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A REVIEW ON THE ANTIDIABETIC DRUG USED IN THE TYPE - 2 DIABETIC MELLITUS GLIMEPIRIDE & GLIMEPIRIDE:- EVIDENCE – BASED AND TREADS

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ABSTRACT
Glimepiride is used along with diet and exercise, and sometimes with other medications, to treat type 2 diabetes (condition in which the body does not use insulin normally and, therefore, cannot control the amount of sugar in the blood). Glimepiride lowers blood sugar by causing the pancreas to produce insulin (a natural substance that is needed to break down sugar in the body) and helping the body use insulin efficiently. This medication will only help lower blood sugar in people whose bodies produce insulin naturally. Glimepiride is not used to treat type 1 diabetes (condition in which the body does not produce insulin and, therefore, cannot control the amount of sugar in the blood) or diabetic ketoacidosis (a serious condition that may occur if high blood sugar is not treated). Over time, people who have diabetes and high blood sugar can develop serious or life-threatening complications, including heart disease, stroke, kidney problems, nerve damage, and eye problems. Taking medication(s), making lifestyle changes (e.g., diet, exercise, quitting smoking), and regularly checking your blood sugar may help to manage your diabetes and improve your health. This therapy may also decrease your chances of having a heart attack, stroke, or other diabetes-related complications such as kidney failure, nerve damage (numb, cold legs or feet; decreased sexual ability in men and women), eye problems, including changes or loss of vision, or gum disease. Your doctor and other healthcare providers will talk to you about the best way to manage your diabetes. Glimepiride is a second-generation sulfonylurea that stimulate pancreatic beta cell to release insulin. Additionally, is has shown to work via several extra pancreatic mechanism. It is administered as monotherapy in patients with type 2 diabetes mellitus in whom glycemic control is not actived by dietary and lifestyle modifications. Type 2 diabetes mellitus is characterized by insulin resistance and progressive beta cell failure, therefore beta cell Secretagogue are useful for achieving sufficient glycemic control. It can also be combined with other antihyperglycemic agents. Including metformin and insulin, in patients who are not adequately controlled by sulfonylureas alone.

KEYWORDS: Glimepiride is a second-generation sulfonylurea that stimulate pancreatic beta cell to release insulin.

INTRODUCTION
Diabetes is a major public health problem affecting 285 million people worldwide.[1] The prevalence of diabetes is projected to double globally by 2030.[2] Complications of diabetes include renal failure, neuropathy, and peripheral vascular disease with potential for loss of limbs; retinopathy with an increased risk of blindness; and an increased risk of cardiovascular disease and stroke, which are related to poorly controlled diabetes.[3] Good glycemic control can prevent or delay chronic disease-related microvascular complications, as shown by the United Kingdom Prospective Diabetes Study (UKPDS) and the landmark Diabetes Control and Complications Trial.[4,5] The pathophysiology of type 2 diabetes mellitus (T2DM) is characterized by a relative decrease in insulin secretion and/or insulin resistance. Insulin resistance is a complex phenomenon exacerbated by obesity, particularly central obesity, and is believed to start at a young age because hyperinsulinemia is observed in preteens when both parents have diabetes.[6] T2DM results in progressive loss of insulin secretion, and the UKPDS showed that 50% loss of β cells had occurred by the time of diagnosis; therefore, β cell secretagogues are useful for achieving sufficient glycemic control.[7,8]

The American Diabetic Association/European for the study of diabetes presented a consensus algorithm for managing T2DMbased on expected glycosylated hemoglobin (HbA1c) levels.[9] International Diabetes

Federation guidelines for the management of T2DM also Recommend lifestyle modifications in the initial stages, and addition of metformin or sulfonylurea is then recommended if additional therapy is required.[10] The goals of pharmacologic therapy in diabetes are to achieve good glycemic control while avoiding hypoglycemia and weight gain so as to decrease the risk of future micro- and microvascular complications. Clinicians have a choice of a number of available glucose-lowering agents for managing T2DM, which have been shown to be effective and well-tolerated in clinical practice.

