hypoglicorachia), the form neuroglicopania's, glucose arising because of broken transport through hemato-encephalic a barrier.

GLUT-1 Also acts as a receptor for T-limfotrop a virus of the person thanks to which the virus gets into cages.

Also possibility of use GLUT-1 as exact histochimic - a marker for infantile hemangioma's has been shown.

Interaction GLUT-1 with fiber GIPC1 has been shown.

In a brain there are two types of fiber GLUT-1: 45k and 55k. GLUT-1 45k meets in cages astroglia's and GLUT-1 55k in capillaries of a brain and is responsible for transport of glucose from blood through hematoencephalic a barrier. The lack of the last leads to decrease in level of glucose in a spinal liquid (less than 60 mg/dl), that can lead to spasms.

DERL3, recently opened inhibitor squirrel GLUT-1, methylated at collateral a cancer. At this such cancer methylation DERL3 apparently mediates Effect Varbutg's.

In oncology as effect Varbutg's. understand the tendency of the majority cancer cages to make energy mainly by means of very active glicoliz's with the subsequent formation of dairy acid, instead of by means of slow glicoliz's and oxidations piruvat's in mitochondrions with oxygen use as in the majority of normal cages. In cages of quickly growing malignant tumour level glicoliz's almost in 200 times above, than in normal fabrics. Thus glicoliz remains preferable even in conditions when oxygen is a lot of.

Otto Varburg believed, that these changes in a metabolism are the fundamental reason of a cancer (hypothesis Varburg's). The main reasons of malignant transformation of cages are mutations in oncogenes and genes-supressorah of tumours and effect Varburg's is considered simply a consequence of these mutations. That is why at a diabetes it is necessary to do researches on a cancer (the note of the author).

At a kidney cancer the same effect can appear because of presence of mutations tumoral supressor's Gippel's - Lindau which activates genes glicolitic enzymes, including M2-splice-every-form piruvatkinaza's.

In March, 2008 Lewis K.Kentli and colleagues declared, that piruvatkinaza's M2-PK, the isoform piruvatkinaza's is an enzyme, which is the reason of effect Varburg's. M2-PK is in all quickly sharing cages, and gives possibility to cancer cages to consume glucose in the accelerated rate; if to force cages to be switched to a normal form piruvatkinaza's, inhibition synthesis tumoral M2-PK speed of their growth essentially falls. Scientists have admitted that fact, that the exact chemistry of a metabolism of glucose will differ most likely in various forms of a cancer, but PKM2 was present at all tested cancer cages. This form of enzyme which usually are not meeting in healthy fabrics though it is obviously necessary for fast reproduction of cages, for example, at healing of wounds or hemopoiesis.

Transport of glucose from blood in cages

Consumption of glucose by cages from a blood-groove occurs also by the facilitated diffusion. Hence, speed transmenbranes a glucose stream depends only on a gradient of its concentration. The exception is made by cages of muscles and a fatty fabric where the facilitated diffusion is regulated by insulin. For lack of insulin the plasmatic membrane of these cages is impenetrable for glucose as it does not contain fibers-carriers (conveyors) of glucose.

Glucose conveyors name also glucose receptors. The conveyor has a site of linkage of glucose on a membrane outer side. After glucose joining conformation the squirrel changes, therefore glucose appears connected with fiber in a site turned in a cage. Then glucose separates from the conveyor, passing in a cage.

The way of the facilitated diffusion in comparison with active transport prevents transport of ions together with glucose if it is transported on a concentration gradient.

Suction carbohydrates in intestines

Suction monosacharids from intestines occurs by the facilitated diffusion by means of special fibers-carriers (conveyors). Besides, glucose and galactoza are transported in enterocyt by the again-active transport dependent on a gradient of concentration of ions of sodium. The Fibers-conveyors dependent on gradient Na^+, provide suction glucose from intestines gleam in enterocyt against a concentration gradient. Concentration Na^+, necessary for this transport, is provided Na^+, K^+-АТФ-za which works as the pump, pumping out from cage Na^+ in exchange for K^+.

Unlike glucose, fructose is transported by the system which is not dependent on a gradient of sodium.

Glucosic conveyors (GLUT) are found out in all fabrics. There are some versions GLUT, they are numbered according to order of their detection.

The structure of fibers of family GLUT differs from the fibers transporting glucose through a membrane in intestines and kidneys against a gradient of concentration.

Described 5 types GLUT have similar primary structure and the domain organisation

- GLUT-1 provides a stable stream of glucose in a brain;
- GLUT-2 it is found out in cages of the bodies allocating glucose in blood. With the assistance of GLUT -2 glucose passes in blood from enterocytes and a liver. GLUT -2 participates in glucose transport in β pancreas-cages;
- GLUT-3 possesses big, than GLUT -1, affinity to glucose. It also provides constant inflow of glucose to cages nervous and other fabrics;
- GLUT-4 - the main carrier of glucose in cages of muscles and a fatty fabric;
- GLUT-5 meets, mainly, in cages of thin intestines. Its functions are known insufficiently.

All types GLUT can be both in a plasmatic membrane, and in cytocindery vesicles. GLUT-4 (and in smaller measure GLUT-1) almost completely are in cytoplasm of cages. Influence of insulin on such cages leads to moving vesicles, containing GLUT, to a plasmatic membrane, merge to it and embedding of conveyors in a membrane. Then the facilitated transport of glucose in these cages is possible. After decrease in concentration of insulin in blood glucose conveyors again move to cytoplasm, and glucose receipt in a cage stops.

Moving of glucose from primary urine in cages nephritic tubules occurs again-active transport just as it is carried out at suction glucose from intestines gleam in enterocyres. Thanks to it glucose can arrive in cages even in the event that its concentration in primary urine less, than in cages. Thus glucose reabsorbed from primary urine almost completely (99%).

Various infringements in work of conveyors of glucose are known. Hereditary defect of these fibers can underlie a diabetes 2 of type. At the same time a cause of infringement of work of the conveyor of glucose can be not only defect of the fiber.

Infringements of function GLUT-4 are possible at following stages

- An insulin signal transmission about moving of this conveyor to a membrane;
- Conveyor moving to cytoplasm;
- Inclusion in membrane structure;
- Lasing from a membrane etc.

Attention! It is necessary to search for the preparations influencing conveyors of glucose (the note of the author). It can give treatment from a diabetes.

I will continue about the characteristic of the preparations applied now for decrease of sugar of blood.

Pharmacokinetics of derivatives Sulfanilurea

Duration of action of all Sulfanilurea - 10-12 hours. At retard forms is - till 24 o'clock.

Gliclazid (Diabeton Slow Liberation (SL) – elimination through kidneys, the semideducing period - 12 hours, a daily dose - 40-320 mg.

Glibenclamid (Maninil) - elimination through stomach an intestinal path (SIP) and kidneys (50x50%), the semideducing period - 10-12 hours, a daily dose - 2, 5-20 mg.

Glipizid (Glibinez retard) - elimination - through kidneys, the semideducing period - 4-6 hours, a daily dose - 2, 5-20 mg.

Glicvidon (Glurenorm) – elimination through stomach an intestinal path (SIP) (95%) and only 5% through kidneys, therefore a preparation it is preferable to at whom nephritic insufficiency. The semideducing period - 4-5 hours, a daily dose - 30-180 mg.

Clinical interpritation the semideducing periods (semi-eliminations)

The most effective preparation from group Sulfanilurea preparations is Glibenclamid (Maninil) - which have been introduced in clinical practice in 1969.

The biological half-life period makes 5 hours, and duration hypoglycemic actions - to 24 hours. The preparation metabolism occurs basically in a liver by transformation into two inactive metabolit's, one of which are excreting to urine, and the second is allocated through a gastroenteric path. The daily dose makes 1, 25-20 mg (the maximum daily dose - 20-25 mg) which appoint in 2, are more rare in 3 receptions for 30-60 mines to meal. Glibenclamid (Maninil) possesses the most expressed hypoglycemic action among all group Sulfanilurea preparations, and thereupon it by right is considered «the gold standard». In domestic market Glibenclamid it is presented in tablets on 5; 3,5; and 1,75 mg. And two last medicinal forms represent micronized the form that allows to support at lower dose of a preparation its therapeutic concentration in blood, i.e. at a smaller dose of a preparation it is possible to reach higher efficiency of its action. If bioavailability Glibenclamid in tablets on 5 mg makes 29-69%, it micronized forms - 100%.

Glibenclamid (Maninil) (5 mg) - are recommended to be accepted for 30-40 mines before food intake, and it micronized forms - for 7-8 minutes the action Maximum micronized Glibenclamid (Maninil) almost completely coincides with postadsorb hyperglicemic, therefore at the patients receiving micronized the forms of a preparation, are much less often observed hypoglycemic conditions and if develop proceed in the easy form.

