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Glimepiride Effective Against Type 2 Diabetes

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ABSTRACT

New low-dose oral sulfonylurea glimepiride offers once-daily dosing for 24-hour glycemic control of non-insulin-dependent diabetic diabetes. Glimepiride reduced blood glucose in experimental animal models by inducing the pancreas to release more insulin and also seemed to have extrapancreatic effects. Notably, glimepiride was linked to fewer direct effects than other sulfonylureas on the cardiovascular system in mammals. Vasoconstriction was not observed in an animal model of hypoxic lactic acidosis when glimepiride was used. Moreover, glimepiride caused less change in coronary flow and resistance than glyburide. These results might be the result of variations in the relative impacts on ATP-sensitive K+ channels between pancreatic 3-cells and cardiomyocytes. Additionally, there was proof of antiatherogenic. All sulfonylureas, including glimepiride, have the potential to cause severe hypoglycemia. Severe hypoglycemia can result in unconsciousness or convulsions, which can cause temporary or permanent impairment of brain function or death. The patient's concentration and reaction time may be disrupted as a result of the hypoglycemia.

Keywords: Glimepiride, sulfonylurea, extrapancreatic, hypoglycemia.

Introduction

Glimepiride was first introduced in 1995 and is used to improve glycemic control in the treatment of diabetes. A metabolic disorder known as type 2 diabetes is becoming more and more common around the world. It is characterized by long-term microvascular and macrovascular complications that lead to co-morbidities and mortality, as well as insulin resistance in accordance with progressive β cell failure. One of the commonly used insulin secretagogues to control type 2 diabetes and lower blood glucose levels is sulfonylureas. When there are still pancreatic β-cells present, the primary effect of SUs is believed to be effective. This is because they stimulate the release of insulin from pancreatic beta cells and also have extra-pancreatic effects, like enhancing insulin-mediated peripheral glucose uptake. In healthy individuals, single oral doses as low as 0.5–0.6 mg initially showed a slight reduction in blood glucose. It took roughly two to three hours to achieve the maximum effect, or the minimum blood glucose level (Tmin). After 14 days of oral dosing, glimepiride (1, 2, 4, and 8 mg once daily) significantly reduced fasting and 2-hour postprandial glucose levels in patients with noninsulin-dependent (Type 2) diabetes mellitus (NIDDM) compared to placebo. Over the course of a full day, the glucose-lowering effect was sustained in all active treatment groups. Over the range of 1 to 4 mg/day of glimepiride, blood glucose, and HbA1c were found to respond in a dose-dependent manner in larger dose-ranging studies. There was no discernible difference in response between once and twice daily administration of glimepiride. Glimepiride therapy enhanced postprandial insulin/C-peptide responses in a long-term, randomized, placebo-controlled study of Type 2 diabetic patients unresponsive to dietary management; 75% of patients achieved and maintained control of blood glucose and HbA1c. Age, gender, weight, or race had no effect on the effectiveness results. After receiving glimepiride therapy for two and a half years, there was no significant decline in mean fasting blood glucose (FBG) or HbA1c levels in long-term extension trials involving patients who had previously received treatment.

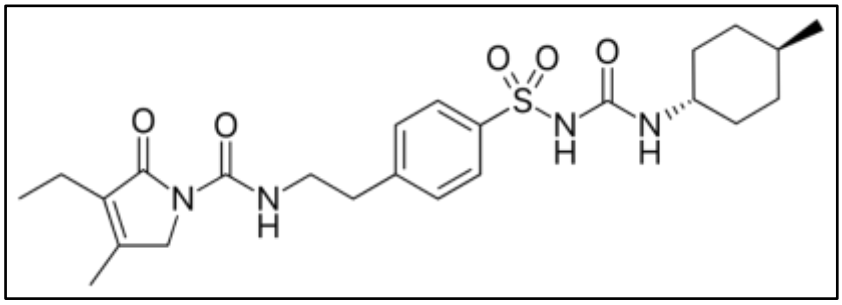

Figure 1: Structure of Glimepiride.

Drug Profile

Molecular Weight	Average: 490.62
Chemical Formula	$C_{24}H_{34}N_4O_5S$
Volume of Distribution	8.8L
Plasma protein binding	99.5%
Half-life	3-6 hours
LD_{50}	> 10000 mg/kg.

Method of Synthesis

To carry out the synthesis, glimepiride polymorph The sample was placed in N-methyl-2-pyrrolidone as a solvent medium and continuously stirred for one hour at a temperature of between 60 and 75°C using a magnetic stirrer and a hot plate (Deepali, Mumbai, India). After that, the sample was stored in a deep freezer for twenty-four hours at a temperature between slightly below 10°C and 15°C. Filtering N-methyl-2 Pyrrolidone through filter paper with a 20µm-pore size produced the crystalline novel form and then dried for eight hours in an oven at 105°C. To guarantee the reproducibility of the novel polymorph, all synthetic steps involved in recrystallization were performed again.