MECHANISM OF ACTION:- Glimepiride is an insulin secretagoue and, like other sulfonylureas, is only effective in patients with residual pancreatic beta cell activity. They act at ATP-dependent potassium channels on cell membrane of pancreatic beta cell causing iatrogenic depolarization by preventing potassium from exiting the cell. The depolarization activates voltage-gated calcium channels on the cell membrane, leading to a rise in intracellular calcium and subsequent exocytosis of insulin into the blood stream.[7] Insulin then acts on cell membrane receptors triggering GLUT-4 expression and the movement of glucose into the cell, lowering blood glucose levels. Additionally, resarcha has shown that glimepiride intereacts with epac3, a nucleotide exchanger that mediates the exocytosis of insulin granules.[8,9,10]

Glimepiride's effectiveness was highlighted in a study conducted on healthy volunteers. Result demonstrated a linear relationship between serum glimepiride and insulin release in englycemic and hyperglycemic conditions.[11]

ADMINISTRATION: The standard dose of glimepiride is between 1 and 2 mg, once daily, taken orally before the patients first meal. Patients who are prone to hypoglycemia should be started at 1 mg once daily and titrated slowly to an appropriate dose initial therapy, the standard maintenance dose is 1 to 4 mg once daily this can be gradually titrated up to 8 mg daily depending on the patients blood glucose and hemoglobin level.[1]

When used for combination therapy with Metformin, the clinician should attempt to identify the minimum effect dose of each drug as the risk of hypoglycemia increase with the uses of metformin with glimepiride.[1]

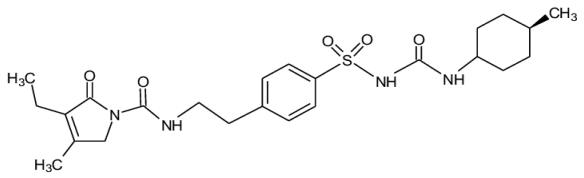
PHARMACODYNAMICS

Pancreatic effects:- Glimepiride acts at ATPase-dependent potassium channels in β cells of the pancreas to stimulate insulin release.[14] using euglycemic and hyperglycemic clamp studies it has been shown to improve both first- and second-phase insulin secretion.[15] Glimepiride binds to 65-kD proteins on β cells. In healthy volunteers, a linear relationship was shown between serum glimepiride concentrations and insulin release during euglycemia and a nearly linear relationship under hyperglycemic conditions.[16,17] Maximal glucose-lowering activity and insulin level in T2DM patients is achieved within 2–3 hours of taking glimepiride and can last for 24 hours.[16] In a 14-week clinical study, peak concentrations 2 hours after administration of 1, 4, and 8 mg doses of glimepiride were associated with decreases in median fasting plasma glucose (FPG) of 43, 70.5, and 74 mg/dL, respectively.[12] Glimepiride reduces blood glucose levels and increases insulin levels in blood. A 3-day study of 14 T2DM patients found greater reductions in blood glucose (4.1 vs 1.9 mmol/L) and increase in C-peptide (1.8 vs 1.4 mg/L) and plasma insulin (41 vs 25 mu/L) with 2 mg/day glimepiride compared to placebo (P, 0.05).[18] Hypoglycemia after exercise while taking glimepiride was observed in 167 patients with T2DM.[19] This was associated with a greater reduction in insulinemia than glibenclamide during exercise, despite similar reductions in blood glucose. Glimepiride may be taken before or after breakfast with similar results. The efficacy of 2 mg/day glimepiride for 2 weeks on blood glucose levels was not significantly different over a period of 0–4 hours when the drug was given either immediately before breakfast or 30 minutes after breakfast.[20]

Extrapancreatic effects:- The extrapancreatic effects of glimepiride are similar to those of other sulfonylureas. Although peripheral tissue response to insulin is potentiated like other SUs, the clinical relevance of this is not yet clear.[21,22] In in vitro studies, glimepiride was found to be two times as potent as glibenclamide in stimulating lipogenesis and glycogenesis.[23] Studies in cultured skeletal muscle also suggest a sensitizing effect of glimepiride.[24] Possible mechanisms include promotion of GLUT4 transport protein activation and/or translocation in fat and muscle.[16,22] Glimepiride reduced insulin resistance and increased hepatic glucose disposal in animal models, but showed no effect in glucose utilization in patients with type 1 diabetes.[25]

