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To Study the Gliclazid and Glibenclamide Drug on Diabetes Mellitus

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ABSTRACT

The end of the present study is to compare the short- term goods of gliclazide and glibenclamide on the oxidative state and vascular endothelium function of Type 2 diabetic cases in an bystander- dazed, randomized crossover study. Thirteen Type 2 diabetic cases were enrolled one group of seven cases took daily 160 mg of gliclazide for the first 4 weeks and also daily 5 mg of glibenclamide for the coming 4 weeks; another group of six cases took daily 5 mg of glibenclamide for the first 4 weeks and 160 mg of gliclazide for the coming 4 weeks. Forearm blood inflow(FBF) dimension for endothelial function and biochemical analyses were conducted before and after each crossover treatment. Four weeks of treatment with either sulfonylurea showed the analogous antihyperglycemic goods and improvement of the peak FBF and total reactive hyperemic inflow(inflow debt prepayment FDR) during reactive hyperemia. Treatment with gliclazide redounded in the significant reduction to about 60 of birth in urinary 8- iso- prostaglandin F2a(8iPGF2a) excretion while no similar change was detected in the glibenclamide period. The increases in peak FBF and FDR were in resemblant with itsanti-hyperglycemic effect, but not with antioxidant state. To confirm these goods we performed a double-eyeless randomized study using glibenclamide as a reference medicine. Thirty- eight hospitals from eight university groups in Japan performed the study on type II diabetic subjects. Evaluation of blood glucose control, platelet cohesion, platelet aggregation and blood lipids over 24 weeks were assessed by the central commission. Two hundred and eighty- nine cases were enrolled in the study.

Keywords:: Gliclazide, Glibenclamide, diabetes mellitus

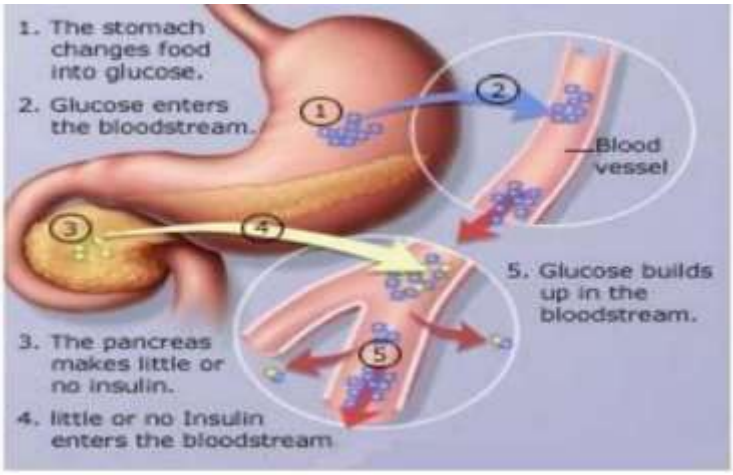
Introduction

Diabetes is a metabolic disorder in which there are high levels of sugar in the blood, a condition called hyperglycemia. Under normal conditions, food is broken down to glucose which then enters the bloodstream and acts as fuel for the body. The pancreas produces a hormone called insulin which helps to carry glucose from the bloodstream into muscle, fat and liver where it can be used as fuel. Diabetics are not able to move this sugar out of the bloodstream because of two primary reasons: 1) their pancreas does not produce enough insulin and/or 2) their cells do not respond normallytoinsulin, a condition called insulin resistance. This is why people with diabetes have high blood sugar level[1]

Type of diabetes

1) Type 1 diabetes(T1D)/ Juvenile diabetes/ Insulin dependent diabetes: T1D affects both adults and children at any age and occurs when the person's pancreas stop producing insulin due to destruction of

the pancreatic beta cells or by inactivity of these insulin-producing cells. Affected individuals depend on daily injections of insulin to maintain normal blood glucose levels. The causes of T1D are not entirely understood however; scientists believe that both genetic and environmental factors are involved.



2) Type 2 diabetes/ Non-insulin dependent diabetes mellitus (T2D or NIDDM): This is the most common form of diabetes that most often occurs in adulthood. However, because of increased obesity rates and Husedentary lifestyles, teens and young adults are also being diagnosed with T2D or the precursor, prediabetes. In T2D, fat, muscle and liver cells do not respond correctly to insulin. This is called insulin resistance. As a result, blood sugar cannot enter these cells to be stored for energy and builds up in the blood. Insulin resistance is a gradual process that develops slowly over time.