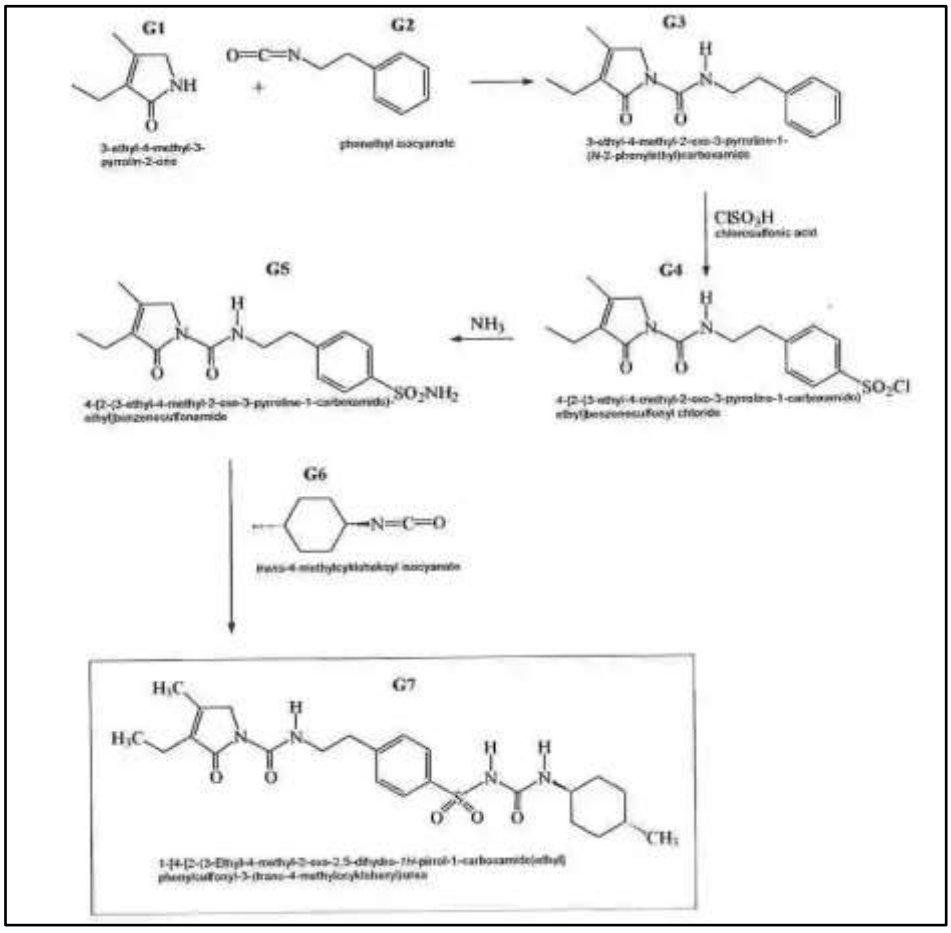

Figure 2: Schematic diagram of Glimepiride synthesis.

Mechanism of Action

Glimepiride's main method of reducing blood sugar levels seems to rely on inducing the release of insulin from active pancreatic beta cells. Furthermore, sulfonylureas like glimepiride may also be active due to extrapancreatic effects. Preclinical and clinical research showing that glimepiride administration can enhance peripheral tissues' sensitivity to insulin supports this. These results are in line with a long-term, randomized, placebo-controlled trial that found that AMARYL therapy improved overall glycemic control and postprandial insulin/C-peptide responses, but did not result in increases in fasting insulin/C-peptide levels that were clinically meaningful.

