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Biodegradable Implant of "Gliclazide" in Diabetes

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ABSTRACT:

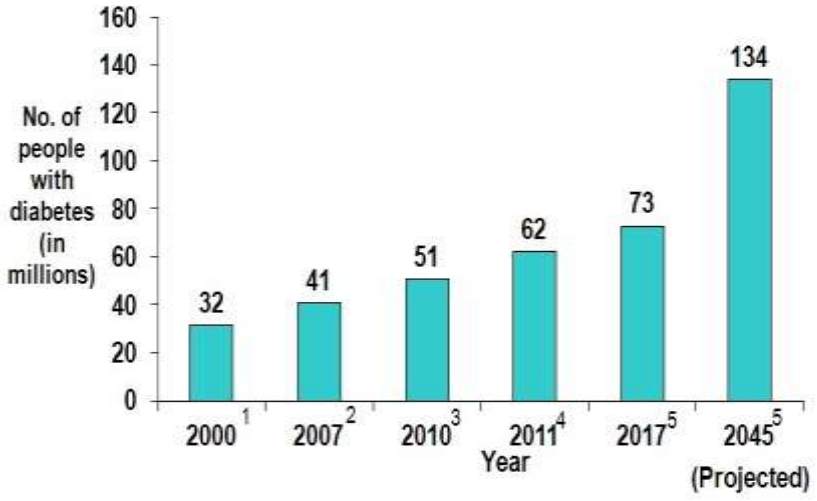
Gliclazide is a second-generation oral hypoglycemic sulfonylurea agent used to treat non-insulin dependent diabetes mellitus (NIDDM). It improves defective insulin secretion and can reverse insulin resistance seen in patients with NIDDM. These effects are reflected in a reduction in blood sugar levels that is sustained during both short- and long-term dosing and is comparable to that achieved by other sulfonylureas. Gradually accumulating evidence suggests that gliclazide may be useful in patients with diabetic retinopathy because of its haemobiological effects and that the addition of gliclazide to insulin therapy allows for a reduction in insulin dose. As such, gliclazide is an effective agent in treating metabolic defects associated with NIDDM and may have the added benefit of potentially slowing the progression of diabetic retinopathy. These effects, together with its good general tolerability and low incidence of hypoglycemia, have allowed gliclazide to rank well within the variety of oral hypoglycemic agents available for the treatment of NIDDM.

KEYWORD: **Gliclazide, oral hypoglycemic agent, diabetes mellitus, tolerability, diabetic retinopathy**

INTRODUCTION:

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficient secretion or action of endogenous insulin. Although the etiology of this disease is not well defined, viral infections, autoimmune diseases, and environmental factors have been implicated. Kidney, retina, lens, peripheral nerve and skin are common and extremely expensive in terms of longevity and quality of life. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications [3-4]. Diabetes is often accompanied by increased free radical production [5-6] or impaired antioxidant defenses [7-8]. The mechanisms by which increased oxidative stress is implicated in diabetic complications are partially understood, including activation of transcription factors, advanced glycosylated end products (AGEs), and protein kinase C. This review focuses on current experimental studies in diabetes and implemented pharmacological interventions in the framework of in vivo test systems. There are also countless in vitro experiments and clinical studies that deserve review. on your own.

Recent studies have shown that the number of diabetes patients projected to 2045 is as follows



(Fig 1) Graphics Presentation

Diabetes Classification –

Type 1 -Diabetes mellitus which is cause by an absolute of near absolute deficiency of insulin

Type 2- Diabetes mellitus which is characterized by the presence of Insulin resistance

Implantable Drug Delivery System

Implants are defined as sterile solid medicinal products manufactured by compression, fusion or sintering. They generally consist of the drug and rate-limiting excipients [9]

Historically, pellets or implants were small, sterile, solid objects, usually cylindrical in shape. for subcutaneous implantation to provide sustained drug release over extended periods of time. To be implanted under the skin (usually in the thigh or abdomen) with a special injector or through a surgical incision. Implantation provides the patient with an inexpensive way to achieve long-lasting drug effects (up to many months after a single implant) and eliminates the need for frequent parenteral or oral hormone therapy. Implanted pellets that may contain 100 times the amount of drug (eg, deoxycorticosterone, testosterone) delivered by a different route of administration so that it is slowly released into the general circulation.

The granules are formulated without binding diluents to allow complete dissolution and absorption of the granules from the implantation site [10]. In 1861, Lafarge pioneered the concept of implantable therapeutic systems for long-term continuous drug delivery with the development of a subcutaneously implantable drug pellet. The technique was rediscovered in 1936 by Densely and Parkes, who administered crystalline hormones in the form of solid steroid pellets to mimic the steady, continuous secretion of hormones from an active gland for hormone replacement therapy.

