AN APPRAISAL TO THE SPECIAL SULPHONYLUREA: GLICLAZIDE

SK. Mastan[1, 2*], G. Chaitanya[3], K. Raghunandan Reddy[3] and K. Eswar Kumar[4]

[1]Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Duvvada, Gajuwaka, Visakhapatnam-530046, Andhra Pradesh, India
[2]Department of Pharmacology, Roland Institute of Pharmaceutical Sciences, Ambapua, Berhampur (GM) - 760 010, Orissa, India
[3] Vikas College of Pharmacy, Jangaon–506 167, Warangal, Andhra Pradesh, India
[4]Pharmacology Division, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003, Andhra Pradesh, India

* Corresponding author, E-mail: shkmastan@gmail.com

Summary

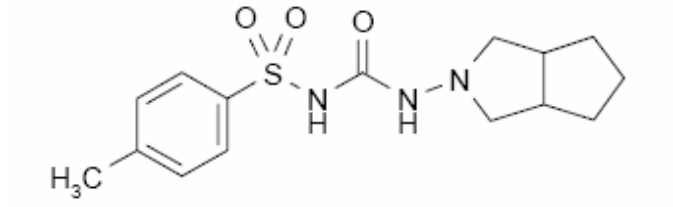
Gliclazide is a second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). The drug, gliclazide effectively maintains glycemic control by pancreatic and possibly extra pancreatic actions, and is well tolerated by most of the patients. This drug was preferred in therapy because of its selective inhibitory activity towards pancreatic K^+ATP channels, low incidence of producing severe hypoglycaemia, and other haemobiological effects. Due to several nonhypoglycemic benefits, this drug may often clinical benefits in selected groups of patients, especially those with or likely to develop micro vascular and macro vascular abnormalities due to diabetes. All these benefits have allowed gliclazide to be well placed within the array of oral hypoglycemic agents available for the control of NIDDM.

Key words: Diabetes mellitus, Hypoglycemia, Antioxidant activity

Introduction

Diabetes mellitus is the most common endocrine disorder characterized by hyperglycemia, altered metabolism of lipids, carbohydrates, proteins and an increased risk of complications from vascular disease (1). Diabetes mellitus may be categorized in to two major types, type I accounting for 5% prevalence and type II for 95% prevalence among diabetics. Sulphonylureas are widely used in the management of type 2 diabetes, as impaired insulin secretion plays an important role in the pathophysiology of hyperglycemia (2).

Sulphonylureas were discovered as a side effect of sulphonamide use in 1942 (3), and tolbutamide and chlorpropamide became therapeutic leaders in the management of type 2 diabetes during the 1950s. Gliclazide was initially used solely in France but progressively became widely accepted. Gliclazide is widely used, second generation sulphonylurea (4). Its effectiveness and safety are well known (5).

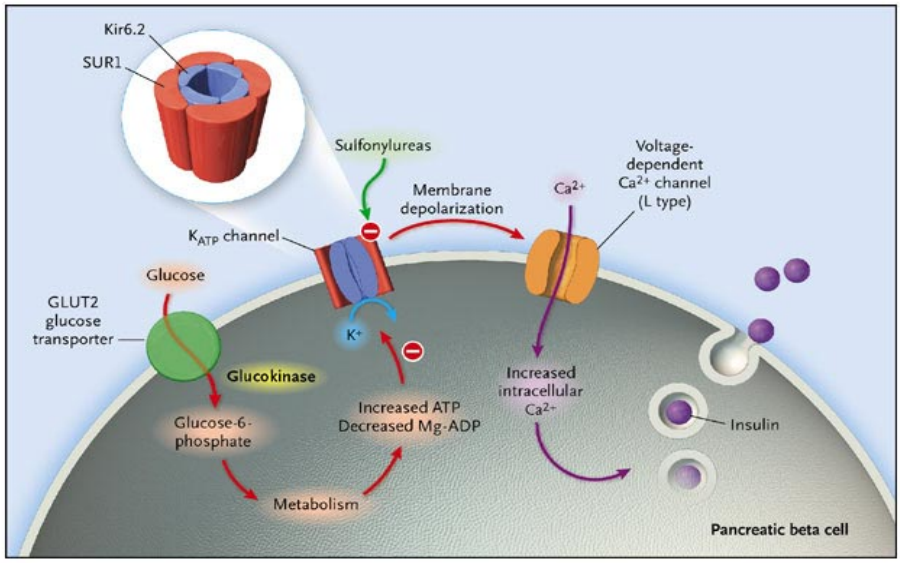


Chemical structure of gliclazide

Gliclazide is a weak acid (pKa=5.8) with a good lipophilicity and a pH dependent solubility (6). Gliclazide chemical name is 1-(3-Azabicyclo[3.3.0]-oct-3-yl)-3-(p-tolysulfonyl)urea. Gliclazide belongs to the class II of the biopharmaceutical classification. Molecular weight is 323.41 and molecular formula is $C_{15}H_{21}N_3O_3S$. It is white or almost white powder. It is insoluble in water, freely soluble in chloroform and methylene chloride, sparingly soluble in acetone, slightly soluble in alcohol. The melting point of gliclazide is approximately 168ºC.

MECHANISM OF ACTION

Sulphonylureas bind to the SUR subunit of K^+-ATP channels on the cell of islet of Langerhans leading to closure of the K^+ channel. This causes membrane depolarization followed by opening of calcium channels with influx of Ca^{++} into the cell. Intracellular calcium mobilizes insulin-containing granules with release of insulin to the exterior. They augment both first and second phase of insulin secretion in a glucose-dependent and independent manner. Gliclazide have additional extrapancreatic actions responsible for their antihyperglycemic effects. (4, 7-9).