3) Gestational diabetes: This refers to diabetes that is first diagnosed during pregnancy. As many as eight out of 100 pregnant women in the U.S develop gestational diabetes. Weight gain and changing hormones that occur during pregnancy can impair insulin function, resulting in high blood sugar. This form of diabetes usually disappears after pregnancy, however, women who have had gestational diabetes have a 40-60% chance of developing T2D within 5 to 10 years Risk factors for Diabetes: The following factors contribute to the risk of developing diabetes

Symptoms:

1. Type 1 diabetes – Symptoms of type 1 diabetes develop over a short period of time and include weight loss, frequent urination, excessive thirst and hunger, weakness and fatigue, nausea and vomiting.

2. Type 2 diabetes – Symptoms develop slowly with some people showing no symptoms at all. They include any of the symptoms of type 1 diabetes, blurred vision, hard to heal skin, gum or bladder infections, and tingling or numbness in the hands or fee

Complications of diabetes: If not cared for appropriately, it may lead to the following complications –

1. Kidney disease (Diabetic nephropathy)

2. Blindness (Diabetic retinopathy)

3. Heart disease and stroke. Diabetics are 2 to 4 times more likely to have a heart disease and suffer a stroke.

4. Nerve damage

5. Sores on feet and skin possibly resulting in amputations

6. Diabetic coma due to extremely high blood sugar

Treatment and management of diabetes:

Although there is no cure for diabetes, treatment and control of diabetes involves the following:

1. Insulin injections

2. Weight loss

3. Constant monitoring of blood glucose through frequent blood

glucose tests or self-monitoring equipments such as glucometers.

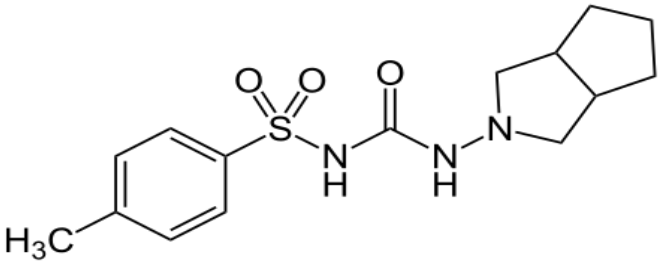
4. Oral medications (recommended by physician) to lower blood glucose

5. Healthy diet including foods with fewer calories, an even amount of carbohydrates and healthy monostaurated fats. Patients should work with their doctor or dietician to design a meal plan to maintain near-normal blood glucose levels.

6. Exercise

In all, a healthy lifestyle, insulin and oral medications to maintain normal glucose levels are the foundations of diabetes management and treatment.[2]

Gliclazide



- *IUPAC NAME _N*-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-ylcarbamoyl)-4-methylbenzenesulfonamide

Gliclazide, sold under the brand nameDiamicron among others, is a sulfonylureatype of anti-diabetic medication, used totreat type 2 diabetes(3)

Formula _$C_{15}H_{21}N_3O_3S$

Molar mass _ 323.41 $g \cdot mol^{-1}$

Melting point_ 180 to 182 °C (356 to 360 °F)

Route of administration _By mouth

Side effects _include the low blood, sugar, vomiting, abdominal pain ,rash & liver problem(4,3)

Medical uses _Gliclazide is used for control ofhyperglycemia in gliclazide-responsivediabetes mellitus of stable, mild, non-ketosis prone, type 2 diabetes. It is usedwhen diabetes cannot be controlled byproper dietary management and exerciseand when metformin has already been(5)

Contraindication _Type 1 diabetes[6]

Hypersensitivity to sulfonylureas

Severe renal or hepatic failure[6]

(Butrelatively useful in mild renal impairment

e.g. CKD stage 3)

Adverse effect _Pregnancy and lactation Common adverse effects over 10%:

Hypoglycemia (11 - 12%) - while it wasshown to have the same efficacy as glimepiride, one of the newersulfonylureas, the European GUIDE study has shown that it hasapproximately 50% less hypoglycemic confirmed episodes in comparison withglimepiride.[7]

Uncommon adverse effect between 1 -10%:[8]

Hypertension (3 - 4% incidence)

Dizziness (2% incidence)

Hyperglycemia (2% incidence)

Viral infection (6 - 8% incidence)

Back pain (4 - 5% incidence)

Rare adverse effects (under 1%):[8]

