



ISSN: 2231-3354
 Received on: 05-10-2011
 Revised on: 18-10-2011
 Accepted on: 11-11-2011

Pharmacological and Pharmaceutical Profile of Gliclazide: A Review

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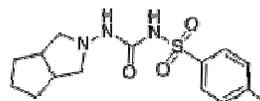
ABSTRACT

Gliclazide is a second generation sulphonylurea oral hypoglycaemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It improves defective insulin secretion and may reverse insulin resistance observed in patients with NIDDM. These actions are reflected in a reduction in blood glucose levels which is maintained during both short and long term administration, and is comparable with that achieved by other sulphonylurea agents. Gradually accumulating evidence suggests that gliclazide may be useful in patients with diabetic retinopathy, due to its haemobiological actions, and that addition of gliclazide to insulin therapy enables insulin dosage to be reduced. Thus, gliclazide is an effective agent for the treatment of the metabolic defects associated with NIDDM and may have the added advantage of potentially slowing the progression of diabetic retinopathy. These actions, together with its good general tolerability and low incidence of hypoglycaemia have allowed gliclazide to be well placed within the array of oral hypoglycaemic agents available for the control of NIDDM.

Keywords: Gliclazide, oral hypoglycaemic agent, diabetes mellitus, tolerability, diabetic retinopathy.

INTRODUCTION

Gliclazide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It belongs to the sulphonylurea class of insulin secretagogues, which act by stimulating β cells of the pancreas to release insulin. (Baba et al., 1983) Sulphonylureas increase both basal insulin secretion and meal-stimulated insulin release. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their target pancreatic β cell receptor. (Campbell et al., 1980) Sulphonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Sulphonylureas are associated with weight gain, though less so than insulin. Due to their mechanism of action, sulphonylureas may cause hypoglycemia and require consistent food intake to decrease this risk. The risk of hypoglycemia is increased in elderly, debilitated and malnourished individuals. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control) (Campbell et al., 1982). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%).



IUPAC Name of Gliclazide ($C_{15}H_{21}N_3O_3S$) is 1-[(4-methylphenyl)sulfonyl]-3-octahydrocyclo

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penta [c] pyrrol-2-yl}urea, which is available in market in the form of different brand like Diamicon (Servier) , Diamicon MR (Servier) , Glimicon, Mylan-Gliclazide (Mylan) , Nordialex , PMS-Gliclazide (Pharmasciences).It may be classified under Hypoglycemic Agents , Sulfonylureas, Antidiabetics

BASICS OF SULPHONYLUREAS

The sulphonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital (Chan et al., 1982).

Sulphonylureas are considered for patients who are not overweight, or in whom metformin is contra-indicated or not tolerated. Several sulphonylureas are available and choice is determined by side-effects and the duration of action as well as the patient's age and renal function. The long-acting sulphonylureas chlorpropamide and glibenclamide are associated with a greater risk of hypoglycaemia; for this reason they should be avoided in the elderly and shorter-acting alternatives, such as gliclazide or tolbutamide, should be used instead. Chlorpropamide also has more side-effects than the other sulphonylureas and therefore it is no longer recommended.

When the combination of strict diet and sulphonylurea treatment fails other options include:

- i) Combining with metformin (reports of increased hazard with this combination remain unconfirmed)
- ii) Combining with acarbose which may have a small beneficial effect, but flatulence can be a problem (Chiasson et al., 1987).
- iii) Combining with pioglitazone or rosiglitazone
- iv) Combining with bedtime isophane insulin but weight gain and hypoglycaemia can occur.

Insulin therapy should be instituted temporarily during intercurrent illness (such as myocardial infarction, coma, infection, and trauma). Sulphonylureas should be omitted on the morning of surgery; insulin is required because of the ensuing hyperglycaemia in these circumstances (Desnoyers P et al., 1972).

CAUTIONS

Sulphonylureas can encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting; metformin is considered the drug of choice in obese patients. Caution is needed in the elderly and in those with mild to moderate hepatic and renal impairment because of the hazard of hypoglycaemia. The short-acting tolbutamide may be used in renal impairment, as gliquidone and gliclazide which are principally metabolised in the liver, but careful monitoring of blood-glucose concentration is essential; care is required to choose the smallest possible dose that produces adequate control of blood glucose (Duhault et al., 1972).

CONTRA-INDICATIONS

Sulphonylureas should be avoided where possible in severe hepatic and renal impairment and in porphyria .They should not be used while breast-feeding and insulin therapy should be substituted during pregnancy. Sulphonylureas are contra-indicated in the presence of ketoacidosis. (Duhault et al. , 1975)

SIDE-EFFECTS

Side-effects of sulphonylureas are generally mild and infrequent and include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and constipation.