Mechanism of action of sulphonylureas

Similarly, it is universally accepted that sulphonylurea drugs are not effective in the absence of functioning β-cells in both animals (10) and humans (11, 12). Its affinity for pancreatic and myocardial sulphonylurea receptors has been studied recently. Evidence has been found of powerful binding of this substance to the pancreatic SUR1/Kir6.2 and smooth muscle SUR2B/Kir6.2 receptors (13). Gliclazide is more potent in stimulating the first phase of insulin release from isolated perfused pancreas (14). Gliclazide augments insulin secretion by concurrently increasing pulse mass and basal insulin secretion without changing secretory burst frequency or regularity (15).

EXTRAPANCREATIC EFFECTS

Gliclazide is known to produce hypoglycemic/antihyperglycemic activity by pancreatic (5, 16) and extrapancreatic (17-19) effects. Gliclazide produce biphasic response in rat model may be due to its enterohepatic circulation in rats (20, 21) and in humans (22). Such effect was not observed in rabbit model and it may be due to the absence of entero-hepatic cycling (1, 23, 24).

The most commonly reported extrapancreatic effects of sulphonylureas are their ability to potentiate insulin action on peripheral tissues (24-27). Sulphonylureas inhibit gluconeogenesis from lactate and pyruvate in experimental models, possibly by raising the intracellular content of fructose 2, 6-biphosphate. Fructose 2, 6-biphosphate plays a key role in regulating the activity of enzymes of the glycolytic/gluconeogenetic pathway (28). Extrapancreatic effects demonstrated for gliclazide include improvement in insulin mediated glucose utilization and potentiation of postreceptor insulin sensitive pathways.

HYPOGLYCEMIA

Hypoglycemia has often been associated with sulphonylurea therapy. However, gliclazide appears to be associated with a low incidence of this adverse effect, possibly due to the relatively physiological effect that the drug has on insulin secretion (4, 7, 29-31).

Literature suggest that gliclazide induces an ‘all or nothing’ effect, such that a threshold dose is required for a hypoglycemic effect to be observed but increasing the dose above this level will not result in greater hypoglycemic activity. Studies in healthy volunteers have demonstrated that the threshold plasma gliclazide concentration is 0.25 mg/L, while in patients with NIDDM (Non insulin dependent diabetes mellitus); a higher threshold concentration of 1.5 mg/L was identified (32). The difference in threshold concentration may be due to decreased sensitivity of pancreatic beta cells in NIDDM. A clinical study found that increasing the dosage of gliclazide to above 160 mg/kg during long term administration may not lead to greater hypoglycemic activity (33).

PHARMACOKINETICS

Absorption: Gliclazide is well absorbed. Administration of a single oral dose of gliclazide 40 to 120 mg to healthy volunteers and patients with NIDDM resulted in peak

plasma concentrations of 2.2 to 8 mg/L with in 2 to 8 h (4, 32, 34-36). Some inter subject variation in gliclazide absorption has been reported, with 'fast' [T_{max} = 0 to 4 h] and 'slow' [T_{max} = 4 to 8 h] absorbers identified in a group of healthy volunteers (32, 34). Mean plasma concentration 24 h after administration of a single dose (40, 80 or 120 mg) was 7-50% of the C_{max} values (34, 36). There does not appear to be any significant difference in the daily absorption profile of gliclazide in healthy volunteers and patients with NIDDM (34). The highly variable systemic bioavailability which may result from variability in the first pass metabolism and/or absorption (37-39). Changes in gliclazide pharmacokinetics in rats could arise due to variability in bile excretion and thus bile salt production. Bile salts have been shown to increase intestinal as well as nasal absorption of insulin (39).

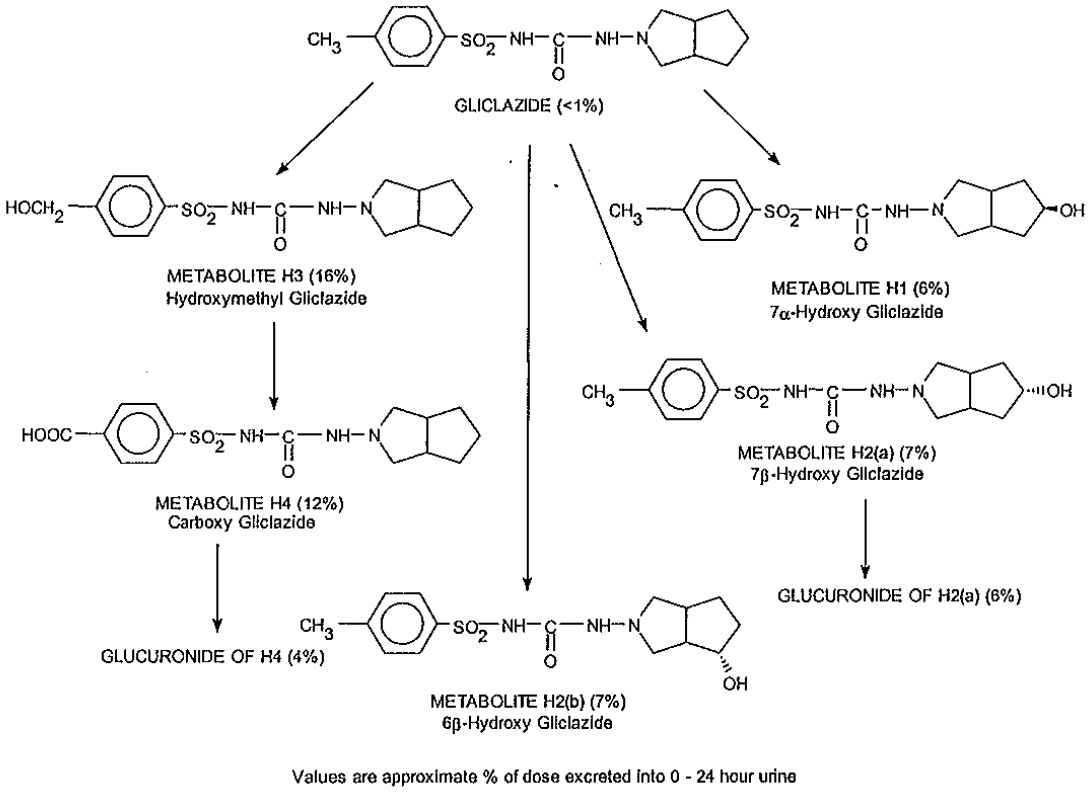
Steady-state concentrations are reached after 2 days administration of gliclazide 40 to 120 mg to patients with NIDDM (36). Age related differences in certain absorption parameters of gliclazide have been reported: C_{max} value significantly lower and occurred significantly later in a group of 5 elderly women (mean age=72 years) compared with a group of 5 younger women (mean age = 26 years); however there was no significant difference in mean steady-state plasma gliclazide concentrations (4.5 mg/L), suggesting that the difference in these absorption parameters are unlikely to be clinically significant (4, 40).