Glipizid (Glibinez retard) - it is applied to treatment of a diabetes of type 2 since 1971 and on force hypoglycemic actions almost corresponds Glibenclamid's (Maninil). It quickly also is completely absorbed from a gastroenteric path. The biological half-life period in plasma makes 2-4 hours, hypoglicemic action proceeds 6-12 hours, and it retard the form possesses duration of action 24 hours.

Together with it medicinal forms of known preparations (Gliclazid (Diabeton Slow Liberation (SL) and Glipizid (Glibinez retard)), possessing the prolonged action are received. Prolongation of action of these preparations is caused by use of the technologies, allowing delay suction a preparation from intestines.

Gliclazid (Diabeton Slow Liberation (SL) - it is offered in quality hypoglycemic a preparation in 1970 Gliclazid (Diabeton Slow Liberation (SL) is also a preparation of II generation, its daily dose makes 30-120 mg (is issued in tablets on 30 mg). The researches carried out by us have shown, that at treatment Gliclazid (Diabeton Slow Liberation (SL) at patients authentic decrease in aggregation thrombocytes, substantial growth of an index relative disaggregation, increase heparine and fibrinolitic activity, tolerance increase to heparine's was noticed, that allowed to speak about normalizing influence Gliclazid's (Diabeton) on a functional condition of blood plates. The authentic tendency to improvement aggregation functions eritrocytes, and also reduction of viscosity of blood is noted at small pressure of shift. Plazma-koagul factors of curling of blood, fibrinoliz, indicators albuminous and lipid an exchange also tended to normalisation. It stabilises a current microangiopatias and even causes in some cases return development.

Glicvidon (Glurenorm) is also to derivatives Sulfanilurea, and it also carry to preparations of the second generation. However, as well as Gliclazid, under the characteristics it not completely possesses all characteristics shown to this group. The preparation is issued in tablets on 30 mg, and the daily dose make 30-120 mg. Difference Glicvidon (Glurenorm) from preparations of this group that 95% accepted in a medicine are allocated through a gastroenteric path and only 5% - through kidneys whereas almost 100% Chlorpropamide, and 50% Glibenclamid excret with urine. Hypoglicemic action Glicvidon (Glurenorm) is weaker in comparison with the listed preparations, but it happens enough for soft clinical effect.

Besides it, to the big satisfaction endocrinologists in second half 90th years for treatment a diabetes 2 types have been offered Glimepirid. It is the first preparation Sulfanilurea, possessing the prolonged action and a low therapeutic dose (1-4 mg a day) in comparison with other preparations Sulfanilurea. These differences have allowed to carry Glimepirid to III generation of preparations Sulfanilurea.

Glimepirid - the first preparation Sulfanilurea, possessing the prolonged action and a low therapeutic dose (1-4 mg a day) in comparison with other preparations Sulfanilurea. These differences have allowed to carry it to the third generation (generation) of preparations Sulfanilurea. The half-life period Glimepirid longer (more than 5 hours), than at other preparations of this group, as provides its therapeutic efficiency within days. The preparation is appointed once a day in a dose of 1-4 mg, as much as possible recommended dose - 6 mg. Glimepirid completely metabolized in a liver to metabol inactive products.

For many years various pharmaceutical firms carry out researches on search new peroral hypoglicemic preparations. One of such workings out is synthesis new peroral hypoglicemic substances – Repaglinid's, being to derivatives benzoic acids. Repaglinid structurally concerns to Metglitinid's, which has non Sulfanil a certain part of a molecule Glibenclamid's and similarly Sulfanilurea to preparations stimulates secretion of insulin by the mechanism described for Sulfanilurea of preparations.

Biguanids. The second group peroral hypoglicemic preparations concern Biguanids which are presented fenetilbiguanid's (Fenformin), N, N – dimetilbiguanid's (Metformin) and L-butilbiguanid's (Buformin).

Distinction of a chemical structure of the named preparations is reflected and on them pharmacodinamic effect, causing only insignificant difference in display hypoglycemic activity of each of them a little. However, Metformin ar'not metabolized in an organism and excret kidneys in not changed kind, whereas Fenformin only on 50% excret in not changed kind, and other part metabolised in a liver. These preparations do not change secretion of insulin and do not give effect in its absence. Biguanids increase in the presence of insulin peripheral recycling of glucose, reduce gluconeogenez, raise recycling of glucose by intestines that is shown by decrease in level of glucose in the blood flowing from intestines; and also reduce the raised maintenance of insulin in whey of blood at the patients, suffering adiposity and a diabetes 2 types. Their long application positively influences on lipid an exchange (decrease in level of cholesterol, trio-acylglicerids). Biguanids increase quantity GLUT-4 that is shown in improvement of transport of glucose through a cage membrane. This effect speaks potentiate their influence on insulin action. A scene of action Biguanids, possibly, is also mitochondrial the membrane. Oppressing gluconeogenez, Biguanids promote maintenance increase lactate's, piruvat's, alanin's, - the substances which are predecessors of glucose in process gluconeogenez's. Whereas at action Biguanids the quantity increasing lactate's exceeds formation piruvat's, it can be a basis for development dairy-sour acydoz's (lactat-acydoz).

In Russia, as well as worldwide, from group Biguanids it is applied only Metformin.

Farmakokinetic parametres Metformin's.

Half-life period Metformin.makes 1, 5-3 hours. The preparation is issued in tablets for 0, 5 and 0, 85 Therapeutic doses 1-2 g a day (a maximum to 2, 55-3 g in day).

Hypoglicemic action Metformin.is caused by several mechanisms

Decrease in level of glucose in the blood flowing from a liver, testifies to reduction, both speed, and total of the glucose produced by a liver that is a consequence of inhibition gluconeogenez's by means of oxidation oppression lipids. Under influence Metformin's glucose recycling on periphery owing to activation postreceptor mechanisms of action of insulin and in particular tirozinkinaza's

and fosfotirozin fosfotaza's raises. Besides, peripheral effects of action Metformin's are mediated also by its specific influence on synthesis and a pool of glucosic conveyors in a cage. Recycling of glucose mucous intestines raises. The quantity of glucosic conveyors (GLUT-1, GLUT-3 and GLUT-4) increases under influence Metformin's in a plasmatic membrane, both adipocities, and monocytes. Glucose transport in ebdotelium's and smooth muscles of vessels, and also in a heart muscle raises. This influence decrease insulin resistance at patients of a diabetes of type 2 under influence Metformin's speaks. Sensitivity increase to insulin thus is not accompanied by increase in its secretion by a pancreas. Thus against reduction insulin resistance decreases bazal insulin level in blood whey. At the patients who are on treatment Metformin's, decrease in weight of a body, contrary to that can take place at overdose Sulfanilurea preparations and insulin is observed. And, decrease in weight of a body occurs mainly at the expense of reduction of a fatty fabric. Besides, Metformin's promotes decrease lipids in blood whey.

Important! In Russia Diagnostics of fractions lipids practically is not considered competently to select AntiLipidemic Therapy (the note of the author) though, it is important both for preventive maintenance and diabetes treatment, and for preventive maintenance atherogenesis and atherosclerosis treatments (the note of the author).

At treatment Metformin's concentration of the general cholesterol, trio-acylglicerids decreases, lipoproteids low and very low density and level lipoproteids high density that positive impact on a current macroangiopatias makes raises.

Last years it is established, that under the influence of Metformin's raises fibrinoliz which is lowered at patients with a diabetes 2 of type and is the additional factor trombo formation's and vascular complications of a diabetes. The basic mechanism of action Metformin's on increase fibrinoliz's is level decrease inhibitor's the activator plazminogen's-1, that takes place at patients with type 2 diabetes without dependence from its dose. Besides activity decrease inhibitor's the activator plazminogena-1, Metformin reduces proliferation smooth muscle cages as well in a vascular wall *in vitro* and speed atherogenez's at animals.

Metformin does not reduce the glucose maintenance in blood below its normal level, that is why at treatment of patients with a diabetes this preparation are absent hypoglycemic conditions.

It was above noticed, that Sulfanilurea preparations stimulate insulin secretion, and Metformin promotes glucose recycling by peripheral fabrics. Preparations, influencing various mechanisms, promote the best indemnification of a diabetes. The combined therapy Sulfanilurea and Metformin's is applied by preparations for a long time and with the good effect, therefore some firms have already mastered manufacture of preparations of the combined action.

Inhibitors the alpha-glukozidaz (Acarboza) is third group peroral hypoglycemic preparations which are widely applied to diabetes treatment last 8-10 years for the purpose of decrease suction from intestines of carbohydrates and which basic action is connected with oppression of activity of the enzymes participating in digestion of carbohydrates. It is known, that food carbohydrates, more than 60 which % are presented by starch, in a gastroenteric path at first are hydrolyzed by specific enzymes (Glucozidazes: beta-glukuronidaza, beta-glukozaminidaza, an alpha-glukozidaza, etc.) And then break up to monosacharids. The last are absorbed through a mucous membrane of intestines and arrive in the central blood circulation. Recently it is shown, that besides the basic action - inhibition glucozidaz's, Inhibitors an alpha-glukozidazs improve peripheral use of glucose by means of increase in an expression of gene GLUT-4. The preparation is well transferred by patients and can be applied to treatment of patients with type 2 diabetes in that case when it is not possible to reach indemnification of a carbohydrate exchange only on a diet and adequate physical activity.