Chlorpropamide has appreciably more side-effects, mainly because of its very prolonged duration of action and the consequent hazard of hypoglycaemia and it should no longer be used. It may also cause facial flushing after drinking alcohol; this effect does not normally occur with other sulphonylureas. Chlorpropamide may also enhance antidiuretic hormone secretion and very rarely cause hyponatraemia (hyponatraemia is also reported with glimepiride and glipizide) (Futijani et al.,1983).

Sulphonylureas can occasionally cause a disturbance in liver function, which may rarely lead to cholestatic jaundice, hepatitis and hepatic failure. Hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy, they consist mainly of allergic skin reactions which progress rarely to erythema multiforme and exfoliative dermatitis, fever and jaundice; photosensitivity has rarely been reported with chlorpropamide and glipizide. Blood disorders are also rare but may include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia (Gamstedt et al., 1987).

CLINICAL PHARMACOLOGY OF GLICLAZIDE

Gliclazide is a sulphonylurea drug with an intermediate half-life of around 11 hours. It is extensively metabolised, and renal clearance accounts for only 4% of total drug clearance. The molecule contains an azabicyclo-octyl group which confers special properties on the basic sulphonylurea moiety. Gliclazide stimulates insulin secretion through the β cell sulphonylurea receptor, and possibly through a direct effect on intracellular calcium transport. It specifically improves the abnormal first phase insulin release in type 2 diabetes, and also has an effect on the second phase. This pattern of insulin release is thought to explain the lower incidence of hypoglycaemic episodes and weight gain compared with some other sulphonylureas. There is also a reduction in hepatic glucose production and improvement in glucose clearance, without changes in insulin receptors. This suggests a possible post-receptor effect on insulin action, perhaps by stimulation of hepatic fructose-2,6-bisphosphatase and muscle glycogen synthase. Gliclazide reduces platelet adhesion, aggregation and hyperactivity and increases fibrinolysis (Golay et al., 1984). These actions, thought to be independent of its hypoglycaemic activity, may make gliclazide useful in halting the progression of diabetic microangiopathy.

PHARMACODYNAMICS

Gliclazide reduces blood glucose levels in patients with

NIDDM by correcting both defective insulin secretion and peripheral insulin resistance. Un-stimulated and stimulated insulin secretions from pancreatic β cells are increased following the administration of gliclazide, with both first and second phases of secretion being affected. This occurs via binding of gliclazide to specific receptor on pancreatic β cells which results in a decrease in potassium efflux and causes depolarization on the cell. Subsequently, calcium channels open, leading to an increase in intracellular calcium and induction of insulin release. In addition, gliclazide increases the sensitivity of β cells to glucose. Gliclazide may have extra pancreatic effect which restores peripheral insulin sensitivity, such as decreasing hepatic glucose production, and increasing glucose clearance and skeletal muscle glycogen synthesis activity. These effects do not appear to be mediated by effect on insulin receptor number, affinity or function. There is some evidence that gliclazide improves defective hematological activity in patients with NIDDM (Harrower et al., 1985).

MECHANISM OF ACTION

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

PHARMACOKINETIC PROPERTIES

Oral absorption of gliclazide is similar in patients and healthy volunteers, but there is intersubject variation in time to reach peak plasma concentrations (t_{max}). Age related differences in plasma peak concentrations (C_{max}) and t_{max} , have been observed. A single oral dose of 40 to 120 mg of gliclazide results in a C_{max} of 2.2 to 8.0 $\mu\text{g/ml}$ within 2 to 8 hours. T_{max} and c_{max} are increased after repeated gliclazide administration. Steady state concentration is achieved after 2 days administration of 40 to 120 mg of gliclazide. Gliclazide has low volume of distribution (13 to 24L) in both patients and healthy volunteers due to its high protein binding affinity (85 to 97%). The elimination half-life ($t_{1/2}$) is about 8.1 to 20.5 hr in healthy volunteers and patients after administration of 40 to 120 mg orally. Moreover, its plasma clearance is 0.78 L/h (13 ml/min). It is extensively metabolized to 7 metabolites and excreted in urine therefore renal insufficiency has no effect in pharmacokinetic of gliclazide (Holmes et al., 1984). The variability in absorption of gliclazide could be related to its early dissolution in the stomach leading to more variability in the absorption in the intestine. This process resulted in low bioavailability of the conventional dosage forms. The use of solubilizing agents like PEG 400 was reported to increase the bioavailability of gliclazide in its oral dosage forms. Also gliclazide was included with α -cyclodextrin or β -cyclodextrin.