Effect of food: From two studies in a total of 18 patients with NIDDM who had been stabilized on gliclazide, found that oral administration of the drug after food significantly delayed T_{max} (by up to 187 min) compared with administration 30 minutes before, immediately before or with a meal. Isibashi and Takashina (1990) reported that administration of gliclazide 30 minutes before a meal was associated with significantly lower postprandial hyperglycemia than administration immediately before or after a meal (41).

Distribution: The mean apparent volume of distribution of gliclazide in healthy volunteers and patients with NIDDM ranged from 13-24 L in different studies [34, 40] or 36.3% of body weight (32) and an age related increase in this parameter was observed (40). Gliclazide is extensively protein bound (85-97%) (32, 34). The mean gliclazide content of macroglobulin, γ-globulin, albumin and small molecular substances in 24 h period after administration of 40 mg to healthy volunteers was 3.7, 0.7, 82.3 and 13.2% respectively (34).

Metabolism: Gliclazide is extensively metabolized in the liver to eight metabolites in both rat and man (32, 42, 43). Among all the sulphonylureas, gliclazide metabolism is special and complex to predict the drug-drug interactions as it is metabolized by CYP2C9 (major) and CYP3A4 (minor) (23, 44). Less than 20% is excreted unchanged (28). Gliclazide undergoes extensive metabolism to several inactive metabolites in humans, mainly methylhydroxygliclazide and carboxygliclazide (45). Rieutord *et al.* have reported that tolbutamide hydroxylase, which is CYP2C9 in man, is involved in the formation of hydroxygliclazde in rats in vitro (46) The metabolites do not have hypoglycemic activity. Gliclazide metabolism includes oxidation and hydroxylation.

Metabolism of gliclazide to hydroxylgliclazide is the initial step in the metabolism of gliclazide in both rat and man (47). Metabolism of the parent compound is extensive, with 1 study failing to detect any unchanged drug in the urine (47).



Metabolic pathway of Gliclazide (48)

Animal studies demonstrated that gliclazide undergoes enterohepatic recirculation (20, 49) and there is some evidence to suggest that this also occurs in humans (32). In plasma, gliclazide represents over 90% of all drug-related material. The main metabolite, a carboxy derivative is present only to the extent of 1%; possess effects on platelet aggregation and micro thrombus formation (50). The carboxy metabolite is the most abundant urinary metabolite (20%) followed by the hydroxyl metabolite (16%) with the other metabolites representing 3 to 9% of dose (35).

Pharmacokinetic parameters of gliclazide in humans (4, 28, 32, 50)**:**

Parameter	**Gliclazide**
C_{max} (mg/L)	2.2 – 8.0 (For 40 – 120 mg tablets)
T_{max} (h)	2.0 – 8.0
Volume of distribution (L)	13.0 – 24.0
Protein binding (%)	85.0 – 97.0
Plasma clearance	Appr. 0.78 L/h (13 mL/min)
$T_{1/2}$ (h)	8.1 – 20.5 (For 40 – 120 mg tablets in healthy and HIV patients)

Urinary elimination of gliclazide and its metabolites in subjects with normal renal function (32, 50)**:**

Drug	% unchanged (Mean)	Metabolites	% of dose (Mean)
Gliclazide	<20	p-Carboxygliclazide (M1)	17
		N-Oxygliclazide (M2)	20
		N-Hydroxygliclazide (M3)	14
		p-Toluenesulphonamide (M4)	1
		Hydroxygliclazide (M5)	7

Pharmacokinetic parameters in animal species after single oral administration (48):

Species	Dose (mg/kg)	Absorption $T_{1/2}$ (h)	T_{max} (h)	Volume of distribution (%body wt)	Plasma $T_{1/2}$ (h)
Rat (N=5)	10	0.5	1	53.8	2.5
Rabbit (N=5)	10	0.7	3	30.8	3.9
	25			51.8	5.9
Beagle (N=3)	3	0.7	2-6	21.3	10.7
	50			22	9.9
Monkey (N=4)	3	0.3	1-2	24.4	2.9
	50			108	6.2

Elimination: The elimination half life of gliclazide is 8 to 12 h in man (7) and it may vary ranges from 6.1 to 14.3 h in healthy volunteers. The half life is longer in males and in the elderly (40) and is increased in renal failure (51). The major route of elimination of gliclazide and its metabolites is via the urine. Following administration of [^{14}C]-gliclazide 60 to 70% of the radioactivity was recovered in the urine and 10-20% in the feces (32). Urinary excretion accounted for 45% of a 40 mg dose after 24 h and 61% after 96 h (20, 35).

DOSAGE AND ADMINISTRATION (7, 48)

Administration: Oral administration

Dosage:

Adults: The total daily dose may vary from 40 to 320 mg taken orally. The dose should be adjusted according to the individual patient's response, commencing with 40-80 mg daily (1/2 - 1 tablet) and increasing until adequate control is achieved. A single dose should not exceed 160 mg (2 tablets). When higher doses are required, gliclazide should be taken twice daily and according to the main meals of the day. In obese patients or those not showing adequate response to gliclazide alone, additional therapy may be required.