Usual doses Acarboza's make from 50 mg a day with gradual increase to 50 mg 3 times a day, and then to 100 mg 3 times a day. In this case it is possible to avoid such undesirable phenomena, as discomfort in a gastroenteric path, flatulence, a liquid chair. The preparation is necessary for accepting with the first drink of food (during meal). At monotherapy Acarboza's is absent hypoglycemia.

Potenciators (or Sensitizers) insulin actions raise sensitivity of peripheral fabrics to insulin. Preparations of this group concern Glitazons or Tiazolidindions - Pioglitazon and Rosiglitazon.

Algorithm of treatment of a diabetes of type 2

Thus, the modern algorithm of treatment diabetes type 2

includes: Diet Therapy, change of a way of life (regular physical activity, refusal of smoking, training of the patient), and in the absence of effect - additional application Acarbosa's. In the presence of adiposity can be recommended Anorectics. In case of insufficient effect from reception Acarbosa's at superfluous weight of a body (ideal weight of a body of 30 kg/m^2 and more) the combined treatment with Metformin's or with preparations Sulfanilurea (at ideal weight of a body to 30 kg/m^2). In these cases the combination Metformin's with Sulfanilurea preparations (in case of superfluous weight) is possible. Sensitizers insulin (Pioglitazon, usually on 30 mg once a day) can be applied in the form of monotherapy or in a combination with Sulfanilurea preparations and Metformin's. All listed peroral hypoglycemic can be used preparations as monotherapy or in their combination.

At unsatisfactory effect from spent treatment further it is shown Insulinotherapy

Criteria for appointment Insulinotherapy at type 2 diabetes are: absence of indemnification of a diabetes at use Diet Therapy in a combination with Inhibitors glucozidazs, Biguanids, Sensitizers insulin or Secretogenes insulin (Sulfanilurea and the preparations, derivative amino acids) and so-called secondary insulin resistance to peroral to preparations. Herbal medicine + Hypoglicemic preparations usually helps. This combination levels action of synthetic preparations (the note of the author).

According to various authors, secondary resistance to Sulfanilurea to preparations meets at 5-20% of the patients, 2 types suffering by a diabetes, and is connected with decrease in residual secretion of insulin. Secondary resistance to peroral to preparations in 1 year from the disease beginning comes to light at 4, 1% of patients, and in 3 years - at 11, 4%, therefore it is necessary to change therapy (the note of the author).

Studying patogenez secondary resistance to peroral to preparations has allowed to establish its various mechanisms.

At a part of patients secondary resistance to hypoglycemic peroral to preparations proceeds with the lowered residual secretion of insulin and C – peptid's whereas antibodies to cellular antigenes of islets of a pancreas are absent.

Proceeding from features of a clinical current of illness, these patients can be divided into 2 groups

- Patients with a diabetes of type 2 with time insulin need;
- Patients with constant requirement for insulin or even with insulin-dependence (LADA-subtype).

The first group is made by patients with a diabetes duration of 10 years and more and bodies having superfluous weight.

For indemnification of a carbohydrate exchange it is recommended in these cases two medical tactics. The first - full transfer of patients on Insulinotherapy during small time (2, 5-4 months). This time happens enough for removal glucose toxicity and lipo toxicity to restoration of sensitivity of beta cages to preparations Sulfanilurea and restoration of reserve possibilities of islets of a pancreas. An obligatory condition for removal glucose toxicity is achievement of full indemnification of a diabetes in carrying out Insulinotherapy. Further patients again translate on peroral therapy with good or satisfactory results of indemnification.

Second tactics consists in carrying out of the combined therapy by insulin and peroral hypoglycemic preparations

2 types with secondary resistance to peroral to preparations both tactics of treatment by us are applied to treatment of patients of a diabetes within 10-12 years. Used the combined therapy by insulin in a daily dose, as a rule, no more than 30 UNITS a day (usually insulin of average duration of action). It is More expedient to appoint insulin to night (in 22 or 23). To the beginning of action of such preparation of insulin to fall morning hour or for that period when superfluous formation of glucose by a liver takes place. Result of it is considerable decrease glicemia's on an empty stomach. In some cases double introduction of the specified preparations of insulin (in the morning and at 22-23) is necessary. Within day for maintenance hypoglycemic effect reception Sulfanilurea preparations (Glipirid in a dose of 2-3 mg a day, Glibenclamid in a dose of 10-15 mg a day or Gliclazid in a dose of 60-180 mg a day) is recommended. Insulinotherapy it is recommended to begin from 10-12 the UNIT and to increase on 2-4. Every 3-4 day until glicemia on an empty stomach will not decrease to 5-6,8 mmol/l. Definition glicemia's within day is necessary at least once a week in selection of doses hypoglycemic preparations (insulin and peroral preparations). It is Extremely necessary besides definition glicemia's on an empty stomach to have data about the glucose maintenance in blood before a dinner and a supper, and also

through 1 hour after food intake.

When it is required to patients Insulinotherapy, last can be spent in a mode of repeated injections or more often in a mode of double injections. In the latter case good results are received by us at use of preparations of insulin of the combined action. Preparations of insulin of the combined action enter before a breakfast and before a supper.

Besides it the mode of double introduction can be used at application of preparations of insulin short and average duration of action. Thus before a breakfast it is necessary to apply insulin short and average duration of action, before a supper - a preparation of insulin of short action and before a dream (in 22 or 23) - insulin of average duration of action. A parity of a preparation of insulin of short action to insulin of average duration of action in the morning 1:3 (25% and 75%), and in the evening - 1:2 or even 1:1. The mode of repeated injections of insulin which is necessary for the control of a diabetes of type 1, was applied and to treatment of patients of a diabetes 2 types. In these cases as insulin базального it is possible to use actions both insulin of average duration of action, and preparations of insulin of long action. However advantage of a mode of repeated injections before a mode of double introduction of insulin practically is not present.

As to an insulin dose for indemnification of a diabetes of type 2 the daily dose from calculation 0 is required, 6-8 unit on 1 kg of weight of a body. In some cases the preparation dose should be increased to 0, 9 -1, 0 unit on 1 kg and even it is more. It speaks insulin resistance, so characteristic for type 2 diabetes. At achievement of indemnification of a diabetes in such cases insulin need decreases, accordingly, doses of the insulin necessary for maintenance of indemnification of a diabetes decrease.

Achievement of indemnification of a diabetes 2 types is an obligatory condition of preventive maintenance of vascular complications, early invation and raised letal this disease.

But it it is possible to do by application Antioxidants and Immunomodulators - Combination Alvitil (tablets) + Derinat (candles).

In second half 90x years for treatment of a diabetes 2 types have been offered Amaril (Glimepirid) an original preparation Sulfanilurea the third generation

It is the first of all preparations Sulfanilurea, possessing the true prolonged action (not at the expense of change of speed of liberation from a capsule or a tablet) and a low therapeutic dose (14 mg a day).

It is necessary to consider in more details certain differences of the mechanism hypoglycemic actions Amaril's and its influences on a condition of cardiovascular function, last aspects of action of preparations Sulfanilurea are repeatedly discussed in the literature.

Throughout long time was considered, that all Sulfanilurea preparations carry out the stimulating influence on insulin secretions by the identical mechanism, by means of them aggregation with receptors Sulfanilurea which are compound components of membranes of a b-cage. However clinical physicians know for a long time, that hypoglicemic action of preparations Sulfanilurea varies in a considerable range that allowed to come out with assumptions of presence of some distinctions in molecular mechanisms of action of preparations of this group.

Studying of molecular mechanisms of action Sulfanilurea preparations has allowed to obtain the data which throwing light on processes of interaction of various stimulators of secretion of insulin and have shown, that Secretogens insulin, despite the identical definitive effect shown in strengthening of secretion and liberation of insulin from b-cages, carry out this action through involving in corresponding process of various albuminous and alarm molecules.

ATF-SENSITIVE calium channels are the primary structures co-operating with various Secretogenes of insulin

ATF-SENSITIVE calium channels represent a complex including a receptor 1 to Sulfanilurea (fiber with мол.м. 140000 (SUR 1)) and specific fiber a so-called internal cleaner calium channels or rectifying subunit KIR6.2. The gene coding receptor SUR 1 is localised on a chromosome 11p15.1 and concerns family ATF-connecting of cassette fibers (ABC-proteins), having 17 transmembran domains (TMD) in which there are two nucleotide-connecting site NBF 1 and NBF 2, specifically complexing with Mg2+ADF/ATF (K Ueda., *et al*. 1999). ATF-sensitive channels represent as though two fibers SUR 1 and KIR6.2, which co-expressing together. Locus KIR6.2 settles down in gene SUR 1, - on the same 11p15.1 to a chromosome.