Absorption

Rapidly and well absorbed but may have wide inter- and

intra-individual variability. Peak plasma concentrations occur within 4-6 hours of oral administration.

Distribution

Gliclazide is distributed in the extracellular fluid, leading to high concentrations in the liver, kidneys, skin, lungs, skeletal muscle, intestinal and cardiac tissue when administered to animals. There appears to be negligible penetration into the central nervous system. Gliclazide also crosses the placental barrier and circulates in the foetal blood system. A low apparent volume of distribution is probably reflected in the high degree of gliclazide binding to proteins (approximately 94% at a plasma concentration of 8mcg/mL).

Protein binding

94%, highly bound to plasma proteins.

Metabolism

Extensively metabolized in the liver. Less than 1% of the orally administered dose appears unchanged in the urine. Metabolites include oxidized and hydroxylated derivatives, as well as glucuronic acid conjugates.

Enzymes	Metabolites	Reaction
Cytochrome P450 2C9	7-Hydroxygliclazide 6-Hydroxygliclazide	7-hydroxylation
Cytochrome P450 2C19	Methylhydroxygliclazide	

Approximately 70% of the administered dose is excreted slowly in the urine, reaching a peak 7 to 10 hours after administration. Metabolites are detectable in the urine 120 hours after administration. Faecal elimination accounts for approximately 11 % of the administered dose (Ings et al., 1986). Gliclazide is usually completely eliminated within 144 hours post dose.

Route of elimination

Metabolites and conjugates are eliminated primarily by the kidneys (60-70%) and also in the feces (10-20%).

Half life

10.4 hours. Duration of action is 10-24 hours.

Toxicity

LD_{50} =3000 mg/kg (orally in mice). Gliclazide and its metabolites may accumulate in those with severe hepatic and/or renal dysfunction. Symptoms of hypoglycemia include: dizziness, lack of energy, drowsiness, headache and sweating (Jerums et al., 1987).

Affected organisms

Humans and other mammals.

Indications

Adult onset diabetes mellitus (type 2) that cannot be controlled by diet alone.

Dosage and Administration

Dosage should be initiated at 40mg (1/2 tablet) daily and may be increased if necessary up to 320 mg daily (4 tablets). Doses up to 160mg daily may be taken in a single dose, preferably at the same time each morning. Doses in excess of 160mg should be taken in divided doses in the morning and the evening. The severity of glycaemia will determine the dosage, requiring adjustment to obtain the optimal response at the lowest dosage. Use of gliclazide does not obviate the necessity of regulating diet.

CONTRAINDICATIONS

Gliclazide should not be used in cases where diabetes is complicated by acidosis, ketosis or coma, or in patients with a history of repeated ketoacidosis or coma. Sulphonylurea hypoglycaemic agents are not effective in juvenile onset, unstable or brittle diabetes, so gliclazide should not be used in these conditions. Gliclazide is contraindicated in severe hepatic or renal insufficiency. Close monitoring of patients taking gliclazide who have impaired renal or hepatic function is necessary. Patients who are sensitive to sulphonylurea agents should not take gliclazide.

Alcohol use: Gliclazide can cause an unpleasant "intolerance reaction" to alcohol. People taking gliclazide may experience flushing, warmth, nausea, giddiness, and possibly increased heart rate when they use alcohol. To prevent this reaction, avoid drinking alcohol.

Diabetes complications: Similar to other medications for diabetes, the use of gliclazide will not prevent the development of diabetes complications.

Hypoglycemia (low blood sugar): Gliclazide, like other sulphonylurea drugs, can cause symptoms of hypoglycemia (low blood sugar) including dizziness, lack of energy, drowsiness, headache, and sweating have been 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 more likely 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 on gliclazide therapy may experience loss of blood sugar control during illness or stressful situations, such as trauma or surgery. Under these conditions, the doctor may consider stopping the medication and prescribing insulin until the situation improves.

Medical conditions: People having kidney problems, liver problems, or a condition called *glucose-6-phosphate dehydrogenase (G6PD) deficiency* (Kilo et al., 1987) have to discuss with doctor how this medication may affect medical condition, how medical condition may affect the dosing and

effectiveness of this medication, and whether any special monitoring is needed.

Proper diet: The use of gliclazide must be considered as treatment in addition to proper diet and not as a substitute for diet.

Worsening of condition: Over a period of time, gliclazide may become less effective because of the worsening of diabetes. If gliclazide no longer controls blood glucose to target levels, it should be stopped and another medication added.

Pregnancy: Pregnant women should not take gliclazide.

Breast-feeding: Breast-feeding women should not take gliclazide.