•cystitis

•weight gain

•Vomiting

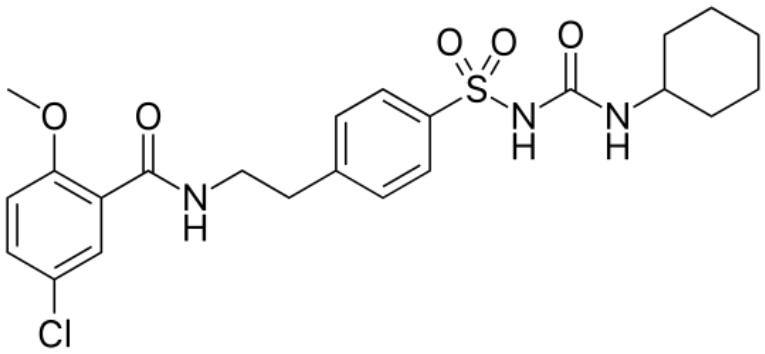
Overdose _Gliclazide overdose may cause severe hypoglycemia, requiring urgent administration of glucose by IV and Monitoring.[9]

Mechanism of action _Gliclazide selectively binds to sulfonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonylurea receptors (SUR-2A) in the heart.[10] This binding effectively closes these K+ ion channels

This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca2+ ion channels to open increasing the Ca2+ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release.[11]The mouse model of Maturity-onset diabetes of the young (MODY) diabetessuggested that the reduced gliclazide clearance stands behind their therapeutic success in human MODY patients, but Urbanova et al. found that human MODY patients respond differently and that therewas no consistent decrease in gliclazide clearance in randomly selected HNF1A-MODY and HNF4A-MODY patients.[12]Its classification has been ambiguous, asliterature uses it as both a first-generation[13] and second-generation[14]sulfonylurea.

Metabolism _Gliclazide undergoes extensive metabolism to several inactive metabolites in human beings, mainly methylhydroxygliclazide and carboxygliclazide. CYP2C9 is involved inthe formation of hydroxygliclazide in human liver microsomes and in a panel of recombinant human P450s in vitro.[15,16] But the pharmacokinetics of gliclazide MRare affected mainly by CYP2C19 geneticpolymorphism instead of CYP2C9 genetic polymorphism.[17,18]

Glibenclamide



IUPAC Name

- 5-chloro-*N*-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-2-methoxybenzamide

Formula_ $C_{23}H_{28}ClN_3O_5S$

Molar mass _494.00 $g \cdot mol^{-1}$

Melting point _169 to 170 °C (336 to 338 °F)

Route of administration _By mouth

Site effect _nausea andheartburn.[19] Serious side effects may include angioedema and low bloodsugar.[19]It is generally not recommended during pregnancy but can be used during breastfeeding.[20]It is in the sulfonylureasbclass of medications and works byincreasing the release of insulin from thepancreas.[19]

Medical uses _Glibenclamide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[21]it is not as good as either metformin or insulin in those who have gestational diabetes.[22]

Side effects _Frequently reported side effects include:nausea, heartburn, weight gain, and bloating.[23] The medication is also a major cause of medication-induced hypoglycemia. The risk is greater than with other sulfonylureas.[24]

Contraindications_ Glibenclamide may be not recommended in those with G6PD deficiency, as it may cause acute hemolysis.[25] **Mechanism of action_** The medication, a sulfonylurea, works by binding to and inhibiting the ATP-sensitive potassium channels (KATP) inhibitory regulatory subunit sulfonylurea receptor 1 (SUR1) [26] in pancreatic beta cells. This inhibition causes cell membrane depolarization, opening voltage-dependent calcium Channels. [27] This results in an increase in intracellular calcium in the pancreatic beta cell and subsequent stimulation of insulin release. [28]After a cerebral ischemic insult, the blood– brain barrier is broken and glibenclamide can reach the central nervous system. Glibenclamide has been shown to bind more efficiently to the ischemic hemisphere. [29] Moreover, under ischemic conditions SUR1, the regulatory subunit of the KATP- and the NCCa-ATP-channels, is expressed in neurons, astrocytes, oligodendrocytes, endothelial cells [30] and by reactive microglia. [14] As per the research papers, this sulphonylurea drugs also has extra hepatic effects. It works by inhibiting the enzyme Carnityl Acyl Transferase I (CAT-I) indirectlywhich is present in the mitochondria. This prevents the transport of long chain fatty acids into the mitochondria for beta- oxidation. This prevents hyperglycemia for which it is prescribed. [31][32]

Conclusion _

The studies in middle agent Type 2 diabetic patients have found that the incidence of hypoglycaemia is less with gliclazide than with glibenclamide Gliclazide is another second-generation sulphonylurea agent. gliclazide group than in the glibenclamide group, and in evaluation of serum lipids, the gliclazide group was also superior to the glibenclamide group.

Author Contribution -

Both the author involved equally in collecting the information, designing the manuscript.

Conflict of Interest –

The author declare no conflict of interest.

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