Course Title

Pharmacology Research Paper on Glyburide

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This paper analyzes Glyburide, also known as glibenclamide. It is a representative of the second generation of sulfonylurea derivatives, one of the most popular and studied antihyperglycemic drugs, which has been widely used since 1969 in many countries of the world as a reliable and proven treatment for type 2 diabetes mellitus (Katsilambros N., 2007) and approved for medical use in the United States in 1984. So, the purpose of this work is to identify this kind of diabetes and the pharmacological way to treat it using glyburide.

The Causes of Type 2 Diabetes Mellitus

There are type 1 and type 2 diabetes which differ in several ways. Unlike type 1, type 2 diabetes usually occurs in people over the age of 40. However, an unhealthy diet and lifestyle can contribute to the development of diabetes at any age. It used to be called adulthood diabetes because it was more common among older people, but with increasing obesity and more sedentary young people, the risk for young adults, adolescents and children has grown. Another important factor that differentiates type 1 and type 2 diabetes is that type 1 diabetes appears within a few weeks, and type 2 diabetes develops slowly over a longer period of time. In this regard, gradually manifesting symptoms are often overlooked. Type 2 diabetes accounts for approximately 90% of all people with diabetes. According to the latest data (Diabetes UK, 2015), the number of patients having type 2 diabetes has increased by 60% for the last 10 years.

In modern clinical practice, the diagnosis of diabetes mellitus is established based on the result of the analysis for glycated hemoglobin (HbA1C). Once in the blood, glucose molecules can penetrate erythrocytes and firmly bind to the hemoglobin protein receptors - glycate it. The more glucose in the blood, the more of its molecules "settle" on the hemoglobin. Glucose is retained on protein for 3-4 months, preventing it from performing its function - to transport oxygen and carbon

dioxide. Analysis for glycated hemoglobin reveals the percentage of such "long-term occupied" molecules. In a healthy person, this figure does not exceed 5.7%. A glycated hemoglobin level of 5.7% to 6% signals the first problems with glucose metabolism. With an increase in HbA1C to 6.1% -6.4%, they speak of prediabetes, a figure higher than these values indicates the presence of the disease.

Before a meal, a person with type 2 diabetes should have a sugar level in the range of 4-7 mmol / L (72-126 mg / dL). After eating (after 90 minutes) - do not exceed 8.5 mmol / l (153 mg / dl).

Treatment Recommendations

If traditional approaches - diet, exercise, or antidiabetic medications - do not work to achieve the desired effect and improve the diabetes, alternative methods may be used. Currently, a significant decrease in the level of hemoglobin HbA1c in patients with type 2 diabetes when using an insulin pump has already been clinically proven (Reznik Y. Cohen O. Aronson R., 2014). This is a small electronic device that injects insulin according to pre-programmed individual settings.

The drug should be used only as directed by a doctor and always with a correction of the diet. The dosage depends on the results of the study of the state of metabolism (glucose levels in the blood and urine). Therapy begins with as little doses as possible, especially for patients with an increased tendency to hypoglycemia and a body weight of less than 50 kg. The first appointment is from ½ to 1 tablet (which corresponds to 2.5–5 mg glibenclamide) per day. With insufficient metabolic correction, the dose is gradually increased at intervals from several days to one week to the required daily therapeutic dose of 3 tablets (which corresponds to 15 mg of glibenclamide) per day.

The tablets should be taken before meals, one should not chew them and drink plenty of liquid (preferably 1 glass of water). With a daily dose of more than 2 tablets of the drug, it is recommended to distribute the entire amount for one morning and one evening intake in a ratio of 2:1. It is very important to use the drug at the same time every time. If the patient missed one appointment, it should never be supplemented with a higher dose (Drugs.com, 2021). The duration of treatment depends on the course of the disease. During treatment, regular monitoring of the state of metabolism should be carried out.

Metformin is another drug used in the treatment of type 2 diabetes mellitus, especially in overweight and obese individuals with normal renal function (Katsilambros N., 2007). It is a tableted antihyperglycemic drug of the biguanide class for oral administration.

Pharmacological Aspects of the Recommended Treatment

The main mechanism of action of glibenclamide, like other representatives of sulfonylurea preparations, is well studied at the molecular receptor level. Glibenclamide blocks ATP-dependent potassium channels (K + -ATP channels) localized on the plasma membrane of pancreatic beta cells (Serrano-Martín X., 2016). Stopping the release of potassium from the cell leads to membrane depolarization and the influx of Ca2 + ions through voltage-gated calcium channels. An increase in the intracellular calcium content through the activation of calcium / calmodulin-dependent protein kinase II stimulates exocytosis of secretory granules with insulin, as a result of which the hormone penetrates into the extracellular fluid and blood. The unequal affinity of sulfonylurea preparations for beta-cell receptors determines their different glucose-lowering activity.

A chemical formula is $C_{23}H_{28}ClN_3O_5S$.

Glibenclamide has the highest affinity for sulfonylurea receptors on beta cells and the most pronounced antihyperglycemic effect among sulfonylurea preparations. The effect of stimulating

insulin secretion directly depends on the dose of glibenclamide taken and manifests itself both in conditions of hyperglycemia and in normoglycemia or hypoglycemia. The entire group of sulfonylurea preparations, to one degree or another, have peripheral (extra-pancreatic) effects, which consist in increasing the sensitivity of peripheral tissues, primarily adipose and muscle, to the action of insulin and improving glucose uptake by cells.