Children: The safety and effectiveness of using this medication have not been established for children

DRUG -INTERACTIONS

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

- 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; gastrointestinal disturbances such as constipation, nausea, epigastric discomfort and heartburn; dermatological reactions such as rash and transient itching; and biochemical abnormalities such as elevated serum creatinine, increased serum alkaline phosphatase, raised serum AST, elevated BUN and raised serum bilirubin. Headache, slight disulfiram-like reactions and lassitude

have been reported. (Kuwashima J et al. , 1979) Although very rare, severe hypoglycaemia may occur in patients receiving gliclazide.

INTERACTIONS

Thiazide diuretics are known to aggravate the diabetic state so caution should be taken when administering thiazide diuretics to patients on gliclazide treatment. Blood sugar control may also be adversely affected where interaction between gliclazide and barbiturates, glucocorticoids or oestrogens occurs.

The hypoglycaemic effect of gliclazide may be potentiated by insulin, biguanides, sulphonamides, salicylates, coumarin derivatives, chloramphenicol, monoamine oxidase inhibitors, β -blockers, oxyphenbutazone, phenylbutazone, clofibrate, cimetidine and ethanol.

Acute alcohol intoxication potentiates the hypoglycaemic action of sulphonylurea agents. Disulfiram-like reactions with characteristic flushing of the face, throbbing headache, giddiness, tachypnoea, tachycardia or angina pectoris may also occur. Chronic alcohol abuse may result in increased metabolism of sulphonylurea drugs, shortening the plasma half-life and duration of action.

OVERDOSAGE

Overdose may result in severe hypoglycaemia. Sulphonylurea agent induced hypoglycaemia is different to insulin coma. Warning symptoms are often absent, neurological syndromes are frequent and coma is often prolonged. Consciousness should be restored by administration of intravenous glucose or glucagon injection. Care should be taken that hypoglycaemia doesn't return by constant monitoring of blood sugar levels.

WARNINGS & PRECAUTIONS

Some acute complications (such as severe trauma, fever, infection or surgery) can occur as a result of metabolic stress. This accentuates the predisposition to hyperglycaemia and ketosis. Insulin must be administered to control these situations. An increase in dosage of gliclazide is not appropriate. Close observation of patients through all stages of administration, particularly in elderly, debilitated, malnourished, semi-starved or those who have neglected dietary restrictions, is necessary to ensure that hypoglycaemia does not occur.

Effects on ability to drive and use machinery

Concentration may be partially impaired if diabetes is not managed well. Therefore, ability to drive or use machinery will be impaired if diabetes is not well managed, including when taking gliclazide.

Use in pregnancy and lactation:

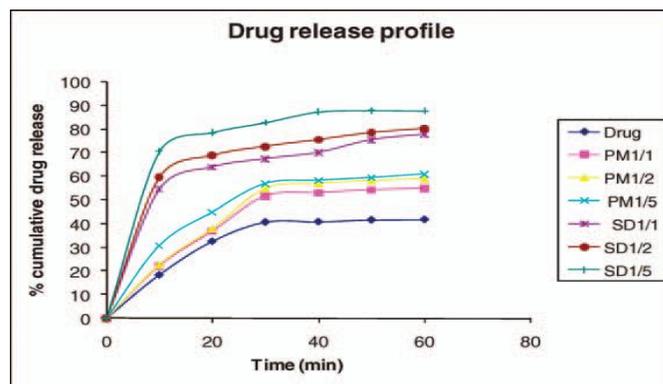
Gliclazide is a category C drug, indicating that it may have caused or be suspected of causing harmful effects to the human foetus or neonate without causing malformations. These effects are reversible. Therefore, gliclazide should not be used in

pregnancy and should be replaced by insulin. Sulphonylureas may enter the foetus and cause foetal hypoglycaemia. Embryotoxicity and/or birth defects have been demonstrated in animal studies. In light of these factors, gliclazide should only be used in women who are likely to become pregnant if the benefits outweigh the potential risk. Gliclazide should not be used during lactation.

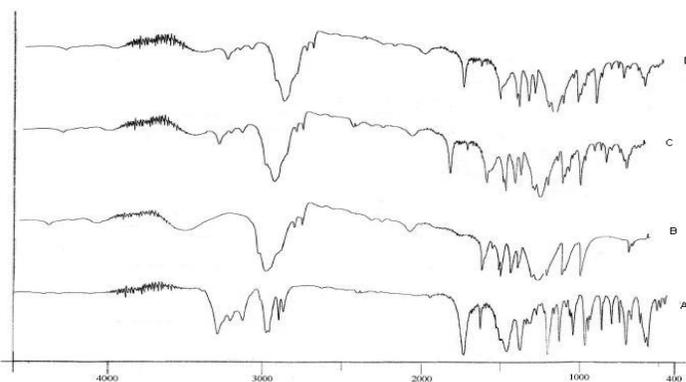
ANALYTICAL PERSPECTIVE

A) Effect of PEG 4000 Concentration and Gibbs Free Energy on Gliclazide Solubility (Biswal et al., 2009)