Elderly: Plasma clearance of gliclazide is not altered in the elderly and steady state plasma levels can therefore be expected to be similar to those in adults under 65 years. Clinical experience in the elderly to date shows that gliclazide is effective and well tolerated. Care should be exercised, however, when prescribing sulphonylureas in the elderly due to a possible age-related increased risk of hypoglycaemia.

Children: gliclazide as with other sulphonylureas is not indicated for the treatment of juvenile onset diabetes mellitus.

Overdose:

The symptom to be expected of overdose would be hypoglycaemia. The treatment is gastric lavage and correction of the hypoglycaemia by appropriate means with continual monitoring of the patient's blood sugar until the effect of the drug has ceased.

Dosage adjustments may be necessary in the following conditions (7, 48)**:**

- On the occurrence of mild symptoms of hypoglycaemia (sweating, pallor, hunger pangs, tachycardia, sensation of malaise). Such findings should be treated with oral glucose and adjustments made in drug dosage and/or meal patterns.
- On the occurrence of severe hypoglycaemic reactions (coma or neurological impairment, see overdose).
- Loss of control of blood glucose (hyperglycaemia). When a patient stabilized 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 increase progressively the dosage of gliclazide and if this is insufficient, to discontinue the treatment with gliclazide and to administer insulin. As with other sulphonylureas, hypoglycaemia will occur if the patients' dietary intake is reduced or if they are receiving a larger dose of gliclazide than required.
- Care should be exercised in patients with hepatic and/or renal impairment and a small starting dose should be used with careful patient monitoring.

UNDESIRABLE EFFECTS (7, 48)

Hypoglycaemia: All sulphonylurea drugs are capable of producing moderate or severe hypoglycaemia, particularly in the following conditions:

In patients controlled by diet alone, in cases of accidental overdose, when calorie or glucose intake is deficient, inn patients with hepatic and/or renal impairment; however, in long-term clinical trials, patients with renal insufficiency have been treated satisfactorily, using gliclazide at reduced doses.

In order to reduce the risk of hypoglycaemia it is therefore recommended:

- To initiate treatment for non-insulin dependent diabetics by diet alone, if this is possible,

- To take into account the age of the patient: blood sugar levels not strictly controlled by diet alone might be acceptable in the elderly,
- To adjust the dose of gliclazide according to the blood glucose response and to the 24 hour urinary glucose during the first days of treatment.

The most frequently reported adverse drug reactions during long-term studies and postmarket experience are gastrointestinal disturbances (including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation).

Gastro-intestinal reactions: Nausea, vomiting, diarrhea, epigastric fullness and gastric irritation can be observed. These reactions are generally dose-related and may disappear when the dose is reduced.

Hepatobiliary reactions: With other sulfonylureas cases were also observed of elevated liver enzyme levels (AST, ALT, alkaline phosphatise) and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases. Rare cases of jaundice have been reported.

Dermatological reactions: Allergic reactions such as pruritus, erythema, urticaria and morbiliform or maculopapular rash have been reported. These reactions may persist during treatment, which must then be interrupted. Cases of cutanea porphyria tarda and of photosensitivity have also been described with sulfonylurea drugs.

Hematological reactions: As with all hypoglycemic sulfonylurea drugs, a few rare cases have been reported of leukopenia, erythrocytopenia agranulocytosis, thrombocytopenia, haemolytic anemia, pancytopenia and allergic vasculitis.

Metabolic reactions: Cases of hepatic porphyria and disulfiram-like reactions have been described with sulfonylurea drugs. Clinical experience to date has shown that gliclazide has a low incidence of disulfiram type reactions.

Cardiovascular: Arteritis, cardiac failure, cerebrovascular disorder, coronary artery disorder, epistaxis, hypotension, myocardial infarction, oedema legs, palpitation, tachycardia, thrombophlebitis and vein disorder.

Laboratory tests: The pattern of laboratory tests abnormalities observed with gliclazide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH and creatinine and decrease in natremia have been observed. These abnormalities frequently encountered with treated or untreated diabetic patients are rarely associated with clinical symptoms and generally not considered to be drug related.

Post-Market Adverse Drug Reactions: Hypoglycaemia, hypoglycaemic coma, pancytopenia, thrombocytopenia, hepatitis, cholestatic jaundice, pyrexia, and skin reactions (pruritus and rash), gastrointestinal disturbances, skin and subcutaneous tissue disorders, rash, pruritus, urticaria, erythema, maculopapular rashes and bullous reactions.

Class attribution effects: Cases of erythrocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and allergic vasculitis, have been described for other sulphonylureas. With other sulfonylureas cases were also observed of elevated liver enzyme levels (AST, ALT, alkaline phosphatise) and even impairment of liver function (e.g. with cholestasis and jaundice) and hepatitis which regressed after withdrawal of the sulfonylurea or led to life-threatening liver failure in isolated cases.

CONTRA INDICATIONS (7, 48)

Gliclazide should not be used in juvenile onset diabetes, diabetes complicated by ketosis and acidosis, pregnancy, diabetics undergoing surgery, after severe trauma or during infections, patients known to have hypersensitivity to other sulphonylureas and related drugs, diabetic pre-coma and coma and severe renal or hepatic insufficiency.

DRUG INTERACTIONS (4, 7, 48)

Care should be taken when giving gliclazide with drugs which are known to alter the diabetic state or potentiate the drug's action. The hypoglycaemic effect of gliclazide may be potentiated by phenylbutazone, salicylates, sulphonamides, coumarin derivatives, MAOIs, beta adrenergic blocking agents, tetracycline compounds, chloramphenicol, clofibrate, disopyramide, miconazole (oral forms), vitamin K antagonists, allopurinol, theophylline, caffeine and cimetidine. The hypoglycaemic effect of gliclazide may be diminished by corticosteroids, oral contraceptives, thiazide diuretics, phenothiazine derivatives, thyroid hormones and abuse of laxatives.