When taken orally on an empty stomach, glibenclamide is rapidly and almost completely absorbed in the gastrointestinal tract. The drug binds to blood proteins (albumin) by more than 98% and is metabolized in the liver. In the process of metabolism, 3-cishydroxyglibenclamide and 4-transhydroxyglibenclamide are formed. It is excreted from the body in urine and bile. T1 / 2 of glibenclamide from blood plasma is 1.5-3.5 hours. The hypoglycemic effect lasts up to 12 hours (Drugs.com, 2021). In patients with reduced liver function, excretion of the drug slows down. In conditions accompanied by moderate renal failure (with creatinine clearance of 30 ml / min), the process of excretion of metabolites does not change, but their cumulation is possible in severe renal failure.

Contraindications are the following: condition after resection of the pancreas, severe liver, renal dysfunction, hypersensitivity to glibenclamide or excipients, sulfonylurea derivatives, sulfonamides, diuretics, sulfonamide derivatives and probenecid. In cases when insulin treatment is required: type I diabetes mellitus, complete secondary ineffectiveness of glibenclamide therapy in type II diabetes mellitus, metabolic disorders towards acidosis, precoma or diabetic coma.

Side effects in metabolic and nutritional disorders: often - hypoglycemia, weight gain; violations of the organ of vision: very rarely - disorders of vision and accommodation, especially at the beginning of treatment; gastrointestinal disorders: sometimes - nausea, a feeling of fullness in the stomach, vomiting, abdominal pain, diarrhea, belching, metallic taste in the mouth;

dysfunction of the liver and gallbladder: very rarely - a transient increase in AST and ALT, ALP, drug-induced hepatitis, intrahepatic cholestasis, which may be caused by an allergic reaction of the hyperergic type of liver cells; violations of the skin and subcutaneous tissue: sometimes - itching, urticaria, erythema nodosum, measles-like or maculopapular exanthema, purpura, photosensitivity; disturbances from the blood and lymphatic system: rarely – thrombocytopenia, very rarely - leukopenia, erythropenia, granulocytopenia, up to the development of agranulocytosis. In some cases - pancytopenia, hemolytic anemia, aplastic anemia, eosinophilia (MedLinePlus, 2018). Other side effects: very rarely - weak diuretic effect, syndrome of inappropriate antidiuretic hormone secretion, reversible proteinuria, hyponatremia, disulfiram-like reaction, cross-allergy with sulfonamides, sulfonamide derivatives and probenecid.

Special instructions when using the drug in patients with impaired renal or liver function of mild to moderate degree or reduced function of the thyroid gland, pituitary gland or adrenal cortex requires special care. In elderly patients, there is a risk of developing prolonged hypoglycemia, therefore, glibenclamide is prescribed to them with extreme caution and their condition is carefully monitored at the beginning of treatment. In this age group, under certain conditions, it is initially more expedient to use sulfonylureas with a shorter duration of action. Long intervals between meals, inadequate carbohydrate supply, unusual exercise, diarrhea, or vomiting can increase the risk of hypoglycemia. With the simultaneous use of the drug Glibenclamide with clonidine, β-adrenergic receptor blockers, guanethidine and reserpine, the patient's perception of symptoms - precursors of hypoglycemia may be impaired (Drugs.com, 2021). The effect of glibenclamide can be unexpectedly increased or weakened by drinking alcohol repeatedly in significant quantities and with its constant use. The constant abuse of laxatives can lead to a deterioration in the state of metabolism. If the treatment regimen is not followed, the

hypoglycemic effect of the drug is insufficient, or if there are stressful situations (trauma, surgery, an infectious disease, which is accompanied by an increase in body temperature), the blood glucose level can sometimes rise so much that a temporary transfer of the patient to insulin may be required.

The use of glibenclamide in pregnant women and during lactation is contraindicated. Children should not use it. Patients should take safety measures to prevent hypoglycemia while driving and working with other mechanisms (MedLinePlus, 2018). This is especially important for those patients who often have cases of hypoglycemia. In such cases, it is necessary to resolve the issue of the expediency of driving a vehicle. Interactions drugs that enhance the effect of glibenclamide with simultaneous use: other antidiabetic drugs and insulin, ACE inhibitors, anabolic steroids and male sex hormones, antidepressants (fluoxetine, MAO inhibitors), β-adrenoreceptor blockers, quinolone derivatives, chloramphenicol and its analogs coumarin, disopyramide, fenfluramine, miconazole, PASK, pentoxifylline (administered parenterally at a high dose), perhexiline, pyrazolone derivatives, probenecid, salicylates, sulfonamides, tetracycline antibiotics, tritoqualin, cytostatics such as cyclophosphamide. Drugs that reduce the effect of glibenclamide with simultaneous use: acetazolamide, β-adrenergic receptor blockers, barbiturates, diazoxide, diuretics, glucagon, isoniazid, corticosteroids, nicotinates, phenothiazine derivatives, phenytoin, rifampicin, thyroid hormones, estrogens, female hormones, hormones, estrogens, female hormones sympathomimetics. H2 receptor blockers, clonidine and reserpine can both reduce and increase the hypoglycemic effect of the drug. In some cases, pentamidine can lead to severe hypoglycemia or hyperglycemia (MedLinePlus, 2018). The effect of coumarin derivatives can either increase or decrease.

A single overdose or the use of slightly increased doses for a long time can lead to severe prolonged hypoglycemia, which is life-threatening.

Conclusion

Glyburide is a tablet sugar-lowering drug of the sulfonamide class for oral administration. It is used in the treatment of type II diabetes when diet and weight loss are ineffective. The most common side effect with gliclazide is hypoglycemia, which is relatively common than with other sulfonamide drugs. The drug is not recommended for use in children and adolescents, the drug is used with caution during pregnancy and breastfeeding.

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