It was found that the subcutaneous release rate of steroids from the granules was slowed and hormonal activities were prolonged by dispersing the steroids in a cholesterol matrix during the preparation of the granules. Unfortunately, subcutaneous steroid absorption of cholesterol granules was observed to vary greatly from disease to disease.

Subcutaneous drug delivery by implanting pellets was later modified by several investigators. The clinical use of implantable pellets for human healthcare has declined in recent years. For example, in 1979 there were three commercially available steroid pellets for medicine; I) testosterone granules (Oreton Schering) ii) deoxycorticosterone acetate granules (Percorten Ciba) and iii) estradiol granules (Progynon Schering). These products were no longer available in 1989. On the other hand, the laboratory use of implantable pellets for test purposes still popular.[11]

Drug – Gliclazide

Gliclazide is a second-generation sulfonylurea. The oral hypoglycemic agent is used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues. Diabetes mellitus (NIDDM). It belongs to the sulfonylurea class of insulin secretagogues, which work by stimulating the β-cells in the pancreas to release insulin. (Baba et al., 1983) Sulfonylureas increase both by

Basal insulin secretion and meal-stimulated insulin release. Drugs in this class vary in their dosage, rate of absorption, duration of action, route of elimination, and site of binding to their target pancreatic β-cell receptor. (Campbell et al., 1980) Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis, and may increase the number and sensitivity of insulin receptors. Sulfonylureas are associated with weight gain, although less so than insulin.

Due to their mechanism of action, sulfonylureas can cause hypoglycemia and require constant food intake to reduce this risk. The risk of hypoglycaemia is increased in elderly, debilitated, and malnourished individuals. Gliclazide has been shown to reduce fasting blood glucose and postprandial blood glucose. and glycated hemoglobin (HbA1c) levels (reflecting the last 8 to 10 weeks of glucose control) (Campbell et al., 1982).

Gliclazide is extensively metabolised in the liver; its metabolites are excreted in both urine (60–70%) and stool (10–20%).[12] Gliclazide is used to treat type 2 diabetes and is a drug known as a sulfonylurea. Sulfonylureas increase the amount of insulin produced by the pancreas.

This lowers blood sugar levels.

Mechanism of Action

Gliclazide binds to the β-cell sulfonylurea receptor (SUR1). This binding subsequently blocks ATP-sensitive potassium channels. Binding leads to the closure of the channels and a consequent decrease in potassium efflux, leading to depolarization of the β-cells. This opens voltage-gated calcium channels in the β-cell, leading to calmodulin activation, which in turn leads to exocytosis of insulin-containing secretory granules (Hoich et al., 1986).

[13] The mechanism of action of gliclazide in lowering blood glucose levels appears to depend on stimulating insulin release from functioning pancreatic beta cells and increasing the sensitivity of peripheral tissues to insulin. Gliclazide likely binds to ATP-sensitive potassium channel receptors on the cell surface of the pancreas, reducing potassium conductance and causing membrane depolarization. Membrane depolarization stimulates the influx of calcium ions through voltage-gated calcium channels. This increase in the concentration of intracellular calcium ions induces the secretion of insulin.

New drug delivery systems have several advantages over traditional multiple dose therapy. Recent trends indicate that microparticle drug delivery systems are particularly well suited to achieve sustained or controlled release oral formulations with low risk of dose drop, mixing flexibility to achieve different release patterns, as well as long gastric residence time, short and reproducible release of the drug from the microparticles depends on a variety of factors including the vehicle used to form the microparticles and the amount of drug contained therein. sustained and controlled release oral formulations that push the frontiers of future pharmaceutical development. One of these approaches is the use of micro-sponges as active ingredient carriers.

It is the reliable means of delivering the drug specifically to the target site when changed and maintaining the desired concentration at the site of interest without side effects.[14]

1) Absorption: Completely (100%) absorbed following oral administration. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished.

2) Distribution: Plasma protein binding is greater than 99%. Volume of Distribution: 1) Volume of Distribution after oral administration was 19.8 to 37.1 L. 2) Volume of Distribution after intravenous administration was 9 L.

