Melizide

Glipizide

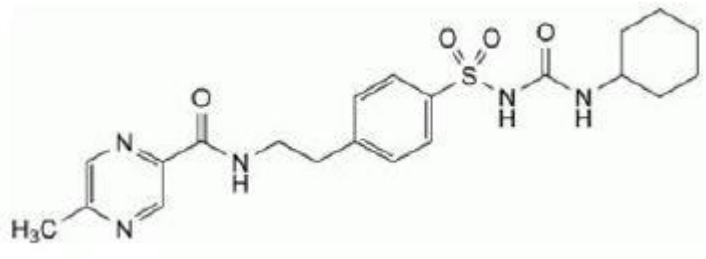
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Glipizide

Chemical name : 1-cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido)ethyl]benzene-sulfonyl}urea

Structural formula :



Molecular formula : $C_{21}H_{27}N_5O_4S$ Molecular weight : 445.55

CAS Registry no. 29094-61-9

DESCRIPTION

Glipizide is an oral blood-glucose lowering drug of the sulfonylurea class.

Glipizide is a whitish, odourless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 N sodium hydroxide and freely soluble in dimethylformamide.

Melizide tablets also contain the following inactive ingredients: lactose, maize-starch, - maize-starch - pregelatinised maize and magnesium stearate.

PHARMACOLOGY

Glipizide is a sulfonylurea hypoglycaemic agent.

Mechanism of action

The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the β cells of pancreatic islet tissue, and is thus dependent on functioning β cells in the pancreatic islets. In humans, glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β cells in the pancreatic islets. The mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. In humans, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycaemic drugs.

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded, or have ceased to respond, to other sulfonylureas.

Duration of action

Clinical studies show that blood sugar control persists in some patients for up to 24 hours after a single dose of glipizide, even though plasma levels have fallen to a small fraction of peak levels by that time.

Pharmacokinetics

Absorption

Gastrointestinal absorption of glipizide in humans is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1 to 3 hours after a single oral dose. The half-life of elimination ranges from 2 to 4 hours in normal subjects, whether given intravenously or orally. Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients.

Distribution

Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 92 to 99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 5 to 11 L, indicative of localisation within the extracellular fluid compartment.

In mice, neither glipizide nor metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given the labelled drug.

Metabolism and excretion

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates, and are excreted mainly in the urine. Less than 3 to 4.3% unchanged glipizide is found in the urine. The metabolic and excretory patterns are similar with both oral and intravenous routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration.

INDICATIONS

Adjunct to diet and exercise for the control of hyperglycaemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus (NIDDM; type II), formerly known as maturity onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

In initiating treatment for non-insulin dependent diabetes, diet should be emphasised as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycaemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified, and corrective measures taken where possible. If this treatment programme fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of Melizide must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of Melizide.

During maintenance programmes, Melizide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgements should be based on regular clinical and laboratory evaluations.

CONTRAINDICATIONS

1. Known hypersensitivity to the drug or to other sulfonylurea derivatives.
2. Allergy to sulfonamides.
3. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
4. Juvenile, growth onset or brittle diabetes mellitus.
5. Severe renal or hepatic insufficiency.
6. Severe thyroid dysfunction.
7. Pregnancy (see **PRECAUTIONS, Use in Pregnancy**).
8. Severe or unstable diabetes.
9. Infections and febrile conditions.
10. Gangrene.
11. Severe trauma.
12. Major surgical procedures.
13. Children.

PRECAUTIONS

General

The risks of hypoglycaemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Patients should be informed of the potential risks and advantages of Melizide and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise programme, and of regular testing of urine and/or blood glucose.

G6PD-Deficiency

Since glipizide belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency. Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to haemolytic anaemia and a non-sulfonylurea alternative should be considered.

Hypoglycaemia

All sulfonylurea drugs are capable of producing severe hypoglycaemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycaemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycaemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycaemic action of glucose lowering drugs. Hypoglycaemia may be difficult to recognise in the elderly, and in people who are taking β-adrenergic blocking drugs. Hypoglycaemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose lowering drug is used.

Loss of Control of Blood Glucose

When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue Melizide and administer insulin.

Secondary Failure

The effectiveness of any oral hypoglycaemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. The phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Renal and Hepatic Disease

The metabolism and excretion of Melizide may be slowed in patients with impaired renal and/or hepatic function. If hypoglycaemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Laboratory Tests

Blood and urine glucose should be monitored periodically. Measurement of glycosylated haemoglobin and/or fructosamine levels may be useful.

Effects on Ability to Drive or Operate Machinery

The treatment of diabetes with glipizide requires regular check-ups. Until optimum stabilisation has been achieved, e.g. during the changeover from other medications or during irregular use, the ability to drive and use machinery may be impaired.

Use in Pregnancy (Category C)

Glipizide was found to be mildly foetotoxic in rat reproductive studies at all dose levels (5 to 50 mg/kg). The foetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacological (hypoglycaemic) action of glipizide. In studies in rats and rabbits, no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women.

Sulfonylureas are not suitable for the treatment of diabetes mellitus during pregnancy as significant metabolic changes occur during this period, which make control difficult.

Use in Lactation

Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycaemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Paediatric Use

Not for use in children (see **CONTRAINDICATIONS**).

INTERACTIONS WITH OTHER MEDICINES

The hypoglycaemic action of sulfonylureas may be potentiated by certain drugs including non-steroidal anti-inflammatory agents, quinolone antibiotics, and other drugs that are highly protein bound, salicylates, sulfonamides, clofibrate, biguanides, diazoxide, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and β-adrenergic blocking agents.