Concentration of PEG 4000 (% w/v)	Concentration of Gliclazide (mg/mL) at 37 °C	Concentration of PEG 4000 (% w/v)	ΔG_{tr}° (J/Mol)
0	0.80 \pm 0.02	0	0
2	0.81 \pm 0.01	0	0
4	1.06 \pm 0.05		-698
6	1.28 \pm 0.01		-1184
8	1.53 \pm 0.05		-1644
10	1.76 \pm 0.08		-2005
12	1.97 \pm 0.09		-2295
14	2.2 \pm 0.01		-2580
16	2.45 \pm 0.02		-2857



B) In vitro dissolution profiles of gliclazide, a physical mixture of gliclazide, and a solid dispersion of gliclazide in 0.1 N HCl (pH 1.2) (Biswal et al. , 2009).



C) FTIR spectra of (A) pure gliclazide, (B) pure PEG 4000, (C) gliclazide-PEG 4000 PM, and (D) gliclazide-PEG 4000 SD (Biswal et al., 2009).

D) Validation parameters for standard gliclazide (Samina A. Jamadar et al. , 2011)

Parameter	Value
γ_{\max} (nm)	229.5
Beer's range ($\mu\text{g/ml}$)	7-27
Molar absorptivity (l/mol/cm)	1.4962 \times 104
Sandell's sensitivity (mg/cm ² /0.001AU)	0.021616
Regression equation	y=0.0463 x-0.2104
Intercept (a)	-0.2104
Slope (b)	0.0463
Limit of detection (LOD $\mu\text{g/ml}$)	0.31
Limit of quantification (LOQ $\mu\text{g/ml}$)	0.92
Precision (% RSD)	0.56
Correlation coefficient (r ²)	0.9998

LONG-TERM COMPARISON OF ORAL HYPOGLYCEMIC AGENTS IN DIABETIC RETINOPATHY GLICLAZIDE VS. OTHER SULFONYLUREAS (Akanuma Y et al. , 2009) :

Gliclazide has been reported to possess the properties of preventing the progression of diabetic retinopathy and of controlling blood glucose levels. This report describes a long-term comparative clinical trial of this agent to assess its efficacy against diabetic retinopathy.

One hundred and fifty-nine NIDDM patients with no retinopathy or with simple retinopathy entered this trial. One hundred and nineteen patients receiving other sulfonylurea agents were randomly allocated to two groups (G: gliclazide, SU: other sulfonylureas). Forty patients continued to be treated with diet alone (D group). Finally a total of 60 patients, that is, 21 patients in the G group, 19 patients in the SU group, and 20 patients in the D group, were followed with fundoscopic examinations for more than 4 years. The results are summarized as follows.

(1) Distribution of background factors between the two drug therapy groups was balanced, but in the D group more male patients and relatively milder cases were involved than in the drug therapy groups.

(2) Fasting blood glucose control in the three groups was not significantly different.

(3) Fundoscopic deterioration was observed less frequently, though not significantly, in the G group than in the other groups.

(4) Progression to preproliferative retinopathy was significantly less frequent in the G group than in the SU group.

Thus, gliclazide seems to have additional properties compared with other sulfonylurea drugs in preventing deterioration of diabetic retinopathy, and particularly in preventing progression to proliferative retinopathy.

PRESENT SCENARIO OF GLICLAZIDE

Gliclazide is first patented by Servier Canada & the drug was approved for therapeutic purpose in the name of Diamicon MR tab. Though it was the first successful antidiabetic concerning patient needs. But release pattern of this formulation is very slow & long processed. So various approaches had been taken to overcome such problems. Dosage formulations had been developed in the form of matrix tablets , sustained release , immediate release, bilayer tablets. Microcapsulation & encapsulation technique has also been tried. Lastly It is reported that Disphar International B.V.7255 PZ Hengelo (NL) has patented Sustained-release

formulation of gliclazide on 05.05.2010, where Inventorship was recorded in the name of Wit, Johannes Bernardus, Maria & 3742 ZD Baarn (NL) Doshi, Hiteshkumar Anilkant Mulund (W), Mumbai 400 080 (IN)(**EP 2 181 705 A1**)

CLINICAL STUDIES ON MARKETED FORMULATION OF GLICLAZIDE (Pr DIAMICRON)

This drug has achieved vast success on diabetic patients & this drug is patented by SERVIER CANADA Inc.(December, 1989).