Cardiovascular Effects:- Glimepiride appears to cause fewer cardiovascular effects than other SUs.[16] It was found to be associated with few cardiac changes, fewer ventricular arrhythmias, and little or no effect on blood pressure compared to glyburide and glipizide in animal studies.[23] The exact mechanism of this difference in cardiovascular activity is not clear; however, involvement of adenosine triphosphate-sensitive potassium (KATP) channels are thought to play an important role.[24,25] Unlike other SUs, glimepiride does not impair ischemic preconditioning of cardiac myocytes. Ischemic preconditioning is an adaptive phenomenon which occurs in response to an ischemic event and delays infarct development during subsequent ischemic episodes, which may help limit tissue damage.[26] The postulated mechanism involves selective interaction of glimepiride with sacrolemmal ATP dependent potassium channels in cardiac myocytes rather than mitochondrial channels.[27] Evidence suggests that glimepiride preserves myocardial preconditioning, a protective mechanism that limits damage in the event of

an ischemic event.[14] Data from animal studies suggests that the effects of glimepiride on KATP channels, cardiac vessels, or blood vessels were insignificant compared to that caused by the same dosage of glyburide.[28] Similarly, glimepiride has less of an effect in promoting ST segment elevation, enhancing coronary resistance and reducing coronary blood flow compared to glyburide or gliclazide.[29] Thus, using glimepiride may be safer than other SUs in cardiac patients due to its lack of detrimental effects on cardiac preconditioning.



Chemical Structure of Glimepiride

COMPARISON WITH OTHER SULFONYLUREAS:- Glimepiride has been compared to other SUs, including glibenclamide, glipizide, and gliclazide in several clinical trials. Glimepiride 1–8 mg/day was found to be as effective as glibenclamide 1.26–20 mg/day in lowering FPG, PPG, and HbA1c. Dills et al evaluated the efficacy of glimepiride (#16 mg) and glyburide (#20 mg) as monotherapy in 577 patients with T2DM.[30] There was no significant glycemic difference between FPG, PPG, or HbA1c in both study groups after the 1-year treatment period. However, the incidence of hypoglycemia was lower with glimepiride (1.7%) than with glibenclamide (5.0%) (P, 0.015). Another multicenter, prospective, double-blind study comparing glimepiride (1 mg daily, n = 524) and glibenclamide (2.5 mg daily, n = 520) by Draeger et al showed similar results.[31] Glimepiride provided equal glycemic control compared to glyburide, with mean FPG and HbA1c of 174 mg/dL and 8.4% for glimepiride and 168 mg/dL and 8.3% for glibenclamide. Additionally, in this study, glimepiride caused fewer hypoglycemic symptoms compared to glibenclamide. Glimepiride was associated with significantly smaller increases in fasting insulin (P = 0.04) and C-peptide (P = 0.03) concentrations than glyburide. In this trial, 11% of glimepiride-treated patients experienced 105 hypoglycemic episodes, and 14% of the glibenclamide treated patients experienced 150 such episodes.(16) Schernthaner et al compared once daily gliclazide MR and glimepiride in patients with T2DM.[32] In this double-blind, 27-week parallel group study, 845 subjects were randomize to either gliclazide modified release (MR) 30–120 mg daily or glimepiride 1–16 mg daily as monotherapy or in combination with their current treatment (metformin or α glucosidase inhibitor). Efficacy was evaluated based on HbA1c and safety by hypoglycemic episodes using the European Agency definition. HbA1c decreased similarly in both groups from 8.4% to 7.2% in patients on gliclazide MR and from 8.2% to 7.2% in patients receiving glimepiride. The study concluded that glimepiride is as effective as gliclazide MR either as monotherapy or in combination therapy; however, the safety of gliclazide MR was significantly better in terms of hypoglycemic episodes compared with glimepiride.[32] Another study using glimepiride or metformin as monotherapy observed changes in serum sialic acid in patients with T2DM over a period of 12 months. The study concluded that there were no statistically significant differences between groups.[32]