Thus, ATF-SENSITIVE calium channels gather and designed from two various subunits a receptor Sulfanilurea, which belongs to family of ATF-CONNECTING cartridges, and subunits calium channels (KIR6x), forming a time and regulator subunit. Three

isoforms of a receptor Sulfanilurea are cloned: SUR 1 high affinity a receptor both SUR 2 and SUR 3 low-affinity receptors. Structurally calium channels in various fabrics not the same on components subinits so, in b-cages of islets of a pancreas and glucose-sensitive neurons hipotalamus's they consist from SUR 1/KIR6.2; in a muscle of heart from SUR 2A/KIR6.2 and in smooth muscle cages of vessels from SUR 2B/KIR6.1 (or KIR6.2).

E. Brekardm., *et al*. (1999) have shown, that ability of various preparations (Glibenclamid, Glipizid, Tolbutamid and Meglitinid) to inhibit calium channels (SUR 1/KIR6.2 and SUR 2B/KIR6.2) was in 36 times above, than their affinity to aggregation with these receptors. For closing calium the channel linkage of one their four Sulfanilurea connecting places on a channel complex which is presented octometric by structure (SUR/KIR6x) 4 is necessary.

Key to understanding of the mechanism of action of various preparations Sulfanilurea were researches in which it has been shown, that the last aggregation with certain sites transmembran domains (TMD).

Glibenclamid aggregation with a site 15 MTD, and Tolbutamid with 1217 TMD, that testifies about modully the structural and functional organisation ATF-SENSITIVE calium channels I. Uhde., *et al*. 1999).

It has visually been confirmed in researches A.P. Babenko., *et al*. (1999) which have shown, that Glibenclamid as a result conformation changes breaks interaction between NBF 1 and 2 SUR 1 on sites TMD 1217 and especially TMD 15. It, in turn, causes moving of complex TMD 2K1P6.2, which is in direct contact with TMD 15 SUR 1 to cause a condition closed calium channels. Such mechanism demands intact aminotermal end KIR6.2. Thus, linkage Sulfanilurea with SUR 1 definitely causes the latent reduction of necessary durability of communication between SUR 1 and KIR6.2, which is required for preservation KIR6.2, at least, partially in an open condition. These received *in vitro* data prove to be true clinical supervision.

The age reasons of occurrence of a diabetes 2 types at children

Homozygous mutations of gene KIR6.2 in pancreas islets are the reason of a family constant a hyperinsulinemic hypoglicemia's at newborns (Thomas P.M., *et al*. 1996). The similar pathological condition meets at monogene mutations of a gene of a receptor Sulfanilurea (Thomas P., *et al*. 1995).

Researches of last years have shown, that at patients a diabetes 2 types come to light mutations of gene SUR 1 (Hani E.H., *et al*. 1997) and mutations of gene KIR6.2 (Hani E.H., *et al*. 1998). Presence of polymorphism of two specified genes regulating synthesis of fibers, being subunits ATF-DEPENDENT calium channels, in certain degree explains heterogeneity of a diabetes 2 types, throwing light on mechanisms hyperinsulinemia's at a diabetes 2 types, and also the assumption of the reasons of the various answer of patients with a diabetes on treatment peroral hypoglycemic preparations allows to come out.

Opening and closing ATF-SENSITIVE calium channels, and, hence, iniciation secretions of insulin and its inhibition, are provided aggregation ATF with various subunits calium channels. Linkage ATF with carboxiterminal domain KIR6.2 stabilises sissociation SUR 1 and KIR6.2, caused Glibenclamid's and promotes closing calium channels. Aggregation ATF with NBF 1 and Mg2 + ADF with NBF 2 on SUR 1 causes opening calium channels.

In spite of the fact that Glibenclamid's and Glimepirid (Amaril) make stimulating impact on secretion of insulin by means of closing ATF-SENSITIVE calium channels, the mechanism of this influence has certain differences.

Constants of speed of association at Amaril's in 2,23 times, and speeds dissociation in 810 times above, than at Glibenclamid's (G. Muller., *et al*. 1994). These data testify that affinity Amaril's to a receptor Sulifanilurea in 23 times lower, than at Glibenclamid's. Besides it, Glibenclamid aggragation with polypeptid a receptor, having mol.mass 140 kilodalton (KDa), whereas Amaril with polypeptid's the same receptor, but having mol.mass 65 KDa which is designated as SUR X. The carried out additional researches have shown, that Glibenclamid, besides the core aggragation with polypeptid's 140 KDa, also specifically aggragation with fibers with мол.м. 40 and 65 KDa (Aschcroft F.M., Gribble F.M., 1999), that has allowed to come out with the assumption that Glibenclamid aggragation with fiber SUR X though, affinity to such aggragation at it also can much more low, than at Amaril's. All listed above allows to consider, that fibers-targets of a receptor to Sulfanilurea for Glibenclamid's and Amaril's are various: for Glibenclamid SUR 1, for Amaril's SUR X. Both fibers co-operate with each other and

supervise through KIR6.2 opening and closing calium channels, and, hence, processes of synthesis and insulin liberation in a pancreas b-cage.

Studying of haemodynamic indicators *in vivo* at application of various preparations Sulfanilurea (Glimepirid's, Gliclazid's, Glibenclamid's), executed in the conditions of controllable experiments on dogs (A. Vegh, J.G. Papp, 1996), has shown, that all preparations considerably reduce frequency ventricular extrasystoles, caused 25-minute occulusion a coronary artery.

However only Glimepirid and Gliclazid, but not Glibenclamid, authentically reduced, both quantity of premature warm reductions, and frequency ventricular tachycardias in a myocardium ischemia. Almost similar data have been received in experiment on rats with endotoxin a shock (К Geisen, 1996). Thus intravenous introduction Glibenclamid in a dose of 2 mg/kg caused considerably большее increase the pressure, than application Glimepirid's. At healthy rats double intravenous application Glibenclamid in a dose of 20 mg/kg with an interval 4 minutes was accompanied by signs of an ischemia of a myocardium on an electrocardiogram practically at all animals while at introduction Glimepirid's ischemic changes of a myocardium actually were absent at rats with streptozotocyn a diabetes. Glibenclamid in all cases caused deadly cardiogenic a shock which development was preceded by the expressed changes on an electrocardiogram while at application Glimepirid's the shock has developed only at 1/5 animals.

The additional researches spent by authors on dogs with an open thorax at carrying out by it intracoronar of infusion Glibenclamid, Gliclazid and Glipirid's in equivalent hypoglycemic doses, have shown decrease in a coronary blood-groove, increase of resistance of coronary vessels, oppression of mechanical activity of heart, strengthening extraction oxygen a myocardium, level decrease calium in blood whey, moderate lifting endocardial segment ST. And at application Glimepirid's the listed changes were authentically less expressed, than at introduction Glibenclamid and Gliclazid's.

From time of application of preparations Sulfanilurea for treatment of a diabetes 2 types do not stop discussions about uot pancreatic (peripheral) action of preparations Sulfanilurea

In laboratory, guided G. Muller, researches are for many years carried out in this direction. At studying *in vitro* and *in vivo* influence Amaril's, Glipirid's, Glibenclamid and Gliclazid on the maximum decrease in level of glucose of blood and the minimum increase in secretion of insulin within 36 hours after reception of the listed preparations, has been established, that Amaril in a dose of 90 mkg/kg caused the maximum decrease in the maintenance of glucose in blood at the minimum secretion of insulin; Glipirid's in a dose of 180 mkg/kg possessed the lowest hypoglicemic activity and caused the maximum increase in secretion of insulin; Glibenclamid, in a dose of 90 mkg/kg and Gliclazid in a dose of 1, 8 mg/kg occupied intermediate position between two extreme indicators. Curves of dynamics of concentration of insulin and glucose in blood at application of the specified preparations Sulfanilurea were practically identical. However at factor definition (average increase in level of insulin in plasma to average decrease in the maintenance of glucose in blood) these indicators have appeared unequal: Amaril 0, 03; Gliclazid 0, 07; Glipirid's 0, 11 and Glibenclamid, s0, 16. This distinction was a consequence of lower secretion of insulin: at Amaril's an insulin average level in plasma 0, 6 mked/ml, at Gliclazid 1, 3; at Glipirid's 1, 6 and Glibenclamid's 3, 3 mked/ml (G. Muller, 2000).

The least stimulating influence Amaril's on insulin secretion provides smaller risk of development hypoglicemia's

As have shown researches on isolated cardiomiocytes rats, peripheral hypoglycemic the effect Glipirid's is caused by its influence on an expression of glucosic conveyors (GLUT-1 and GLUT-4 on 164 and 148% accordingly), that was accompanied by increase in absorption of glucose in a cardiac muscle (J. Eckel).

Results of these researches show, that preparations Sulfanilurea have to some extent expressivenesses peripheral effect, but this effect is more expressed at Amaril's (Glimepirid).