PHARMACOKINETICS & METABOLISM

This has been studied in four animal species (monkey, dog, rabbit and rat) and in man after single or repeated administration of gliclazide. The principal characteristics are shown in the table below.

BLOOD KINETICS OF GLICLAZIDE (PO) IN DIFFERENT SPECIES (Boulevard Armand et al. , 1989) (single doses)

Species	Number Of Subjects & Doses	Absorption T 1/2(H)	Plasma Peak (H)	Volume Of Distribution (% Body Weight)	Plasma Half-Time (H)
Man	4 & 3 mg/kg	1.3 (1)	4-6 (1)	4-6 (1)	10.4 (1)
Monkey	4 & 3 and 50 mg/kg	0.3 (1)	1-2 (1)	24.4 (1) 108 (4)	2.9 (1) 6.2 (4)
Beagle	3 & 3 and 50 mg/kg	0.7 (1)	2-6 (1)	21..3 (1) 22 (4)	10.7 (1) 9.9 (4)
Rabbit	5 & 10 and 25 mg/kg	0.7 (2)	3 (2)	30.8 (2) 51.8 (3)	3.9 (2) 5.9 (3)
Rat	5 & 10 mg/kg	0.5 (2)	1 (2)	53.8 (2)	2.5 (2)

[(1) = 3 mg/kg PO , (2) = 10 mg/kg PO , (3) = 25 mg/kg PO , (4) = 50 mg/kg PO]

ACUTE TOXICITY (Boulevard Armand et al. , 1989)

Species	Mean Weight	Number of animals per lot	DL 50 (mg/kg)
Mouse CD-SPF	25 g	10 M 10 F	> 3 000
Mouse ICR-HAN	20 g	10 M 10 F	> 4 000
Rat SD-SPF	250 g	10 M 10 F	3733 $\left\{ \begin{array}{l} 5200 \\ 2679 \end{array} \right.$ 3407 $\left\{ \begin{array}{l} 5467 \\ 2123 \end{array} \right.$
Rat CFY	110 g	6 M 6 F	> 4 000
Tricolor Guinea Pig	240 g	4 M 4 F	48 hours $\left\{ \begin{array}{l} 1999 \\ 1501 \\ 2509 \end{array} \right.$ 10 days $\left\{ \begin{array}{l} 2016 \\ 1269 \\ 2553 \end{array} \right.$ 2244 $\left\{ \begin{array}{l} 2068 \\ 1675 \end{array} \right.$
Beagle dog	7 kg	3 M 3 F	> 3000

Gliclazide is rapidly absorbed in all species, with a plasma peak observed between 1 and 6 hours. More than 90% of gliclazide is found unchanged in the plasma. Elimination from plasma is monophasic with inter-species variations concerning half-life (2.5

hours in the rat, 10.4 hours in man). Excretion is similar in all species with 60 to 70% of the dose found in urine and 10 to 20% in faeces. The drug is intensively metabolized into at least 5 metabolites and only small amounts of unchanged compound are excreted in the urine.

The LD 50 is greater than 3000 mg/kg in the mouse, rat and dog (i.e. 750 times the therapeutic dose) (Serradas et al. , 1989) and than 2000 mg/kg in the guinea-pig (i.e. 500 times the therapeutic dose). Symptomatology is essentially linked to the hypoglycemic effect of the drug.

SUB-CHRONIC 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 hispathological results.

CHRONIC TOXICITY

Six-month study in the Sprague-Dawley rat: Groups of 20 rats (10 males, 10 females) weighing 300 g, were treated for 6 days out of 7 for 6 months with 0, 25, 100 or 200 mg/kg/day. Seven deaths occurred as a result of technical problems. All other animals showed normal behaviour and haematological results. From a biochemical standpoint, blood urea decreased significantly in the male rats as did blood glucose in the males of the 100 mg/kg/day group. Histological examination showed an increase in the weight of the liver and kidneys in male animals, not accompanied by any histological lesion. A six-month rat study carried out in Japan with higher doses (50, 100, 200, 400 and 800 mg/kg) indicates a possible higher sensibility in the female to the product: slight increases in liver enzymes together with slight decreases in erythrocytes counts, hematocrit values and haemoglobin concentrations at doses of 200 mg/kg and higher.

Six-month study in the Beagle dog: Groups of 6 dogs (3 males, 3 females) were treated daily for 6 months with 15 or 30 mg/kg of gliclazide or 30 mg/kg of gliclazide or 50 mg/kg of tolbutamide.

From a clinical standpoint:

- 3 deaths (one at 15 mg/kg, two at 30 mg/kg) in the gliclazide group as a result of hypoglycemic coma.
- 1 convulsion, 4 cases of severe gastro-intestinal disturbances in the tolbutamide group.
- Weight changes and food consumption were similar with both drugs.