BENEFITS OF GLICLAZIDE BEYOND GLYCEMIC CONTROL

Antioxidant activity: Recently, a number of in vivo and in vitro studies have shown that gliclazide functions effectively as an antioxidant as well (52-56). The free radical scavenging area of the molecule is the aminoazabicyclo-octane ring, which is not found on other sulphonylureas (57, 58).

Anti-atherosclerotic effect: Several reports indicated that gliclazide-inhibited atherosclerotic lesions are induced by an atherogenic diet (58, 59).

Prevention of microvascular complications: Gliclazide also prevents the progression of microvascular complications such as diabetic retinopathy, irrespective of improvement of the glycemic control (60, 61).

Reversing high insulin-mediated neutrophil-endothelial cell interactions: Gliclazide may provide an anti-inflammatory effect in the increased leucocyte-endothelial cell interactions seen during hyperinsulinemia, which also might contribute in preventing atherosclerotic disease. Among K^+-ATP channel blockers, only gliclazide was effective in reversing high insulin-mediated neutrophil-endothelial cell interactions, despite the fact that gliclazide shares many common properties of typical K^+-ATP channel blockers (62).

Restore impaired insulin signaling: Gliclazide was reported to restore impaired insulin signaling on insulin-resistant skeletal muscle cells by increasing tyrosine phosphorylation of the insulin receptor and increasing phosphotidylinositol-3 kinase activity (63).

Effect on platelet aggregation: Gliclazide has been shown to inhibit platelet function in experimental animals (64) and in diabetic patients (65, 66). Gliclazide has been shown to reduce markedly platelet adhesiveness (67) to decrease strongly platelet aggregation by an inhibition of platelet ADP release (68) to enhance fibrinolysis and to reduce the exaggerated vasoconstrictor responses to adrenaline in experimental diabetes (69).

Vascular actions: Gliclazide improves impaired vasodilation, inadequately response to exogenous NO streptozotocin-induced diabetic rats (70). Gliclazide has been reported to potentially benefit the vasculature through improvements in plasma lipids and in platelet function (4). Treatment with gliclazide decreases the release of, or response to vasoconstrictor prostanoids, or the production or scavenging of superoxide anion which contributes to the improved vascular function in diabetic rabbits (71).

Novel anti-inflammatory mechanisms: Gliclazide acts as a potent free radical scavenger and inhibits tumor necrosis factor (TNF) alpha production, platelet aggregation and prostanoid release (57, 61, 72). Gliclazide protects against high insulin-induced neutrophil-transendothelial migration and endothelial PECAM-1 expression through inhibition of MAP kinase activation, and are unrelated to NO metabolism. These findings are contributed to the novel anti-inflammatory mechanisms of gliclazide in neutrophil-endothelial cell interactions in hyperinsulinemia (62).

Restoration of endothelial function: Gliclazide in therapeutic concentrations, dose-dependently restored endothelial function, an effect mediated via reduced oxidative stress, an equimolar vitamin C and 100 u/L SOD have similar effects. Restoration of endothelial function in diabetes by gliclazide has also been documented in human micro vessels (57, 73).

Effect on proliferation: Gliclazide inhibits proliferation, stimulates differentiation of adipocytes via down-regulation of the EGFR signaling, and also inhibits the PPARγ activity of mature adipocytes. Thus, gliclazide has the potential to inhibit the increase of preadipocytes and reduce the survival of mature adipocytes. Therefore, gliclazide may have preventive and therapeutic effects on obesity, as well as type 2 diabetes. (74).

Effect on disorders of glucose metabolism and insulin resistance in HIV-infected patients treated with protease inhibitors (75)**:** Both efficacy and safety of either gliclazide or metformin or rosiglitazone were evaluated in patients with altered glucose metabolism, in a randomized, prospective study in which 289 patients who had started a novel Protease Inhibitor-based HAART (highly active antiretroviral therapy) from 1998 to 2002 were prospectively followed for 12 months to detect the frequency of hyperglycemia and its correlates. All enrolled patients had a normal fasting glycemia at start of their novel HAART regimen; 32.5% of these patients were naïve to all antiretroviral therapy. Later, all patients with hyperglycemia persisting for ≥ 6 months

and resistant to a diet-exercise program of ≥ 3-month duration underwent therapy with gliclazide (80 mg/day), metformin (500 mg twice daily), or rosiglitazone (4 mg/day), and were followed for ≥ 12 months. A 12-month gliclazide, metformin, or rosiglitazone adjunct achieved a drop of mean serum glycemia of 27.2 mg/dL ($p < 0.02$), 24.1 mg/dL ($p < 0.02$), and 30.3 mg/dL ($p < 0.02$), respectively, vs baseline levels, and without significant differences according to the different administered compounds. An oral gliclazide, metformin, or rosiglitazone therapy proved equally safe and effective.

Conclusion

Much of the morbidity and mortality of type 2 diabetes is due to the microvascular and macrovascular abnormalities. The drug, gliclazide effectively maintains glycemic control by pancreatic and possibly extrapancreatic actions, and is well tolerated by most of the patients. The low incidence of hypoglycemia associated with the drug represents an advantage over the other agents. Nevertheless, improvement in the oxidative status of patients by using gliclazide for its hemovascular properties independent of its hypoglycemic action has led to improvements in oxidative stress, hypercoagubility, endothelial function, and platelet reactivity, which have not been demonstrated by other sulphonylurea. All these nonhypoglycemic benefits, the drug may often clinical benefits in selected groups of patients, especially those with or likely to develop micro vascular abnormalities due to diabetes. Moreover, gliclazide is most preferable sulphonylurea to treat glucose disorders associated with antiretroviral therapy due to the special characteristics of gliclazide.