Thus, peripheral action Amaril's is caused by activation of translocation GLUT-4 and GLUT-1, and also increase in synthesis of fat and glicogen's in fatty and muscular fabrics accordingly. Amaril as have shown researches J.E. Pessin., *et al*. (1999), etc., increased in a plasmatic membrane adipocytes quantity GLUT-4 in 33, 5 times, and insulin in 78 times. Besides, Amaril causes dephosphorylation transfer GLUT-4, that is obligate a condition of stimulation of

key enzymes lipoliz's (glycerine-3-fosfatatiltransferaza) and glucogenez's (glicogen-sintetaza). Amaril, as well as Glibenclamid (Maninil), raises activity factor glicogen-sintetaza's to 45-50% from the maximum effect of insulin. Simultaneously activity glycerine-3-fosfatatiltransferazy increases to 35-40% from the maximum influence of insulin. Amaril oppresses activity proteincinaza's A and lipoliz by means of activation ts-ts-specific fosfodiezteraza's and glicozilfosfatidilinozitozol-specific fosfolipaza's B with the subsequent reduction of the maintenance cicle-AMF in cytoashes. At Amaril's this effect is expressed more than at Glibenclamid's. Under the influence of Amaril's speed of formation of glucose a liver that is mediated by maintenance increase fruktozo-6-bisfosfat's decreases.

Thus, Amaril and Glibenclamid the glucose occurring to the help glicozilfosfatidilinozitol-specific fosfolipaza's B has the peripheral an effect through processes dephosphorylation transfer and activations of key enzymes of transport and a metabolism.

Amaril possesses lower, than other preparations Sulfanilurea, glucogonotropic activity

One more distinctive feature of action Amaril's is its influence on phosphorylation tirozins the squirrel caveolon's. It membran fiber with mol.mass.29к0, which together with other fibers (flottilin, etc.) is localised in certain sites of a membrane in caveolas, representing intussusceptions a membrane and types of cages present on the majority (fatty, epitalial, endothelial, miocytes, etc.). Now researches on specification of the biological importance caveolin's are carried out. It is shown, that Amaril complexed with caveolin's fatty cages and it is not excluded, what exactly this mechanism explains specificity of influence Amaril's on activization of recycling of glucose in a fatty fabric.

In researches on dogs it is shown, that at intravenous introduction Glibenclamid's in a dose of 0, 15 mg/kg, Glipizid's in a dose of 1,5 mg/kg caused immediate increase of arterial pressure whereas introduction Amaril's in a dose of 0,45 mg/kg did not cause any changes of arterial pressure (D.W. Landry., *et al*. 1992).

At the same experimental researches infusion identical on сахароснижающей activity of doses Amaril's (2 mkg/kg/mines), Glibenclamid's (25 mkg/kg/mines) or Gliclazid's (500 mkg/kg/mines) within 1 minute in the left descending coronal artery of heart caused reduction of a coronary blood-groove with resistance increase in them, easing of mechanical work of the heart, the strengthened deducing of oxygen from a cardiac muscle. Influence on the listed indicators of infusion Amaril's were considerably less expressed in comparison with infusion Gliclazid's or Glibenclamid. On the isolated muscle of heart Glibenclamid. caused dose-dependent increase of a threshold of sensitivity to an electricity, time of conductivity and the effective refractory period, reduced ability of heart to automatism. Amaril in the same concentration practically did not render influence on the listed indicators of activity of heart (G. BallangiPordmy., *et al*. 1992). It shows all, that Amaril has considerably smaller influence on cardiovascular system, than traditional Sulfanilurea preparations - Glibenclamid, Gliclazid or Glipizid.

There are messages about antiagrregation and antiaterogenic effect Amaril's. Amaril (Glimepirid) in concentration 40 microns selectively inhibit ciclooxigenaza's transformation arachidonic also reduces acids in tromboxan A2 which promotes aggregation trombocytes whereas Glibenclamid oppresses how ciclooxigenaza's (COG) so lipooxigenaza's (LOG), which supervises transformation arachidonic acids in leukotrienes. Gliclazid does not render any influence neither on ciclooxigenaza's, nor on lipooxigenaza's (Y. Ozaki., *et al*. 1992).

Application Amaril's for patients a diabetes 2 types 30 minutes prior to a breakfast or directly ahead of it have not revealed essential distinctions in pharmacokinetics, hypoglycemic action Amaril's, therefore the preparation is recommended to be accepted to or during a breakfast.

Combination of preparations at treatment

Joint uncontrollable or controllable application Amaril's with acetylsalicylic acid, Cemetidin's or Ranitidine's, Ramipril's, blocators Calcium channels, Fibrates, not steroid anti-inflammatory preparations or tireoid hormones practically does not change pharmacokinetics and action Amaril's and is well transferred by patients.

Potentiate effect Amaril's

Hypoglikemichesky action Amaril's amplifies Salicilats, Suiganilamids, Chloramfenicol's, Cumerines, Probenecid's, Inhibitors monoavinooxida's, b-adrenergic preparations. Such preparations as Nicotinic acid, Izoniazid, Corticosterionds, Oral Contraceptives,

Simpatomimetics, an Estrogen, Phenitoin, Tiazid, on the contrary, reduces hypoglycemic action Amaril's and can cause hypoglycemic at their joint application, and at their cancellation can arise hypoglycemia's therefore at combitation application of the specified preparations it is necessary to correct dose Amaril's accordingly.

Amaril's it is appointed once a day in a dose of 123 or 4 mg. In case of absence of indemnification of a carbohydrate exchange on the minimum dose (12 mg a day) should be spent increase of doses of a preparation with an interval of 7-10 days. As much as possible recommended dose of 6 mg. It is shown, that efficiency of action Amaril's is identical at reception of a certain dose unitary (morning) or the same dose divided into 2 receptions (in the morning and in the evening), therefore unitary reception of a preparation is more preferable for many reasons (less possibility to forget about reception of the second part of a dose, necessity to have a preparation at itself etc.). In case of development hypoglycemic on a dose of 1 mg a day should be cancelled a preparation, as diabetes indemnification thus can be reached only application of a diet, regular physical activity.

Thus, for medicamentous treatment of a diabetes 2 types are used various peroral means (Secretogenes insulin, Biguanids, as in the form of monotherapy, and the combined treatment).

Cautions for reception of preparations

It is necessary to mean, that simultaneous application of two preparations possessing the identical mechanism of action (various Secretogenes) is not recommended. Use Secretogenes insulin together with Biguanids or Sensitizers is more preferable. In the absence of effect peroral preparations (as in the form of monotherapy, and the combined treatment) transfer of patients on insulinotherapy is necessary. New approaches in modern tactics of treatment of a diabetes 2 types are use prandial regulators glicemia's, and also the early combined therapy. A treatment basis there are preparations Sulfanilurea, which mechanism of action is studied well enough. In an arsenal endocrinogolist's, there are well-known and applied in clinical practice almost all Sulfanilurea preparations 2 generations, as in the form of preparations usual for them duration of action, and the medicinal forms possessing prolonged effect of action as a result of delay suction in intestines. Special interest represents a new and original preparation of the prolonged action Glimepirid (Amaril) which has essential differences in the mechanism hypoglycemic actions and its influences on cardiovascular activity in comparison with traditional preparations Sulfanilurea, that specifies in its certain advantages.

Sulfanilamids for treatment of a diabetes 2 types

I will give the short characteristic to the most widespread Sulfanilamids.

Tolbutamid (Butamid, Orabet), tablets on 0, 25 and 0, 5g - the least active among Sulfanilamids, possesses the shortest duration of action (6-10) and 2-3 times a day can be appointed. Though it is one of the first preparations Sulfanilurea, it is applied till now, since. Has few by-effects.

Chlorpropamid (Diabenez), tablets on 0, 1 and 0, 25g - has the greatest duration of action (more than 24, is accepted once a day, in the morning. Causes many by-effects, very serious - long and difficultly eliminated hypoglycemia. Were observed also expressed hyponatrienia and antabuse such reactions. Now Chlorpropamid it is used seldom.

Glibenclamid (Maninil, Betanaz, Daonil, Euglucon), tablets on 5 mg - one of often used in Europe Sulfanilamids. 2 times a day, in the morning and are appointed, as a rule, in the evening. The modern pharmaceutical form - micronized Maninil on 1, 75 and 3, 5 mg, it is better transferred and more powerfully operates.

Glipizid (Movogleken, Antidiab, Glibenez, Minidiab), tablets on 5 mg/tab.

Similarly Glicenclamid's, this preparation in 100 times is more active Tolbutamid's duration of action reaches 10 hours, is usually appointed 2 times a day.

Gliclazid (Diabeton, Predian, Glidiab, Glizid), tablets on 80 mg - it pharmacokinetic parametres are somewhere in between parametres Glibenclamid's and Glipizid's. 2 times a day are usually appointed, now is available Diabeton the modified liberation, it accept once a day.