From a laboratory standpoint:

- 40% fall in blood glucose in animals treated with gliclazide.
- Signs of hepatotoxicity in the tolbutamide group.

From a histological standpoint:

- Increase in weight of the liver in the 3 deaths of the gliclazide group.
- Increase in the weight of the liver and lesions of toxic hepatitis in 5 animals out of 6 of the tolbutamide group.

Twelve-month oral toxicity study in the Beagle dog: Groups of 8 dogs (4 males, 4 females) were treated for 12 months with 0, 12 or 24 mg/kg/day of gliclazide.

Four animals in each group were sacrificed after 90 days.

- There were no deaths;
- No evidence of any modification in behaviour and body weight;
- Significant fall in blood glucose;
- Fluctuation in certain parameters (liver enzymes, lipid profile, creatinine);
- at autopsy:

Swelling of the renal and hepatic parenchyma and at the highest dose a slight increase in the weight of the thyroid and slight decrease in the weight of the pituitary gland.

Twelve-month oral toxicity study in the rhesus monkey:

Groups of 8 rhesus monkeys (4 males, 4 females) were treated daily for 12 months with 0, 20, 60 or 180 mg/kg of gliclazide.

- No evidence was found of any modification in weight gain nor food consumption;
- Significant fall in blood glucose;
- Irregular rise in some liver enzymes in some animals;
- No abnormality by histopathological examination.

TERATOGENICITY

Teratogenicity studies have been carried out in three species: mouse, rat and rabbit.

In the CD/SPF mouse (group of 30 females), administration of gliclazide at doses of 0, 50, 200 and 500 mg/kg/day starting from mating and throughout gestation did not modify fertilization and abortion rates and had no apparent teratogenic effect.

In the CFY-SPF rat (groups of 20 females), administration of gliclazide at doses of 0, 50, 100 and 200 mg/kg/day from the 6th to the 15th day of gestation did not show any embryotoxic effect (Tournaire et al. , 1980).

In the SD/SPF rat (groups of 60 females), administration of gliclazide at the doses of 0, 15, 60, 120, 240 and 480 mg/kg/day throughout gestation had no effect on fertilization, gestation, mean number of foetuses or incidence of foetal abnormalities. The number of offspring surviving at 48 hours was decreased in the 15, 60, 120 and 480 mg/kg groups. No other abnormality was seen.

In the common rabbit (group of 15 females), administration of gliclazide at doses of 0, 10, 25 and 50 mg/kg/day from the 6th to the 18th day of gestation had no effect on the number of foetal resorptions, percentage of abortion nor the mean number of fetuses per litter.

In the New Zealand rabbit (group of 6 females), administration of gliclazide at doses of 0, 50, 75, 100 and 200 mg/kg/day for 13 days followed by an observation period of 8 days, was associated with maternotoxicity and embryotoxicity in

the form of gastrointestinal and renal lesions accompanied by anorexia and weight loss. However, there was no evidence of any teratogenic effect.

FERTILITY AND REPRODUCTION

In the SD rat, groups of 40 females and of 20 males were treated for 8 and 70 days respectively before mating and until weaning in the females, and until 15 days after littering in the males, with gliclazide at doses of 0, 10, 50 and 200 mg/kg/day. There was no evidence of any change in fertilization or abortion rates. Foetal resorption, placental haemorrhage and foetal atrophy rates were unaffected. The genital tract of treated parents showed no abnormality imputable to treatment.³⁰ No embryotoxic effect was seen on foetuses of females sacrificed before littering. In females in which gestation was allowed to run to term, a significant decrease in the viability of offspring was seen at 48 hours. No abnormality was seen during the study of fertility and reproduction in first generation offspring born of treated animals (Tsuboi et al. , 1981).

MUTAGENICITY

The mutagenic potential of gliclazide has been sought using five mutagenesis tests (Turner et al. , 1989), i.e.:

- 2 gene mutation tests (Ames test),
- 1 in vitro chromosomal aberration test (human lymphocyte test),
- 2 in vivo chromosomal tests (micronucleus test).

GENE MUTATION TESTS

1st Ames test: In this test, gliclazide was used in the presence of 5 strains of Salmonella typhimurium (TA 1535/1537/1538/98/100) at the doses of 0, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 3, 5 and 8 mg/petri dish, with and without metabolic activators. Positive controls were used for each strain with and without metabolic activators.

The qualitative test showed no mutagenic effect. The quantitative test at doses of 0.005 mg to 8 mg/dish showed no significant increase in the number of revertants.

Thus no mutagenic effect was seen under the experimental conditions adopted.