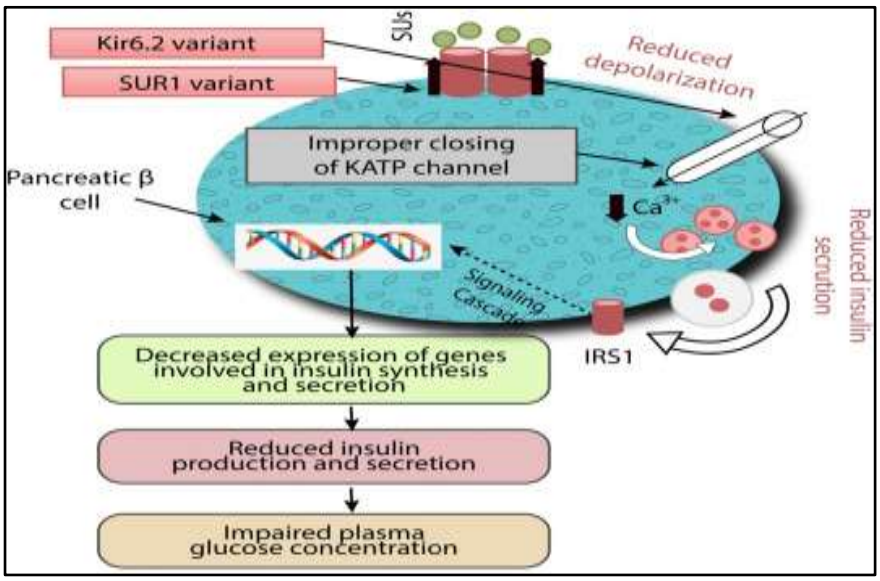

Figure 3: Schematic diagram of the mechanism of action of glimepiride

Medicinal Use

Glimepiride is used to treat type 2 diabetes, a condition in which the body does not use insulin normally and cannot control blood sugar levels. By encouraging the pancreas to produce insulin, a naturally occurring substance required for the body to break down sugar, and assisting the body in effectively utilizing insulin, glimepiride lowers blood sugar. This drug is only effective in lowering blood sugar in those whose bodies naturally generate insulin. Glimepiride is not used to treat diabetic ketoacidosis, a dangerous condition that can develop if high blood sugar is not treated, or type 1 diabetes.

Diabetes and high blood sugar patients may eventually experience major or potentially fatal side effects, such as heart disease, stroke, kidney issues, nerve damage, and vision issues. Manage your diabetes and enhance your health by taking your medication(s), changing your lifestyle (diet, exercise, stopping smoking), and monitoring your blood sugar levels on a regular basis. This treatment may also lower your risk of a heart attack, stroke, kidney failure, nerve damage (numb, cold legs or feet; reduced sexual function in men and women), eye issues (visual abnormalities, including changes or loss of vision), and gum disease, among other diabetes-related complications. The best approach to managing your diabetes will be discussed with you by your doctor and other medical professionals.

Glimepiride-Metformin Combination Therapy

The addition of metformin may be considered if patients do not respond appropriately to the maximum dose of glimepiride monotherapy. The use of other sulfonylureas, such as glipizide, tolbutamide, chlorpropamide, and glyburide, in conjunction with metformin has been documented in clinical literature. The appropriate blood glucose control with concurrent glimepiride and metformin therapy may be achieved by varying the dosage of each medication. To accomplish this, though, efforts should be made to determine each drug's minimal effective dose. The risk of hypoglycemia related to glimepiride therapy persists and may even rise when metformin and glimepiride are taken concurrently. Precautions that are appropriate should be taken.

Glimepiride-Insulin Combination Therapy

Patients with secondary failure may also benefit from combination therapy utilizing insulin and glimepiride. Depending on the patient, a fasting glucose level of >150 mg/dL in plasma or serum is required before starting combination therapy. glimepiride dosage recommendations are 8 mg once daily, to be taken with the first substantial meal. Insulin can be increased gradually after starting at a low dose and once a week or so, based on regular fasting blood glucose checks. Patients receiving combination therapy should continue to check their capillary blood glucose levels, ideally every day, once they have stabilized. During maintenance, periodic insulin adjustments may also be required based on HbA1c and glucose levels.

Pharmacokinetics

Absorption: Glimepiride is entirely (100%) absorbed from the GI system after oral treatment. Studies using single oral doses in healthy subjects and multiple oral doses in patients with Type 2 diabetes have demonstrated that glimepiride is significantly absorbed within an hour of administration, with peak drug levels (Cmax) occurring two to three hours later. The mean Tmax (time to reach Cmax) and AUC (area under the curve) were marginally reduced (8% and 9%, respectively) and slightly increased (12%) when glimepiride was administered with meals.

Distribution: Following intravenous (IV) administration, the total body clearance (CL) was 47.8 mL/min and the volume of distribution (Vd) was 8.8

Metabolism: It has been demonstrated that glimepiride's biotransformation into M1 involves cytochrome P450 2C9. One or more cytosolic enzymes convert M1 into M2 through additional metabolism. In an animal model, M1, but not M2, has roughly one-third the pharmacological activity of its parent; however, it is unclear whether the glucose-lowering effect of M1 is clinically significant.