References

1. Murthy TEGK, Mayuren C. Influence of calcium channel antagonist on the pharmacodynamics of a second-generation sulphonylurea in rats and rabbits. Asian J Pharmaceutics. 2008; 2(3): 163-166.
2. Kahn SE. The relative contribution of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetes. 2003; 46: 3-19.
3. Janbon M, Chaptal J, Uedel A, Schaap J. Accidents hypoglycaemiaques graves par un sulfamide-thiodazole (le VK 57 ou 2254, RP). Communications Soc Sci Med Biol Montpellier. 1942; 222-250.
4. Palmer KJ, Brogden RN. Gliclazide. An update of its pharmacologic properties and therapeutic efficacy in non-insulin-dependent diabetes mellitus. Drugs. 1993; 46: 92-125.
5. Campbell DB, Lavielle R, Nathan C. The mode of action and clinical pharmacology of gliclazide: a review. Diabetes Res Clin Prac. 1991; 14: S21–S36.
6. Jin X, Zhang Y, Xiao Li, Zhao Z. Optimization of extended zero-order release gliclazide tablets using D-optimal mixture design. Yakugaku Zasshi 2008; 128(10): 1475-1483.
7. Diamicron product information, Servier Laboratories Limited (5 July 2005). http://emc.medicines.org.uk/printfriendlydocument.aspx?documentid=1942&companyid=122 (Accessed on 09th February 2009).

8. Desai A, Tandon N. Management of type 2 diabetes mellitus with oral antihyperglycemic therapy. The National Medical Journal of India. 2007; 20(4): 192-198.
9. Stetinova V, Kvetina J, Pastera J, Polaskova A, Prazakova M. Gliclazide: Pharmacokinetic-Pharmacodynamic relationship in rats. Biopharm Drug Dispos. 2007; 28: 241-248.
10. Musbah MO, Furman BL. In vitro metabolic effects of gliclazide and glibenclamide in the rat. J Pharm Pharmacol. 1980; 32: 550-553.
11. Stock AE, Ma A, Howlett V, Cameron DP. Lack of effect of glibenclamide on insulin requirements and diabetic control in persons with insulin-dependent diabetes. Med J Aust. 1988; 149: 472-473.
12. Tanira MOM, Furman BL. The in vivo interaction between gliclazide and glibenclamide and insulin on glucose disposal in the rat. Pharmacol Res. 1999; 39(5): 349-356.
13. Gribble FM, Askcroft FM. Differential sensitivity of beta-cell and extrapancreatic K_{ATP} channels to gliclazide. Diabetologia. 1999; 42: 845-848.
14. Gregorio F, Ambrosi F, Cristallini S, Pedetti M, Filipponi P, Santeusanio F. The therapeutical concentrations of tolbutamide, glibenclamide, gliclazide and gliquidone at different glucose levels in vitro effects of a pancreatic α- and β-cell function. Diabet Res Clin Pract. 1992; 18: 197-206.
15. Claus BJ, Porksen N, Pincuss M, Hansen AP, Veldhuis JD, Schmitz O. Acute and short-term administration of a sulphonylurea (gliclazide) increases pulsative insulin secretion in type 2 diabetes. Diabetes. 2001; 50: 1778-1784.
16. Viggneri R, Pezzino V, Wang KY. Comparison of the in-vitro effect of biguanides and sulphonylureas on the insulin binding of its receptors in target cells. J Clin Endocrionol Metab. 1982; 54: 95-100.
17. Ma A, Kamp M, Bird D. The effects of long term gliclazide administration on insulin secretion and insulin sensitivity. Aus NZJ Med. 1989; 19: 44-49.
18. Vanhaeften TW, Vaneman TF, Gerich JE. Influence of gliclazide on glucose stimulated insulin release in man. Metabolism. 1991; 40: 751-755.
19. Wajchenberg BL, Santomano ATMG, Porrelli RN. Effect of sulphonylurea (Gliclazide) treatment on insulin sensitivity and glucose mediated, glucose disposal in patients with non-insulin dependent diabetes mellitus (NIDDM). Diabetes Res Clin Pract. 1993; 20: 147-154.
20. Miyazaki H, Fujii T, Yoshida K, Arakawa S, Furukawa H. Disposition and metabolism of [^{3}H] gliclazide in rats. European J Drug Metab Pharmacokinet. 1983; 8(2): 117-131.
21. Benakis A, Glassen B. "Metabolic study of ^{14}C-labelled gliclazide in normal rats and in rats with streptozotocin-induced diabetes" in gliclazide and treatment of diabetes, H. Keen, Ed., pp. 57-69. Academic Press and the Royal Society of Medicine, London, UK, 1980.
22. Rollins DE, Klassen CD. Biliary excretion of drugs in man. Clin Pharmacokinet. 1979; 4: 368-379.
23. Satyanarayana S, Eswar Kumar K, Rajasekhar J, Thomas L, Rajanna S, Rajanna B. Influence of aqueous extract of fenugreek-seed powder on the pharmacodynamics and pharmacokinetics of gliclazide in rats and rabbits. Therapy. 2007; 4: 457-463.