ADVERSE EFFECT

Glimepiride, like other sulfonylureas, has multiple adverse effects, the most deadly and not orious being its metabolic effects. As Glimepiride increases endogenous insulin secretion, this can lead to hypoglycemia. In patients with long-standing diabetes mellitus, hypoglycemic unawareness can manifest where autonomic symptoms and potential hypoglycemic coma.

Weight gain is another significant side effect of sulfonylureas such as glimepiride, which can interface with management as weight loss is often a major target in the treatment of diabetes other adverse effects include vomiting, abdominal pain, diarrhea, erythema multiform and exfoliative dermatitis.[1,13]

CONTRAINDICATIONS

1. Diabetic ketoacidosis
2. Type 1 diabetic mellitus
3. Hypersensitivity to glimepiride

TOXICITY:-In case of overdose of sulfonylureas such an glimepiride, hypoglycemia can occur. It is essential to recognized the sings and symptoms to hypoglycemia, which can fall into the following two categories

1. Automatic symptoms such as tremor, palpitations, nausea, tachycardia, diaphoresis and anxiety.
2. Neuroglycopenic symptoms such as confusion, fatigue, headache, drowsiness, seizure and coma.

Initial management is intravenous dextrose, however this is quickly switch to octreotide as many patient will have sufficient pancreatic function to stimulate endogenous insulin production in response leading to a cycle of dextrose infusion and rebound hyperglycemia activated charcoal should be given as soon as possible for decontamination.[1,4]

INDICATION

Glimepiride is a second-generation sulfonylurea that received FDA approval in 1995 to improve glycemic control in adults with type 2 diabetes mellitus.(1) It can serve as a second-line drug in the treatment of type 2 diabetes mellitus in combination therapy in conjunction with metformin in patients who do not have any form of atherosclerosis cardiovascular disease and are not at their target hemoglobin A1C.(2) Additionally, it is worth noting that glimepiride is the only sulfonylurea approved by the FDA for combination therapy with insulin in patients that are not responsive to combination therapy.(1) Glimepiride is also prescribable as monotherrapy in patients that are unable to tolerate metformin.(3) Glimepiride is sometimes referred to as a

third-generation sulfonylurea, as it has a better safety profile and a prolonged duration of action of up to 24 hours.(4,1) Glimepiride has few cardiovascular effects compared to other sulfonylureas, which are primarily not orious for their effect on myocytes due to the blockade of ATP-dependent potassium channels.(5) Further more, unlike other sulfonylureas, glimepiride does not affect the ischemic preconditioning of cardiac myocytes, defined as an adaptive physiological mechanism, in response to an ischemic event to dealy infraction and limit cardiac tissue damage. Researchers postulate that glimepiride selectively blocks sarcolemmal ATP-dependent potassium channels in cardiac myocytes over mitochondrial preconditioning.(6) This difference from other drugs in the class means that the use of glimepiride may be safer and more ideal in patients with cardiovascular comorbidities.(1)

CONCLUSION

to either gliclazide modified release (MR) 30–120 mg daily or glimepiride 1–16 mg daily as monotherapy or in combination with their current treatment (metformin or α glucosidase inhibitor). Efficacy was evaluated based on HbA1c and safety by hypoglycemic episodes using the European Agency definition. HbA1c decreased similarly in both groups from 8.4% to 7.2% in patients on gliclazide MR and from 8.2% to 7.2% in patients receiving glimepiride. The study concluded that glimepiride is as effective as gliclazide MR either as monotherapy or in combination therapy; however, the safety of gliclazide MR was significantly better in terms of hypoglycemic episodes compared with glimepiride. Another study using glimepiride or metformin as monotherapy observed changes in serum sialic acid in patients with type 2 diabetes mellitus over a period of 12 months. The study concluded that there were no statistically significant differences between groups.

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