Fluconazole:

There have been reports of hypoglycaemia following the co-administration of glipizide and fluconazole, possibly the result of an increased half-life of glipizide.

Alcohol:

Alcohol may increase the hypoglycaemic effect of Melizide, which could lead to hypoglycaemic coma.

Angiotensin converting enzyme inhibitors:

The use of angiotensin converting enzyme inhibitors may lead to an increase hypoglycaemic effect in diabetic patients treated with sulfonylureas, including Melizide. Therefore, a reduction in Melizide dosage may be required.

H_2 Receptor Antagonists:

The use of H_2 receptor antagonists (i.e. cimetidine) may potentiate the hypoglycaemic effects of sulfonylureas, including Melizide.

Voriconazole:

Although not studied, voriconazole may increase plasma level of sulfonylureas (e.g. tolbutamide, glipizide and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration.

When such drugs are administered to a patient receiving Melizide, the patient should be observed closely for hypoglycaemia. When such drugs are withdrawn from a patient receiving Melizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicated that glipizide binds differently than tolbutamide and does not interact with salicylate or dicoumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycaemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, alcohol (chronic abuse), glucagon and isoniazid. When such drugs are administered to a patient receiving Melizide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving Melizide, the patient should be observed closely for hypoglycaemia.

A potential interaction between oral miconazole and oral hypoglycaemic agents leading to severe hypoglycaemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

The risk of increase of effect of barbiturates is extremely low for pharmacokinetic reasons (non-ionic protein binding).

Tetracycline may interfere with determination of urine glucose. Cyclophosphamide and derivatives should also be used with care in diabetic patients since increased and decreased effects of sulfonylureas have been reported.

ADVERSE EFFECTS

In controlled studies, the frequency of serious adverse reactions reported was low. Of 702 patients, 11.8% reported adverse reactions, and in only 1.5% was glipizide discontinued.

Hypoglycaemia

See **PRECAUTIONS** and **OVERDOSAGE**.

Gastrointestinal

Gastrointestinal disturbances are the most common reactions, and were reported with the following approximate incidence: nausea and diarrhoea, (1.4%); constipation and gastralgia, (1%); vomiting (> 1%). They appear to be dose related and may disappear on division or reduction of dosage. Abdominal pain has also been reported. Cholestatic jaundice may occur rarely with sulfonylureas; Melizide should be discontinued if this occurs.

Dermatological

Allergic skin reactions including rash, erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about 1 in 70 patients. These may be transient and may disappear despite continued use of Melizide; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Metabolic

Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Haematological

Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia and pancytopenia have been reported with sulfonylureas.

Endocrine

Cases of hyponatraemia, and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous

Dizziness, drowsiness, vertigo and headache have each been reported in about 1 in 50 patients treated with glipizide. Confusion, tremor and malaise have also been reported. They are usually transient and rarely require discontinuance of therapy. These symptoms together with weakness, clouding of vision, etc. may be signs of hypoglycaemia. However, the risk of severe or prolonged hypoglycaemia is low.

Eye disorders

Visual disturbances such as blurred vision, diplopia and abnormal vision including visual impairment and decreased vision, have each been reported in patients treated with glipizide. They are usually transient and do not require discontinuance of therapy. However, they may also be symptoms of hypoglycaemia.

Hepatobiliary disorders

Impaired hepatic function and hepatitis have been reported.

Laboratory tests

The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

DOSAGE AND ADMINISTRATION

Generally, the drug should be taken about 30 minutes before meals in order to achieve the greatest reduction in postprandial hyperglycaemia.

There is no fixed dosage regimen for the management of diabetes mellitus with Melizide or any other hypoglycaemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure i.e. inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e. loss of an adequate blood glucose lowering response after an initial period of effectiveness. Monitoring of glycosylated haemoglobin levels may also be of value.

Initial dose

The recommended starting dose is 5 mg given before breakfast. Elderly patients or those with liver disease may be started on 2.5 mg.

Dosage titration

Dosage adjustments should ordinarily be in increments of 2.5 to 5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

Maintenance

Some patients may be effectively controlled on a once daily regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a twice daily basis to long-term patients. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycaemic reactions (see **PRECAUTIONS**).

Patients receiving insulin agents

As with other sulfonylurea class hypoglycaemics, many stable non-insulin dependent diabetic patients receiving insulin may be safely placed on Melizide.

Patients receiving other oral hypoglycaemic agents

As with other sulfonylurea class hypoglycaemics, no transition period is necessary when transferring patients to Melizide. Patients should be observed carefully (1 to 2 weeks) for hypoglycaemia when being transferred from longer half-life sulfonylureas (e.g. chlorpropamide) to Melizide due to potential overlapping of drug effect.

OVERDOSAGE

There is no well documented experience with glipizide overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4 g/kg).

Symptoms

Overdosage with sulfonylureas including glipizide can produce hypoglycaemia.

Treatment

Mild hypoglycaemic symptoms without loss of consciousness or neurological findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycaemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalisation.

If hypoglycaemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 5.55 mmol/L. Patients should be

closely monitored for a minimum of 24 to 48 hours since hypoglycaemia may recur after apparent clinical recovery.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Clearance of Melizide from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

Contact the Poison Information Centre on 131126 (Australia) for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Melizide 5 mg tablet: white, oval, scored, marked "GP/5" on one side, "α" on the reverse; 100's.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

3/11/1993

DATE OF MOST RECENT AMENDMENT

15/10/2015