Excretion: After taking 14C-glimepiride orally, urine contained 60–80% of the total radioactivity recovered in 7 days, with M1 (predominant) and M2 accounting for 80–90% of the recovered radioactivity. Feces contained about 40% of the total radioactivity recovered, with M1 and M2 (predominant) accounting for about 70% of the radioactivity recovered. In both the urine and feces, no parent drug was found. Following an IV dose in patients, there hasn't been any discernible glimepiride or its M1 metabolite excretion in the biliary system.

Indication and Clinical Use

ratio-GLIMEPIRIDE (glimepiride) is indicated for:

- Glimepiride, or ratio-GLIMEPIRIDE, is recommended as an additional treatment to appropriate diet, exercise, and weight loss in individuals with type 2 diabetes whose hyperglycemia cannot be managed with diet and exercise alone.
- When diet and exercise alone are insufficient to achieve adequate glycemic control, ratio-GLIMEPIRIDE or metformin alone may be used in conjunction with it.
- In patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet, ratio-GLIMEPIRIDE is also recommended for use in conjunction with insulin to lower blood glucose and exercise in conjunction with an oral hypoglycemic agent alone.

Pediatrics (<18 years of age): Safety and efficacy in pediatric type 2 diabetes patients have not been established.

Geriatrics (>65 years of age): There were no significant differences in glimepiride pharmacokinetics below or above 65 years.

General Precautions

Macrovascular Outcomes: Glimepiride or any other anti-diabetic medication has not been proven to reduce macrovascular risk in any clinical study.

Hypoglycemia: Every sulfonylurea medication has the potential to cause extremely low blood sugar. To prevent hypoglycemic episodes, proper patient selection, dosage, and instructions are crucial. Individuals who have compromised renal function might be more vulnerable to glimepiride's ability to lower blood glucose levels. For those patients, a starting dose of 1 mg once daily is advised, along with the proper dose titration. Patients who are malnourished or disabled, as well as those who have adrenal, pituitary, or hepatic insufficiency, are more vulnerable to the hypoglycemic effects of glucose-lowering medications. Patients with autonomic neuropathy, the elderly. Hypoglycemia is more likely to happen when there is a decrease in caloric intake, following intense or prolonged physical activity, when alcohol is consumed, or when multiple glucose-lowering medications are taken. Hypoglycemia risk may rise if glimepiride, insulin, or metformin are used together.

Loss of control of blood glucose: A loss of control may happen to a patient who is stabilized on any diabetic regimen and is then subjected to stressors like fever, trauma, infection, or surgery. In these situations, it might be essential to use insulin monotherapy or to add insulin in addition to glimepiride. Over time, many patients experience a decrease in the efficacy of oral hypoglycemic drugs, such as glimepiride, in achieving the desired blood glucose level. This decrease may be attributed to either a worsening of the patient's diabetes or a reduced drug response. To differentiate it from primary failure—when a drug is ineffective in a single patient when it is first administered—this phenomenon is referred to as secondary failure. In the event that metformin or glimepiride monotherapy leads to secondary failure, a combination of glimepiride and insulin or glimepiride and metformin may produce a response. It might be necessary to start insulin therapy if combined glimepiride/metformin therapy results in secondary failure.

Hemolytic anemia: Hemolytic anemia may occur if patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency are treated with sulfonylurea medications. Given that glimepiride is a member of the sulfonylurea agent class, patients who lack G6PD should exercise caution when using this medication and should think about switching to a non-sulfonylurea alternative. Hemolytic anemia has been observed in post-marketing reports in patients without a known G6PD deficiency.

Overdosage

Hypoglycemia can occur when sulfonylureas, such as Glimepride, are taken in excess. When treating mild hypoglycemic symptoms that do not result in unconsciousness or neurological symptoms, oral glucose and alterations to medication dosage and/or meal schedules should be administered with vigor. Until the doctor is certain that the patient is safe, close observation should be maintained. Although rare, severe hypoglycemic reactions accompanied by coma, seizures, or other neurological impairments are medical emergencies that need to be hospitalized right away. A quick intravenous injection of a concentrated (50%) glucose solution should be administered to the patient in the event that hypoglycemic coma is identified or suspected. Patients should have close observation for at least 24 to 48 hours following apparent clinical recovery, as hypoglycemia can recur.

Conclusion

Glimepiride is a safe, efficient oral medication that can be taken once daily by patients with non-insulin-dependent diabetic reticulopathy (NIDDM) to lower plasma glucose levels. Eight milligrams of glimepiride given once daily was just as effective as the same dose given in two equally divided doses, and a sixteen-milligram regimen given once daily or in two equally divided doses is just as effective. In summary, glimepiride is a safe and efficient glucose-lowering medication for the treatment of non-insulin-dependent diabetic diabetes (NIDDM), according to the study's findings. The once-daily dosage of this novel sulfonylurea may enhance long-term compliance.

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