3) Metabolism: Gliclazide undergoes hepatic metabolism. Following either an intravenous or oral dose, Gliclazide is completely metabolized by oxidative biotransformation to a major metabolite, cyclohexyl hydroxymethyl derivative (M1), via the hepatic cytochrome P450 II C9 subsystem. M1 is further metabolized to the carboxyl derivative (M2) by one or several cytosolic enzymes. M1, but not M2, possessed approximately one third of the pharmacologic activity of its parent in an animal model. However, whether the glucose-lowering effect of M1 is clinically significant and is not clear.

4) Excretion: Gliclazide is mainly excreted through kidney. Most of a dose of Gliclazide is excreted in the urine as metabolites (up to 60%). No parent compound is recovered unchanged. About 40% is excreted through Faces. Gliclazide, clearance increases with decreasing renal function probably due to more unbound drug with hypo albuminemia. The clearance of both metabolites decreased with worsening renal function. Patients with diabetes mellitus and creatinine clearance less than 20 ml/min to more than 50 ml/min were treated with Gliclazide 1 to 8 mg/day for 3 months. The dosage was adjusted based on blood glucose response. Total Body Clearance is 48 to 53 ml/min; and elimination half-life is 5 to 8 hrs after oral administration [15,16]

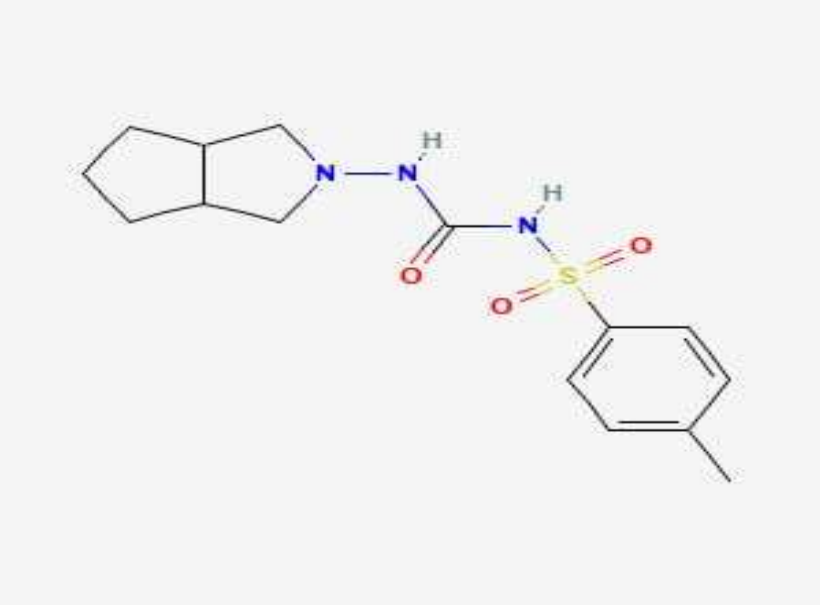
DRUG PROFILE. GLICLAZIDE:

1. Synonym: Gliclazid Gliclazide, Gliclazidum.

2. Category: Anti diabetic drug.

3. Chemical name: Benzenesulfonamide, N-[[(hexadydrocyclopenta[c] Pyrol – 2(1H)-yl) amino] carbonyl]-4-methyl

4. Structure {14}



(Fig -2) Structure Gliclazide

5. Molecular formula : C15H21N3O3S

6. Molecular weight: 323.42

7. Melting point: 180-1820 c

8. Description: Gliclazide is a white powder, relatively insoluble in water.

9. Bio classification: Class 2

10. Solubility: Gliclazide is freely soluble in dimethyl formamide; slightly soluble in methanol sparingly soluble in methylene chloride; practically insoluble in water. It also dissolves in dilute alkali hydroxides and in dilute acids

CONTRAINDICATIONS:

Gliclazide should not be used in cases where diabetes is complicated by acidosis, ketosis, or coma, or in patients with a history of recurrent ketoacidosis or coma. should not be used under these conditions. Gliclazide is contraindicated in severe hepatic or renal insufficiency. Close monitoring is required in patients taking gliclazide who have impaired kidney or liver function. Patients sensitive to sulfonylureas should not take gliclazide.

Alcohol consumption: Gliclazide can cause an uncomfortable "intolerance reaction" to alcohol. People taking gliclazide may experience flushing, flushing, nausea, dizziness, and possibly an increased heart rate when consuming alcohol. Avoid drinking alcohol to prevent this reaction. Diabetes complications: Like other diabetes medicines, the use of gliclazide will not prevent the development of diabetes complications. , lack of energy, drowsiness, headache and sweating were observed.