24. Feldman JM, Lebovitz HE. Appraisal of the extrapancreatic actions of sulphonylureas. Arch Int Med. 1969; 123: 314-322.
25. Tanira M, Furman BL. The in vivo interaction between gliclazide and glibenclamide and insulin on glucose disposal in the rat. Pharmacol Res. 1999; 39(5): 349-356.
26. Rogers BJ, Standaert ML, Polett RJ. Direct effects of sulphonylureas agents on glucose transport in the BC3H-1 myocyte. Diabetes. 1987; 36: 1292-1296.
27. Farene RV, Ishizuka T, Standaert ML, Cooper DR. Sulphonylureas activate glucose transport and protein kinase C in rat adipocytes. Metabolism. 1991; 40(2): 196-200.
28. Marchetti P, Navalesi R. Pharmacokinetic-pharmacodynamic relationships of oral hypoglycemic agents. Clin Pharmacokinet. 1989; 16: 100-128.
29. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. Diabet Care. 1989; 12: 203-208.
30. Tessier D, Dawson K, Tetrault JP, Bravo G, Meneilly GS. Glibenclamide versus gliclazide in type 2 diabetes of the elderly. Diabet Med. 1994; 11: 974-980.
31. Van Staa T, Abenhaim L, Monette J. Pharmacoepidemiology report. Rate of hypoglycemia in users of sulphonylureas. J Clin Edpidemiol. 1997; 50: 735-741.
32. Campbell DB, Adrianessens P, Hopkins YW, Goroon B, Williams JRB. Pharmacokinetics and metabolism of gliclazide: a review. In Keen et al. (Eds). Gliclazide and the treatment of diabetes. International Congress and Symposium Series No.20. Proceedings of the International Symposium, London, April, 5-6, 1979, pp. 71-82, Academic Press and Royal Society of Medicine, London, 1980.
33. Shaw KM, Wheely MSG, Campbell DB, Word JD. Home blood glucose monitoring in non-insulin dependent diabetes. The effect of gliclazide on blood glucose and weight control, a multi centre trial. Diabetic Medicine. 1985; 2: 484-490.
34. Kobayashi K, Kimura M, Sakoguchi T, Kitani Y, Hata M et al. Influence of blood proteins on biomedical analysis. III. Pharmacokinetics and protein binding of gliclazide. J Pharmacobio-Dynamics. 1981; 4: 436-442.
35. Oida T, Yoshida K, Kagemoto A, Sekine Y. The metabolism of gliclazide in man. Xenobiotica. 1985; 15: 87-96.
36. Shiba T, Kajinuma H, Suzuki K, Hagura R, Kawai R et al. Serum gliclazide concentration in diabetic patients, relationship between gliclazide and serum concentrations. Diabet Res and Clin Pract. 1986; 2: 301-306.
37. Delrat P, Paraire M, Jochemsen R. Complete bioavailability and lack of food effect on pharmacokinetics of gliclazide 30 mg modified release in healthy volunteers. Biopharm Drug Dispos. 2002; 23: 151-157.
38. Mikor M, Boni N, Al-Salami H, Kuhajada K, Kevresan S, Golocorbin-Kon S, Fawette J. Bioavailability and hypoglycemic activity of the semi synthetic bile acid salt, sodium, 3α, 7α-hydroxy-12-oxo-5β-cholanate in healthy and diabetic rats. Eur J Drug Metab Pharmacoinet. 2007; 32: 7-12.
39. Salami HA, Bult G, Tucker I, Mikou M. Influence of the semi synthetic bile acid (MKC) on the permeation of gliclazide in healthy and diabetic rats. Pharmacological Reports. 2008; 60: 532-541.
40. Forette B, Rolland A, Hopkins Y, Gordon B, Campbell B. Gliclazide pharmacokinetics in the elderly, 11th Congress of the International Diabetes Federation, Nairobi, 10-17 Nov 1982, Abstract pp. 8-9, Excerpta Medica, Amsterdam, 1982.

41. Ishibashi F, Takkashina S. The effect of timing on gliclazide absorption and action. Hiroshima Journal of Medical Science. 1990; 39: 7-9.
42. Rieutord A, Stupans I, Shenfield M, Gross AS. Gliclazide hydroxylation by rat liver microsomes. Xenobiotica. 1995; 25(12): 1345-1354.
43. Holmes B, Heel RC, Brogden RN, Speight TM. Avery GS. Gliclazide: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in diabetes mellitus. Drugs. 1984; 27: 301-327.
44. Ferner RE, Chaplin S. The relationship between the pharmacokinetics and pharmacodynamic effects of oral hypoglycaemic drugs. Clin Pharmacokinet, 1987; 12(6): 379–401.
45. Taylor AR, Brownsill RD, Grandon H, Lefoulon F, Petit A, Luijten W, Kopelman PG, Walther B. Synthesis of putative metabolism and investigation of the metabolic fate of gliclazide, [1-(3-azabicyclo (3,3,0) oct-3-yl)-3-(4--methylphenylsulfonyl) urea], in diabetic patients. Drug Metab Dispos. 1996; 24: 55–64.
46. Rieutord A, Stupans I, Shenfield GM, Gross AS. Gliclazide hydroxylation by rat liver microsomes. Xenobiotica 1995; 25: 1345–1354.
47. Oida T, Yoshida K, Kagemoto A, Sekine Y, Higashijima T. The metabolism of gliclazide in man. Xenobiotica. 1985; 15: 87-96.
48. Gliclazide product information, SERVIER CANADA Inc (January 15 2009). http://webprod.hc-sc.gc.ca/dpd-bdpp/item-iteme.do?pm-mp=00007471 (Accessed on 20th March 2009).
49. Benakin A, Glasson B. Metabolic study of ^{14}C-labelled gliclazide in normal rats and in rats with streptozotocin-induced diabetes. In Keen et al (Eds.). Gliclazide and the treatment of diabetes. International Congress and Symposium Series No. 20. Proceedings of the International Symposium, Landon, April 5-6, 1979, pp. 57-69. Academic Press and Royal Society of Medicine, London, 1980.
50. Balant L. Clinical Pharmacokinetics of sulphonylurea hypoglycemic drugs. Clin Pharmacokinet. 1981; 6: 215-241.
51. Campbell DB, Gordon BH, Ings RMJ, Beaufils M, Meynier A et al. The effect of renal disease on the pharmacokinetics of gliclazide in diabetic patients. Br J Clin Pharmacol. 1986; 21: 57-59.
52. Scott NA, Jennings PE, Brown J, Belch JJ. Gliclazide: a general free radical scavenger. Eur J Pharmacol. 1991; 14: 175-177.
53. Renier G, Desfaits AC, Serri O. Effect of gliclazide on monocyte-endothelium interactions in diabetes. J Diabetes Complications. 2000; 14: 215-223.
54. Desfaits AC, Serri O, Renier G. Gliclazide decreases cell-mediated low-density lipoprotein (LDL) oxidation and reduces monocyte adhesion to endothelial cells induced by oxidatively modified LDL. Metabolism. 1997; 46: 1150-1160.
55. Renier G, Desfaits AC, Serri O. Gliclazide decreases low density lipoprotein oxidation and monocyte adhesion to the endothelium. Metabolism. 2000; 49: 17-22.
56. Jennings PF, Belch JJ. Free radical scavenging activity of sulphonylureas: a clinical assessment of the effect of gliclazide. Metabolism. 2000; 49: 23-26.
57. Jennings PE. Vascular benefits of gliclazide beyond glycemic control. Metabolism.2000; 49(10): Suppl. 2: 17-20.