Glicvidon (Grurenorm), tablets on 30 and 60 mg. The preparation metabolized a liver completely to the inactive form, therefore can be applied at chronic nephritic insufficiency. Practically does not cause heavy hypoglucemic, therefore it is especially shown elderly patients.

To modern Sulfanilamids 3 generations concerns Glimepirid (Amaril), tablets on 1, 2, 3, 4 mg. Possesses powerful prolonged hypoglycemic the action close to Maninil's. 1 time a day, the maximum daily dose of 6 mg is applied.

Collateral actions Sulfanilamids

Heavy hypoglicemia's meet infrequently at treatment Sulfanilamids, mainly, at the patients receiving Chlorpropamid or Glibenclamid (Maninil). The risk of development hypoglicemia's at elderly patients with chronic nephritic insufficiency or against sharp intercurrent diseases when food intake is reduced is especially high. At elderly hypoglicemia's it is shown basically by the mental or neurologic symptoms complicating its recognition. In this connection it is not recommended to appoint it is long operating Sulfanilamids to older persons!

Very seldom skin hypersensitivity or system reaction develop in the first weeks of treatment Sulfanilamids hemopoiesis, dyspepsia.

As alcohol suppresses gluconeogenez in a liver its reception can cause hypoglicemia's in the patient receiving Sulfanilamids.

Reserpin, Klofellin (Clonidine) and not selective β-blokatory also promote development hypoglicemia's, suppressing in an organism contrainsular mechanisms of regulation and, besides, can mask early symptoms hypoglicemia's, therefore to apply them in a combination it is not desirable (the note of the author).

Important! Reduce action Sulfanilamids, Diuretic, Glucocorticoids, Simpatomimetics and Nicotinic Acid. It should be considered in clinical practice (the note of the author).

Biguanids (Metformin) for treatment of a diabetes 2 types

Biguanids, derivatives Guanidin's, strengthen glucose absorption by skeletal muscles. Biguanids stimulate production lactat's in muscles and-or bodies of a belly cavity, therefore at many patients receiving Biguanids, level lactat's is raised. However lactic acidoz develops only at patients with lowered elimination Biguanids and lactat's or at raised production lactat's, in particular, at patients with the lowered function of kidneys (they are counter-indicative at the raised level creatinin's whey), with illnesses of a liver, an alcoholism and is warm-pulmonary insufficiency. Dairy-sour acidoz it was especially often observed against reception Fenfotmin's and Buformin's because of what they are laid off.

For today only Metformin (Glucofag, Siofor, Diformin, Dianormet) 2 types are used in clinical practice for treatment of a diabetes. As Metformin reduces appetite and does not stimulate hyperinsulinemia's, its application is most justified at a diabetes corpulent, facilitating such patients observance of a diet and promoting decrease in weight of bodies. Metformin also improves lipid an exchange, reducing level lipoproteids low density.

Interest to Metformin's has sharply increased now. It is connected with features of the mechanism of action of this preparation. It is possible to tell, that basically Metformin raises sensitivity of fabrics to insulin, suppresses production of glucose a liver and, naturally, reduces glicemia's on an empty stomach, slows down suction glucose in gastrointestinal. There are also the additional effects of this preparation positively influencing a fatty exchange, coagulability of blood and arterial pressure.

The semideducing period Metformin which is completely soaked up in intestines and metanolized in a liver, makes 1, 5-3 hours and consequently it is appointed 2-3 times a day during time or after meal. Treatment begin with the minimum doses (0, 25-0, 5 g in the morning) to prevent collateral reactions in a kind dyspepsic the phenomena which are observed at 10% of patients, but at the majority quickly pass. Further, at necessity, the dose can be increased to 0, 5-0, 75 g by reception, appointing a preparation 3 times a day. A supporting dose - 0, 25-0, 5 g 3 times a day.

Treatment Biguanids is necessary for cancelling at once when at the patient disease of kidneys sharply develops, a liver or is warm-pulmonary insufficiency is shown.

Pharmacokinetics Biguanids

Buformin (Glibutid) - duration of action, 6-8 hours, elimination through kidneys, the period of semideducing of 4-5 hours, a single dose - 100-500 mg.

Metformin (Diformin) - duration of action, 3-6 hours, elimination through kidneys, the period of semideducing of 1-2 hours, a single dose - 500-850 mg.

As Suifanilamids basically stimulate insulin secretion, and Metformin improves, mainly, its action they can supplement

hypoclicemic action each other. The combination of these preparations does not raise risk of by-effects, is not accompanied by their adverse interaction and consequently they with success are combined at treatment of a diabetes of 2 type.

Combinations of preparations at treatment of a diabetes 2 types

The expediency of use of preparations Sulfanilurea is not subject to doubt, therefore as the major link patogenez's a diabetes of 2 type – secret defect β-cages. On the other hand, insulin resistance - almost constant sign of a diabetes 2 of type that causes necessity of application Metformin's.

Metformin in a combination with preparations Sulfanilurea - the component of effective treatment, is intensively used many years and allows to achieve decrease in a dose of preparations Sulfanilurea. According to the researchers, the combined therapy Metformin and preparations Sulfanilurea as is effective, as well as the combined therapy by insulin and preparations Sulfanilurea.

Acknowledgement of supervision of that the combined therapy Sulfanilurea and Metformin has essential advantages before monotherapy, promoted creation official forms of the preparation containing both components (Glibomet).

For achievement of main objectives of treatment of a diabetes it is necessary to change earlier established stereotype of treatment of patients and to pass to more aggressive tactics of therapy: to the early beginning of the combined treatment peroral hypoclycemic preparations, at some patients - practically from the moment of diagnosis statement.

Simplicity, efficiency and relative cheapness explain that fact, that Secretogenes successfully supplement Metformin. The combined preparation Glucovance - containing in one tablet Metformin and micronized the form Glibenclamid's (Maninil), the most perspective representative of the new form of antidiabetic preparations. It has appeared, that creation Glucovance obviously improves not only compliance the patient, but also reduces the general number and intensity of by-effects at the same or best efficiency.

Advantages Glucovance's before Glibomet's (Metformin 400 mg + Glibenclamid 2, 5 mg): Metformin forms soluble matrix in which particles micronized Glibenclamid's are in regular intervals distributed. It allows Glibenclamid's to operate faster non micronized forms. Fast achievement of peak of concentration Glibenclamid's allows to accept Glucovance during meal, it, in turn, reduces frequency gastrointerstinal the effects arising at reception Glibomet's. Doubtless advantage Glucovance - presence of 2 dosages (Metformin 500 + Glibenclamid's 2, 5, Metformin 500 + Glibenclamid's 5), that allows to pick up effective treatment faster.

Addition bazal insulin (type Monotard NM) in an average dose 0, 2 units on 1 kg of weight of a body to the spent combined therapy recommend to begin in the form of a unitary injection for night (22.00), usually the dose raises on 2 units each 3 days before achievement of target values glicemia's 3, 9-7, 2 mmol/l. In case of high initial level glycemia's the increase in a dose on 4 units is possible each 3 days.

Secondary resistance to Sulfanilamids to preparations

In spite of the fact that as the leading mechanism of development of a diabetes of 2nd type serves insulin resistance fabrics, secretion of insulin at these patients in the course of time also decreases, and consequently efficiency of treatment Sulfanilamids falls in due course: at 5-10% of patients annually and at the majority - in 12-15 years of therapy. Such loss of sensitivity is called as secondary resistance to Sulfanilamids, contrary to primary when they appear inefficient from the very beginning of treatment.

Resistance to Sulfanilamids is shown by progressing loss of weight, development hyperglicemia's on an empty stomach, postalimentary hyperglicemia's, increase glucozuria's and increase of level HbA1c.

At secondary resistance to Sulfanilamids the insulin combination insulines prolonged action's (IPA) and Sulfanilamids in the beginning is appointed. The probability of a positive effect of the combined therapy is high in that case when it is appointed at the earliest stages of development of secondary resistance. At level skinny glycemia's between 7, 5-9 mmol/l.

Application Pioglitazon's (Actos) - a preparation reducing insulin resistance is possible, allowing to lower dose prolonged action's (IPA) and in some cases it to cancel. Accept актос on 30 mg of 1 times a day. It can be combined both with Metformin's and with preparations Sulfanilamids.

But the most widespread scheme of the combined treatment consists that earlier appointed treatment Sulfanilamids is supplemented with small doses (8-10 units) preparations of average duration of action (for example, ADA or ready «mixts» - mixes of preparations of the short and prolonged action) 1-2 times a day (8.00, 21.00). The dose raises with step 2-4 units each 2-4 days. Thus dose Sulfanilamids should be maximum.

Such treatment can be combined with a low-calorie diet (1000-1200 kkal/days) at a diabetes at the corpulent.

At an inefficiency of a mode of unitary introduction of insulin it is entered 2 times a day, with the control glicemia's in critical points: on an empty stomach and at 17.00.