Weakness, nervousness, shakiness, and numbness or tingling have also been reported.Seniors, those with reduced liver or kidney function, and those who are fragile or malnourished are more likely to have low blood sugar when they take these medications.Low blood sugar is morelikely to occur when food intake is inadequate or after strenuous or prolonged physical exercise.Blood glucose should be monitored regularly and emergency glucose (and glucagon kit) kept available in case the need arises to increase blood sugar levels.

Illness/Stress: People being treated with gliclazide may lose glycemic control during illness or in stressful situations such as trauma or surgery. Under these conditions, the doctor may consider stopping the drug and prescribing insulin until the situation improves. Medical Conditions: People with kidney problems, liver problems, or a condition called glucose-6-phosphate dehydrogenase (G6PD) deficiency (Kilo et al., 1) need to discuss with the doctor how this drug may affect the condition, how the condition may affect the dosage and effectiveness of this drug, and whether special monitoring is needed.

Adequate nutrition: The use of gliclazide should be considered as an adjunct to, and not a substitute for, adequate nutrition. Worsening of the condition: Over time, gliclazide may become less effective due to the worsening of the diabetes. Gliclazide is no longer controlling blood sugar at desired levels, it should be discontinued and another drug added. Pregnancy: Pregnant women should not take gliclazide.

Breastfeeding: Women who are breastfeeding should not take gliclazide. Children: The safety and effectiveness of using this medication in children has not been established

DRUG -INTERACTIONS :

There may be an interaction between gliclazide and any of the following (Kosaka K et al. , 1983):[17]

- ACE inhibitors (e.g., enalapril)
- Alcohol
- Anticoagulants (e.g., warfarin, heparin)
- Azole antifungal drugs (e.g., miconazole, clotrimazole)
- Barbiturates (e.g., phenobarbital, thiopental)
- Beta-blockers (e.g., metoprolol, propranolol)
- Chlorpromazine
- Clarithromycin
- Corticosteroids (e.g., prednisone)
- Danazol
- Disopyramide
- Diuretics (e.g., thiazides, furosemide)
- Fibrates (e.g., fenofibrate)
- H2 receptor antagonists (e.g., ranitidine, famotidine, cimetidine)
- Monoamine oxidase inhibitors(e.g., selegiline, phenelzine)
- Nicotinic acid

- Nonsteroidal anti inflammatory drugs (e.g., ibuprofen, naproxen)
- Oral contraceptives
- Other antidiabetic drugs (e.g., insulin, metformin)
- Phenylbutazone
- Probenecid
- Salbutamol
- Salicylates (e.g., acetylsalicylic acid [ASA])
- Terbutaline
- Tuberculosis medications (e.g., isoniazid, ethambutol) ADVERSE EFFECTS The most notable effects are hypoglycaemia (Journal of Applied Pharmaceutical Science 01 (09); 2011: 11-19 www.japso)

Toxicity-

Maximum tolerated dose: In the dog, this dose is between 150 and 200 mg/kg by daily administration. Four-week oral toxicity study in the Beagle dog: Groups of 4 Beagle dogs (2 males, 2 females), were treated for 30 days with 0, 15, 30, 45 or 90 mg/kg/day. At the dose of 90 mg/kg, 2 animals died as a result of prolonged hypoglycemic coma following 2 weeks of treatment. All others showed normal behaviour, with the exception of an increase in the weight of the liver. No evidence was found of any change in biochemical (apart from the fall in blood glucose), haematological and histopathological parameters (Shimizu et al. , 1976). Two-month oral toxicity study in the guinea-pig: Groups of 10 guinea-pigs (5 males, 5 females), were treated 6 days out of 7 for 2 months with 0, 25, 50 or 100 mg/kg/day. Only male animals in the 50 mg/kg group showed delayed weight gain. All others had normal biochemical, haematological and histopathological results.nline.com)[18]

Drug Interactions:

Acebutolol :

Acebutolol is Beta blocking agents, administration of this with Gliclazide produce: hypoglycaemia, hyperglycaemia, or hypertension.

NSAID:

Concomitant use of an NSAID and a sulfonylurea suggest an increased risk of hypoglycaemia may occur.

Example: - Aceclofenac Acemetacin

Over dosage:

• After ingestion of an over dosage hypoglycaemia may occur, lasting from 12 to 72 hour, and is accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination problems, sleepiness, coma and convulsions.

• Nausea, vomiting and epigastric pain may occur.

Adverse effects:

• Asthma

• Blurred vision

• Cholestasis

• Hepatic porphyria

• Hepatitis

• Hyponatremia

• Hypoglycaemia

• Photosensitivity

• Diarrhoea, Nausea, Vomiting, and Abdominal pain

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