2nd Ames test: This test used 7 strains of Salmonella typhimurium (TA 97/98/100/102/1535/1537/1538) at the doses of 0, 0.05, 0.1, 0.5, 1, 3, 5 and 8 mg of gliclazide per petri dish, in the presence and absence of metabolic activator. Positive controls were used for each strain, with and without metabolic activators. No mutagenic effect was seen in the qualitative test. No mutagenic activity was detected in the quantitative test under the experimental conditions described.

IN VITRO CHROMOSOMAL ABBERATION TEST

Possible clastogenic potential action of gliclazide on activated lymphocytes in culture was studied by the human lymphocyte test with and without metabolic activators. Maximum tolerated doses determined in the preliminary toxicity test were 0.033 mg/ml with metabolic activators and 0.1 mg/ml without metabolic activator.

Gliclazide was used at the following concentrations:

- 0, 0.003, 0.01 and 0.033 mg/ml with metabolic activators;
- 0, 0.01, 0.033 and 0.1 mg/ml without metabolic activator.

Cyclophosphamide (0.02 mg/ml) and bleomycin (0.250 mg/ml) were used as positive controls with and without metabolic activators. Gliclazide was not found to have any clastogenic activity under the experimental conditions described.

IN VIVO CHROMOSOMAL ABERRATION TEST MICRONUCLEUS TEST

1st test: The test used three groups of 10 OF1 mice: 1 negative control, 1 gliclazide high dose (2 g/kg x 2), 1 gliclazide low dose (1 g/kg x 2) and one group of 5 positive control mice given cyclophosphamide (50 mg/kg x 2). No evidence was found of any significant variation in the number of erythrocyte micronuclei. Gliclazide was not associated with any mutagenic action detectable by the micronucleus test.

2nd test:

The test used SPF Swiss mice as follows:

24 mice for the preliminary toxicology test which determined the maximum administrable dose as 3 g/kg;

-108 mice in the phase 1 genetic toxicology test with study of effect/time relationship at the maximum administrable dose (MAD) (sacrifice of animals at times 24, 48 and 72 hours);

-60 mice in the phase 2 genetic toxicology test with study of the dose/effect relationship at the time defined in phase 1 (t = 24 h) and using the following doses: 0, 750 (MAD/4), 1500 (MAD/2) and 3000 mg/kg (MAD).

Cyclophosphamide 50 mg/kg was used as positive control. Gliclazide was found to be free of any clastogenic activity under the experimental conditions adopted in this trial involving oral administration in the Swiss mouse.

EFFICACY OF GLICLAZIDE

Three studies were performed to assess the efficacy of various sulphonylureas in the management of diet-failed NIDDM patients. In the first study, 224 patients inadequately controlled by diet alone or with oral hypoglycaemics received gliclazide in addition to diet or in place of existing drugs for three months. The dosage was adjusted to obtain adequate control or up to the maximum recommended dosage. Good glycaemic control was achieved in 65% of patients. Conversion from other oral hypoglycaemics to gliclazide led to an improvement in control except in cases previously treated with glibenclamide. In the second study, diabetic control was compared in 112 NIDDM patients treated concurrently for one year with chlorpropamide, glipizide, gliquidone, glibenclamide or gliclazide. On the basis of HbA1 levels, the best results were obtained with glibenclamide and gliclazide, leading to normal HbA1 levels in 74% and 80% of patients, respectively. In the third study, secondary failure rates were assessed in 248 NIDDM patients treated for five years with gliclazide, glibenclamide or glipizide. Gliclazide had the lowest secondary failure rate (7%) and was significantly better than glipizide (25.6% failures in five years), but the difference relative to glibenclamide (17.9%) just failed to reach the threshold of significance (Yasuo Akanuma et al. , 1988).

CONCLUSION

Gliclazide is rapidly absorbed in all species, with a plasma peak observed between 1 and 6 hours. Gliclazide reduces blood glucose levels in patients with NIDDM by correcting both defective insulin secretion and peripheral insulin resistance. It is

extensively metabolized to 7 metabolites and excreted in urine therefore renal insufficiency has no effect in pharmacokinetic of gliclazide. Gliclazide can be categorized to possess the properties of preventing the progression of diabetic retinopathy and of controlling blood glucose levels. Modern analytical techniques has been developed to detect and quantify gliclazide for in vivo studies with optimum retention time. The results of these studies show that gliclazide is a potent, well tolerated hypoglycaemic agent which compares favourably with others of its type. It has a low incidence of side effects, few problems with hypoglycaemia, and retains its efficacy longer than other sulphonylureas. Gliclazide may therefore be considered a first choice for the therapy of diet-failed NIDDM patients.

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