Usually necessary dose IPA makes 10-20 UNITS/DAYS requirement for insulin above, it testifies to full resistance to Sulfanilamids and then monotherapy by insulin is appointed, Sulfanilamids preparations are completely cancelled.

The arsenal hypoglycemic the preparations applied at treatment of a diabetes of 2 type, enough big also continues to replenish. Besides derivatives Sulfanilurea and Biguanids, Secretogenes, Derivatives of Amino Acids, Sensitasers insulin (Tiazolidindions), Inhibitors α-glukozidazy (Glucobay) and insulin here enter.

Regulators glycemia's for treatment of a diabetes 2 types

Being based on the important role of amino acids in the course of insulin secretion β-cages directly in the course of meal, scientists investigated hypoglycemic activity of analogues fenilalanin's, benzoic acids, synthesised Nateglinid and Repaglinid (Novonorm). But fenilalanin and benzoic acid contains in products (meat, milk, grain, fish, eggs, bean, dried fruit).

It should be used for diabetes treatment (the note of the author).

Natural acids

Fenilalanin represents aromatic amino acid which is a part some fibers, and besides is available in an organism in a free kind. From Fenilalanin's in an organism new very important amino acid Tirosin is formed. But to receive real advantage of this amino acid, presence of Vitamins B3, B6, Vitamin C, and also copper and gland is necessary.

For the person Fenilalanin's is irreplaceable amino acid as it is not developed by an organism independently, and it is delivered in an organism together with food. The given amino acid has 2 basic forms - L and D.

The L-form is most extended. It is a part some fibers of a body of the person. The D-form is excellent ahalgetic's. There is still the mixed LD-form possessing combined properties. The LD-form is sometimes appointed in the form of BUDS at premenstrual a syndrome.

Being the predecessor Tirosin's, Fenilalanin's has property to cause feeling of satiety, therefore can use at the persons, suffering adiposity or from excess weight, to reduce hunger.

Therapeutic doses vary from 350 mg to 2, 25 g in day for Dl-fenilalanin's and from 500 mg to 1, 5 g for L-fenilalanin's, depending on the recipe (doses are given for adults).

This amino acid has appeared effective, thanks to ability to regulate melanin synthesis, depression treatment that is valuable to diabetes treatment (the note of the author).

Bensoic acid - is natural connection. Contains in a cranberry, a bilberry, a cowberry, a raspberry, a bark of a cherry tree. In the connected kind meets in honey. It is interesting, that bensoic acid is formed in the course of microbic decomposition N – benzoilglicin's in the dairy fermented products (kefir, fermented baked milk, yoghurt, curdled milk). Thanks to antiseptic properties it is used in the food-processing industry as natural preservative (E210) at manufacturing of a foodstuff, drinks.

At hit in an organism bensoic acid reacts with albuminous molecules, turning in N - benzoilglicin's (hipporove acid). After transformation connection is deduced with urine. The given process «loads» secretory system of the person, therefore in order to avoid drawing of harm to health, the legislation of each state establishes admissible norm of application of acid at manufacturing of a foodstuff. Today it is authorised to use to five milligramme of substance on finished goods kg.

Simultaneous reception of the products rich on ascorbic and bensoic of acid leads to formation of toxic free benzene. Therefore the minimum break between receptions of such products (soft drinks and citrus) makes two hours.

Novonorm – peroral high-speed hypoglycemic a preparation. Quickly reduces glucose level in blood, stimulating liberation of insulin from functioning β pancreas-cages. The action mechanism is connected with ability of a preparation to close ATF-DEPENDENT channels in membranes β-cages at the expense of influence on specific receptors that leads деполяризации cages and to opening calcium channels. As a result raised inflow of calcium induces insulin secretion β-cages. To children also it is necessary colloid calcium (it contains only in herbs) for development endogenic insulin (the note of the author). For diagnostics of a lack of calcium it is necessary to do blood biochemistry - on vitamins and microcells (these researches it is necessary to include 2 types in standards of diagnostics of a diabetes).

After preparation reception insulinotropic the answer to food intake is observed during 30 mines that leads to decrease in level of glucose in blood. During the periods between food intakes it is not marked increases of concentration of insulin. At patients with insulin-nondependent a diabetes 2 types at preparation reception in doses from 0, 5 to 4 mg are marked dose-dependent decrease in level of glucose in blood.

The secretion of insulin stimulated Nateglinid's and Repaglinid's, is close to a physiological early phase of secretion of a hormone at healthy faces after food intake that leads to effective decrease in peaks of concentration of glucose in postprandiale the period. They possess fast and short-term effect on insulin secretion thanks to what warn sharp increase glycemia's after meal. At the food intake admission these preparations are not applied.

Nateglinid (Starlix) - derivative fenialanin's. The preparation restores early secretion of insulin that leads to reduction postprandiale tto concentration of glucose in blood and level glycetid haemoglobin (HbA1c).

Under influence Nateglinid's, accepted to meal, there is a restoration early (or the first) phases of secretion of insulin. The mechanism of this phenomenon consists in fast and reversible interaction of a preparation with K+ATF-dependent channels β pancreas-cages.

Selectivity Nateglinid's concerning K+ATF- dependent channels β pancreas-cages in 300 times surpasses that concerning channels of heart and vessels.

Nateglinid, unlike others peroral hypoglycemic means, causes the expressed secretion of insulin within the first 15 mines after food intake thanks to what smooth out postprandial fluctuations ("peaks") of concentration of glucose in blood. In the subsequent 3-4 ч insulin level comes back to reference values. Thus, it is possible to avoid postprandial hyperinsulinemia's, which can lead delayed hypoglycemic.

Starlix it is necessary to accept before meal. The time interval between reception of a preparation and should not exceed 30 minutes At application Starlix's as monotherapy a recommended dose makes 120 mg 3 times/sut (before a breakfast, a dinner and a supper) food intake. If at such mode of dispensing it is not possible to reach desirable effect, a single dose it is possible to increase about 180 mg.

To another prandial as a regulator glycemia's serves Acarboza (Glucobay). Its action is developed in the top department of thin intestines where it is reversible blocks α-glukozidazy (glucoamilaza, sucrose, maltase) and interferes fermentative with splitting poly- and oligosaccharids. It warns suction monosaccharids (glucose) and reduces sharp lifting of sugar of blood after meal.

The inhibition α-glukozidazy Acarboza's occurs by a competition principle for the active centre of the enzyme located on a surface of microfibers of thin intestines. Preventing lifting glycemia's after food intake, акарбоза authentically reduces insulin level in blood that promotes improvement of quality of metabolic indemnification. Confirms this decrease in level glycolized haemoglobin (HbA1c).

Application Acarboz's as the only thing peroral is enough antidiabetic means, that it is essential to reduce metabolic infringements at 2nd type sick of a diabetes which are not compensated by one diet. When similar tactics does not lead to desirable results, appointment Acarboza's with preparations Sulfanilurea (Glurenorm) leads to substantial improvement of metabolic indicators. It is especially important for the elderly patients not always ready to transition on insulinotherapy.

With a diabetes of 2 type, receiving insulinotherapy and Acarboza's, the daily dose of insulin decreased on the average on 10 units while at the patients receiving placebo, the insulin dose has

increased on 0,7 UNITS.

Application Acarboza's considerably reduces a dose of preparations Sulfanilurea. Advantage Acarboza's and that at monotherapy it does not cause hypoglicemia's.

Modern conditions dictate necessity of creation of the new preparations allowing not only to eliminate metabolic infringements, but also to keep functional activity of cages of a pancreas, stimulating and activating physiological mechanisms of regulation of secretion of insulin and the glucose maintenance in blood. Last years it is shown, that regulation of level of glucose in an organism, besides insulin and glucogen's, participate as well hormones Incretines, developed in intestines in reply to food intake. To 70% postprandial secretions of insulin at healthy faces it is caused by effect Incretines.

Incretines in treatment of a diabetes 2 types

As the basic representatives Incretines serve glucose-dependent insulinotropic polypeptide (GDIP) and glucagon-like peptide-1 (GLP-1).

Food receipt in a digestive path quickly stimulates emission glucose-dependent insulinotropic polypeptide (GDIP) and glucagon-like peptide-1 (GLP-1). Incretines can reduce level glycemia's and for the account non insulin mechanisms by delay emptying a stomach and decrease in consumption of food. At a diabetes 2 types the maintenance Incretines and their effect are lowered, and glucose level in blood is raised.

Ability glucagon-like peptide-1 (GLP-1) to cause improvement of indicators glycemic the control 2 types (class occurrence Incretomimetics) are of interest in respect of treatment of a diabetes. Glucagon-like peptide-1 (GLP-1) possesses plural influence on endocrine a pancreas part, but its basic action in potentiation glucose-dependent insulin secretions.