58. Nomura H, Natio M, Kodama M, Kato Y, Iguchi A. Effects of gliclazide on low-density lipoprotein oxidizability and atherosclerosis in cholesterol-fed rabbits. J Atheroscler Thromb. 2000; 7(2): 104-109.
59. Marqui G. Preventive effect of gliclazide on experimental atherosclerosis in rabbits. Diabetologia. 1978; 14(4): 269-275.
60. Akanuma Y, Kosaka K, Kanazawa Y, Kasuga M, Fukuda M, Aoki S. Long-term comparison of oral hypoglycemic agents in diabetic retinopathy. Gliclazide vs. other sulphonylureas. Diabetes Res Clin Pract. 1988; 5(2): 81-90.
61. Qiang X, Satoh J, Sagara M et al., Gliclazide inhibits diabetic neuropathy irrespective of blood glucose levels in streptozotocin induced diabetic rats. Metabolism. 1998; 47(8): 977-981.
62. Okouchi M, Okayama N, Omi H, Imaeda K, Fukutomi T, Nakamura A, Itoh M. The antidiabetic agent, gliclazide reduces high insulin-enhanced neutrophil-transendothelial migration through direct effects on the endothelium. Diabet Metab Res Rev. 2004; 20: 232-238.
63. Kumar N, Dey CS. Gliclazide increases insulin receptor tyrosine phosphorylation but not P38 phosphorylation in insulin-resistant skeletal muscle cells. J Exp Biol. 2002; 205(23): 3739-3746.
64. Shimizu M, Tsuboi T, Fujitani B, Yoshida K, Tamura Y. Pharmacological studies on gliclazide: effect of gliclazide on platelet aggregation, adhesion, and blood coagulation. Pharmacometrics. 1976; 12: 295-302.
65. Ponari O, Civardi E, Megha S, Pini M, Portioli D, Dettori AG. Anti-platelet effect of long term treatment with gliclazide in diabetic patients. Thrombus Res. 1979; 16: 191-203.
66. Fujitani B, Maeda T, Buboi T, Kadokawa T, Schimizu M. Effect of gliclazide on prostaglandin I2 formation in normal and streptozotocin-induced diabetic animals. Japan J Pharmacol. 1983; 33: 965-970.
67. Desnoyers P, Labaume J, Anstett M, Herrera M, Pesquet J, Sebastien J. The pharmacology of 1702SE, a new highly effective antidiabetic drug with unusual properties.III. Antistickness activity, fibrinolytic properties and haemostatic parameters study. Arzneim Forsch. 1972; 22: 1691-1695.
68. Verrg M, Desnoyers P, Thouverez JP. Active anti-adhesive plaquettaired'un novel andidiabetique, le 1702 SE. 2nd Mediterranean Congress on Thromboembolism, 11-14th October, 1971: Istanbul.
69. Dhault J, Lebon F, Beregi L. Protective action of 1702 SE on the microvascular system in the normal and diabetic rats. Diabetes. 1971; 20(suppl.1): 353.
70. Vallejo S, Angulo J, Perio C et al., Prevention of endothelial dysfunction in streptozotocin-induced diabetic rats by gliclazide treatment. Journal of Diabetes Complications. 2000; 14(4): 224-233.
71. Pagano PJ, Griswold MC, Ravel D, Cohen RA. Vascular action of the hypoglycaemic agent gliclazide in diabetic rabbits. Diabetologia. 1998; 41: 9-15.
72. Ziegler O, Drouin P. Hematological activity of gliclazide in diabetes mellitus. Diabet Res Clin Pract. 1991; 14(Suppl. 2): S83-S89.
73. Vallejo S, Angulo J, Peiro C et al., Highly glycosylated oxyhaemoglobin impairs nitric oxide relaxations in human mesenteric microvessels. Diabetologic. 2000; 43: 83-90.

74. Norihiko NY, Miyazawa N, Sakurai T, Kizaki T, Kimoto K, Takahashi K, Ishida H, Takahashi M, Suzuki K, Ohno H. Gliclazide Inhibits Proliferation but Stimulates Differentiation of White and Brown Adipocytes. J. Biochem. 2007; 142: 639–645.
75. Calza L, Manfredi R, Chiodo F. Disorders of Glucose Metabolism and Insulin Resistance in HIV-infected Patients Treated with Protease Inhibitors. Considerations on Frequency and Clinical Management, in a Prospective Randomized Study. Session 147, Paper No: 853, Poster Abstracts. February 22-25, 2005, Hynes Convention Center, Boston, Massachusetts, USA. 1.30-3.30 PM, 12th Conference on retroviruses and opportunistic infections. Accessed on 05th February 2009: http://www.retroconference.org/2005/cd/Abstracts/24062.htm.