The increased levels endocellular cycle-AMF stimulate receptors RGLP-1 glucagon-like peptide-1 (GLP-1), that leads exacytoz's insulin granules from β-cages. Level increase cycle-AMF, thus, serves primary mediator's glucagon-like peptide-1 (GLP-1) to the induced secretion of insulin. Glucagon-like peptide-1 (GLP-1) strengthens a transcription of a gene of insulin, biosynthesis of insulin and promotes β-cellular proliferation through activation receptors glucagon-like peptide-1 (GLP-1). Glucagon-like peptide-1 (GLP-1) also potentiate glucose-dependent secretion of insulin by means of endocellular ways. In research C. Orskov and соавт. It has been shown *in vivo*, that glucagon-like peptide-1 (GLP-1) at action on α-cages causes secretion decrease glucagon's.

Improvement glycemic indicators after appointment glucagon-like peptide-1 (GLP-1) can be result of restoration of normal function β-cages. Research *in vitro* testifies that β-cages, resistant to glucose, become glucose-competent after introduction glucagon-like peptide-1 (GLP-1).

The term "glucose-competent" is used for the description of a functional condition β the-cages sensitive to glucose and secreting insulin. Glucagon-like peptide-1 (GLP-1) possesses additional glycemic the effect which has been not connected with influence on a pancreas and a stomach. In a liver glucagon-like peptide-1 (GLP-1) inhibition production of glucose also promotes mastering of glucose by a fatty and muscular fabric, but these effects are secondary in relation to regulation of secretion of insulin and glucagon's.

The weight increase β-cages and their reduction apoptoz's - valuable quality glucagon-like peptide-1 (GLP-1) also represents special interest for treatment of a diabetes 2 types, thus, the basic patofisiological as the mechanism of the given disease served progressing β by-cellular dysfunction.

To Incretomimetics, used in treatment of a diabetes of 2 type, 2 classes of preparations concern

- Agonists glucagon-like peptide-1 (GLP-1) - (Exenatid, Liraglutid)
- Inhibitors dipeptidilpeptidazy-4 (DPP-4), destroying glucagon-like peptide-1 (GLP-1) - (Sitagliptin (Yanuvia), Vildagliptin).

Exenatid (Baetta, Exendin-4, Bydureon) - it is allocated from a saliva of huge lizard Gila monster. Aminoacid the sequence Exenatid's on 50% coincides with human glucagon-like peptide-1 (GLP-1). At hypodermic introduction Exenatid's the peak of its concentration in plasma comes through 2-3 hours, and the semilife period is equal 2-6 ч. It allows to spend therapy Exenatid's in the form of 2 hypodermic injections in day before a breakfast and a supper. It is created, but it is not registered yet in Russia Exenatid of long action - Exenatid LAP, entered once a week.

Liraglutid - the new preparation, analogue human glucagon-like peptide-1 (GLP-1), on structure on 97% is similar to the human. Liraglutid supports stable concentration glucagon-like peptide-1 (GLP-1) throughout 24 ч at introduction of 1 times a day.

Inhibitors IDPP-4 (Inhibitors dipeptidilpeptidazy-4) for treatment of a diabetes 2 types

The preparations developed for today glucagon-like peptide-1 (GLP-1) have peroral no forms and demand obligatory hypodermic introduction. This lack are deprived preparations from group Inhibitors of dipeptidyl peptidase-4 (IDPP-4). Suppressing action of this enzyme, inhibitors of dipeptidyl peptidase-4 (IDPP-4) increase level and life expectancy endogenic glucose-dependent insulinotropic polypeptide (GDIP) and glucagon-like peptide-1 (GLP-1), promoting their strengthening physiological insulintropic actions. Preparations are issued in tableted to the form, are appointed, as a rule, once a day, that essentially raises adherence of patients of spent therapy. Inhibitors of dipeptidyl peptidase-4 (IDPP-4) is membrane connecting serin proteaza from group propiloligopeptidaz, as the basic substratum for it serve short peptides, such as glucose-dependent insulinotropic polypeptide (GDIP) and glucagon-like peptide-1 (GLP-1). Fermentative activity inhibitors of dipeptidyl peptidase-4 (IDPP-4) in the relation Incretines, especially glucagon-like peptide-1 (GLP-1), assumes use possibility inhibitors of dipeptidyl peptidase-4 (IDPP-4) in treatment of patients with a diabetes 2 types.

Feature of the given approach to treatment in increase in duration of action endogenic Incretines (glucagon-like peptide-1 (GLP-1)) - mobilisation of own reserves of an organism for struggle with hyperglicemia's.

2 types concern number inhibitors of dipeptidyl peptidase-4 (IDPP-4), both in the form of monotherapy, and in a combination with Metformin's or Tioazolidindiones Sitagliptin (Yanuvia) and Vildagliptin (Galvus), recommended FDA (USA) and the European Union for treatment of a diabetes.

The combination inhibitors of dipeptidyl peptidase-4 (IDPP-4) and Metformin's is represented to the most perspective, that allows to influence all basic pathogenetic mechanisms of a diabetes of 2nd type – insulin resistance, secret the answer β-cages and hyperproduction of glucose a liver.

Preparation GalvusMet (50 mg Vildagliptin + Metformin 500, 850 or 100 mg) which is registered in 2009 is created.

Vildagliptin - new inhibitor of dipeptidyl peptidase-4 (IDPP-4) which improves the control glycemia's by correction of the broken function β pancreas-cages, thus strengthening secretion of insulin and reducing secretion glucagon's. The preparation not bio-is transformed with participation of cytochrome P-450, also is not revealed medicinal interactions with most often appointed preparations.

Peroral antidiabetic monotherapy directly influences only one of links patogenez's a diabetes 2 types

At many patients this treatment does not provide the sufficient long-term control of level of glucose in blood, and there is a requirement for the combined therapy. By results of UKPDS (R. C. Turner., *et al*. 1999), monotherapy peroral glycemic preparations in 3 years from the treatment beginning was effective only at 50% of patients, and in 9 years only at 25%. It causes growing interest to various schemes of the combined therapy.

The combined therapy is spent in case of a monotherapy inefficiency by the first glycemic a preparation appointed in the maximum dose. Use of a combination of the preparations influencing both on secretion of insulin, and on sensitivity of peripheral fabrics to insulin action is expedient.

Recommended combinations of preparations

- Derivatives Sulfanilurea + Biguanids;
- Derivatives Sulfanilurea + Tioazolidindions;
- Glinids + Biguanids;
- Glinids + Tioazolidindions;
- Biguanids + Tioazolidindions;
- Acarboza + any glycemic preparations.

As have shown results of the spent researches, the greatest indicator of decrease in level glicolized haemoglobin at the combined therapy by two peroral preparations does not exceed 1, 7% (J. Rosenstock, 2000). The further improvement of indemnification of a carbohydrate exchange can be reached at use of a combination from three preparations or at insulin addition. Or it is necessary to change natural therapy (the note of the author).

Tactics of appointment of the combined therapy the following

1. Originally at monotherapy carrying out by the first glycemic a preparation if necessary increase a dose of a preparation to the maximum.
2. If therapy is inefficient, add to it a preparation of other group in an average therapeutic dose.
3. At insufficient efficiency of a combination increase a dose of the second preparation to the maximum.
4. The combination of three preparations if the maximum doses previous are not effective is possible.
5. My opinion - it is necessary to change approaches to therapy. Not in a consequence to be engaged, and to affect on the reason, even an illness original cause (the note of the author).

Interaction of derivatives Sulfanilurea with other medical products

During reception of other medicines their compatibility with derivatives Sulfanilurea is considered. Increase hypoglucemic action anabolic hormones, energizers, beta-blokatory, Sulfanilamids, Clofibrat, man's hormones, Kumatines, medicines Tetracyclin a number, Miconazol, Salicylates, others hypoglycemic means and insulin. Reduce action – Corticosteroids, Barbiturats, Glucagon, laxatives, an estrogen and gestagenes, Nicotinic Acid, Chlorpromazin, Fenotiazin, Diuretics, thyroid gland hormones, Izoniazid, Tiasids.

The effective combined therapy

Glibomet (Glibenclamid + Metformin) - combined peroral hypoglycemic the preparation, contains derivative Sulfanilurea II generations and Biguanid. Possesses pancreatic and outpancreatic effects. The Hypoglikemic effect preparation's develops through 2 hours and proceeds 12 hours. Linkage with fibers of plasma - 97%. The initial dose makes, as a rule, 1-3 tab/day with the further gradual selection of an effective dose before achievement of steady normalisation of concentration of glucose in blood.

The maximum daily dose of preparation Glibomet makes 6 tablets.

Preparation application is counter-indicative at children and teenagers is elderly till 18 years. The described cases of development lactoacydoz's at the patients receiving Metformin, were observed mainly at patients with a diabetes with the expressed warm and nephritic insufficiency. Preventive maintenance lactoacydoz's assumes definition of all concomitant factors of risk, such as decompensation a diabetes, cetoz, long starvation, the excessive use of alcohol, hepatic insufficiency and any condition connected with hypoxia. For children rather antioxidants and antihyppoxants, but it there the separate book (it is not published yet).

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